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European Textbook on Ethics in Research

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Foreword

Ethics is of great importance to science and technology. There are many developments in science and technology that regularly give rise to ethical questions in European societies – stem cell research, genetically modified food, human enhancement, to name just a few. The intense social debate such developments trigger, highlights the importance of high ethics standards for science and technology. These standards reflect our adherence to the ethical values and fundamental rights, such as human dignity, freedom, democracy, pluralism, solidarity, integrity and non-discrimination, on which the EU is founded. To underline their importance, these values and rights have been reaffirmed at the highest European level with the entry into force on 1 December 2009 of the Lisbon treaty, which makes explicit reference to the European Charter of Fundamental Rights.

High ethics standards also add to the quality of research and increase its likely social impact. They promote research integrity and a better alignment of research with social needs and expectations. They support the societal uptake of the new products, processes and services that are the result of scientific research, because high ethical standards generally merit public trust. This second aspect is equally relevant, as science and technology are vital for addressing the many economic, ecological and social challenges that confront us.

The importance of ethics for science and technology has long been recognised by the European Commission. We have stimulated bioethics research, education and ethics review since the early 1990s, and have provided funding for numerous international bioethics research projects, networks, conferences and capacity building actions.

This textbook is the result of just one of the projects funded under the Science in Society theme of the Seventh Framework Programme and was skilfully produced by a team of specialists in bioethics education from the Centre for Professional Ethics at Keele University. The aim of this textbook is to contribute to the infrastructure for ethics deliberation and ethics review in Europe – and beyond – by facilitating access to information and education about research ethics.

Today, the research and ethical issues described in this textbook occur throughout the globe – and research projects are increasingly carried out by worldwide consortia of research teams. I am sure, therefore, that the textbook will find a wide readership both within and outside Europe.

Jean-Michel Baer
Director for Science, Economy and Society

Acknowledgements by the authors

This textbook results from a contract awarded by the European Commission to the Centre for Professional Ethics at Keele University (also known as PEAK). The tender for the contract was written by Jonathan Hughes and Mark Sheehan, and incorporated a provisional outline for the textbook based on PEAK's experience as a leading provider of training for research ethics committees in the health and university sectors in the UK and Ireland since 2003.

In writing the textbook we have been fortunate in being able to draw upon PEAK's extensive library of teaching resources, developed for its research ethics committee training programmes and its distance learning master's degree in research ethics. We are grateful to the past and present members of staff who have produced these materials and to the Centre itself for permission to incorporate them into the textbook.

The textbook is edited by Jonathan Hughes, who also wrote the Introduction and Chapters 5 and 6. Authorship of the other chapters is as follows (all members of PEAK except where indicated). Chapter 1: David Hunter; Chapter 2: Stephen Wilkinson; Chapters 3 and 4: Anthony Wrigley; Chapters 7 and 8: Mark Sheehan (formerly a member of PEAK but now at Oxford University and the Oxford NIHR Biomedical Research Centre). Allison Ross contributed to the planning of the textbook and Monique Jonas made contributions to the content and editing of several chapters.

We also received valuable input from outside Keele. A draft syllabus of the book, incorporating the case studies, was sent out for consultation to a variety of academic experts and research ethics practitioners from across Europe. We are grateful to the individuals and organisations that took the trouble to respond, and we have endeavoured to incorporate their suggestions.

Lino Paula, the Scientific Officer at the European Commission responsible for this project, helped to organise the consultation and provided valuable suggestions at various stages in the planning and writing process. Roger Burns, Michelle Cunningham, Celia Diver-Hall and Anne Evans commented on the final draft of the textbook from the perspective of students recently enrolled on courses in professional or research ethics. Andrew Astley commented from the perspective of a lay member of an ethical review panel at Keele. Beverley Sykes provided professional copy editing of the final draft.

Introduction

Aims and scope

This textbook is designed for use in the training of researchers and research ethics committee members throughout Europe and beyond. It is intended to be accessible to scientific and lay readers, including those with no previous experience of ethical theory and analysis. The book covers key issues in the ethics of research involving human participants, including some of the ethical issues associated with new technologies.

The scope of the textbook is the ethics of scientific research involving human beings. It contains case studies relating to a variety of scientific disciplines including biomedical and human life sciences, new technologies and the social sciences. These have been chosen to illustrate and facilitate discussion of key ethical issues, and to give a flavour of the range of research settings in which these issues occur. It is of course impossible, even in a fairly large book such as this, to include examples of every type of research. However, the ethical problems illustrated by the case studies, and the principles that are invoked in the discussions of these problems, are relevant to many different kinds of research; and the textbook should equip students to recognise ethical problems and apply the principles in relation to other kinds of research that they might encounter either in their own work or as members of research ethics committees.

Discussion of the ethical issues arising from the case studies is informed by a range of philosophical perspectives and concepts introduced in the first chapter. Although the first chapter contains some discussion of the strengths and limitations of the various approaches, no attempt is made to reach conclusive judgements about them, and the subsequent discussion does not favour or promote any particular perspective. Similarly, reference will be made to major religious views where relevant (for example in relation to research involving human embryos), but without endorsing or rejecting any particular view. This approach is based on a recognition that these are matters on which reasonable people can (and do) disagree. Nevertheless, an understanding of the key differences between different moral perspectives is important for those wishing to engage in debates about practical moral issues. Often, people approaching ethical problems from different philosophical perspectives can agree at a practical level about what ought to be done, because they share many values though for different underlying reasons. Nevertheless, different philosophical perspectives tend to emphasise different factors as being ethically important, so thinking about an ethical issue from a variety of perspectives can alert us to considerations that we might have missed had we addressed it from a single perspective. When there is disagreement at a practical level, awareness of the philosophical perspectives underlying the competing views can help to identify what is at issue between them and to find grounds for agreement or compromise.

The textbook does not aim to teach students about the law in relation to research, or about regulatory provisions relating to the running of research ethics committees. Firstly, these fall outside the book's Terms of Reference, and secondly, although there have been important moves towards harmonisation, for example through the *European Union Clinical Trials Directive* and the *Oviedo Convention* and its additional protocols, much variation remains, which would make it impossible to provide comprehensive coverage in a book aimed at a Europe-wide audience. The *Clinical Trials Directive,* for example, only applies to clinical trials of medicinal products, while the *Oviedo Convention* remains unsigned and/or unratified by several European countries. Nevertheless such legislation provides an important point of reference, reflecting ethical principles upon which a broad consensus across Europe has been reached. These and other legal instruments are therefore referred to where appropriate to illustrate such principles. It is of course important that researchers and research ethics committees comply with all relevant laws, and to this end reference is made to resources which can guide them in identifying relevant legislation.

Structure

The textbook may be thought of as having three parts. The first consists of Chapter 1 and provides a historical and philosophical introduction to research ethics. The chapter starts with a discussion of the nature and value of research, going on to consider some of the instances of unethical research that have led to the development of the current system of ethical review, the key principles and theoretical perspectives that will provide a framework for later discussion of particular cases and ethical issues, and the role of research ethics committees. A number of these issues are taken up again and explored more critically, in the light of new biotechnological developments and the changing relationship between science and society, in the final two chapters.

The next five chapters form the core of the textbook, each being focused either on a key issue in research ethics or a set of closely related ethical issues. Organising the material in this way, rather than by type of research, has two advantages. First, it minimises repetition since each ethical issue arises in many types of research. Second, it maximises the book's relevance to researchers and ethics committee members across a wide range of scientific (and other) fields, since the ethical issues can easily be extrapolated to types of research other than those that are used to illustrate them. In the experience of the authors, researchers and research ethics committee members, having been introduced to an ethical issue in one context, are readily able to suggest further examples from their own experience.

Within this core part of the book, Chapter 2 focuses on consent, considering amongst other things why consent is important, what conditions must be met for a participant's consent to be valid, and what grounds there might be for conducting research without the consent of participants.

Chapter 3 considers the ethical issues raised by research involving vulnerable participants. 'Vulnerability' is a concept that is widely used in research ethics, but it can mean different things. Sometimes vulnerable participants are understood as those who are unable to give valid consent either due to lack of competence or because of circumstances which cast doubt upon its voluntariness. The part of the chapter which deals with this extends the previous chapter's account of what makes a consent valid and what should be done in cases where valid consent cannot be obtained. 'Vulnerability' can also relate to susceptibility to harm or exploitation, and in addressing this Chapter 3 looks ahead to the discussions of these issues in Chapters 5 and 6.

Chapter 4 addresses two issues related to the acquisition or communication of information: privacy and confidentiality. These also relate to consent to the extent that they are about controlling access to our persons and personal information, but also concern the harms that can result from disclosure of personal information.

Chapter 5 is about the balancing of harms (or risks) and benefits, both in research generally and in the special case of randomised controlled trials. These raise particular issues about whether doctors engaged in research have the same duty to benefit their patients that they would have in a clinical setting, and about the use of placebos and controls, and the baseline against which assessments of harm should be made. The general part of the chapter includes discussion of the concept of minimal risk and an introduction to the precautionary principle.

Chapter 6, the last in the core section of the textbook, examines two ways in which research can violate norms of distributive justice: by exploiting research participants so that they bear an unfair share of the burdens of research, and by excluding certain sections of the population from research in ways that may be discriminatory and deny them the benefits that participation can bring.

The final two chapters address broader concerns that go beyond research itself, including the relationship between researchers and society and examples of how new biotechnologies can give rise to ethical issues that both

exist independently of the research context and provide challenges to existing modes of ethical review. These chapters contain more, and more diverse, cases than the preceding ones, and may be thought of as extension materials to be drawn on as appropriate to the context of a particular course.

More specifically, Chapter 7 introduces and develops several themes involved in understanding the relationship between science and society. It considers the range of ways in which the progress and processes of scientific research might and should engage with and involve the broader public. The cases in Chapter 7 examine the issues raised by transnational research (raising issues about moral differences across cultures), by the prospect of malevolent uses of research (raising the issue of dual use), the proper conduct of researchers and the role of social categories in research.

The general themes relating to science and society raised in Chapter 7 are also raised in Chapter 8, where the case studies deal more closely with the ethical issues involved in developing biotechnological research. These include the use of new technologies in assisted reproduction (raising questions about the use of human embryos in research as well as broader questions about human enhancement), the significance of new technology in our understanding of disability, nanotechnology (giving rise to a further discussion of the precautionary principles), and genetic and biobanking.

Pedagogical approaches

This textbook is primarily aimed at people who are responsible for the ethical review of research, or who are themselves engaged in research, or preparation for research, that will be subject to ethical approval. These may include: members and staff of research ethics committees, researchers, and students undertaking research-oriented degree programmes. The book may be used in different ways for and by these different audiences.

For example, the book as a whole may be used as a core text for research ethics modules within university science programmes and research degrees. For use in these academic contexts, the references and further readings will provide useful sources for students to draw upon in assessed work. Much of the content of this book is informed by the authors' experience in providing short courses (of one, two or three days) to members of research ethics committees serving health authorities or universities. For courses of this type individual chapters may be chosen as the basis for particular sessions in accordance with the needs and interests of the group being trained. Although the sequence of topics has been carefully chosen, and later chapters do sometimes refer back to earlier ones, they are sufficiently independent to enable the sequence to be varied in accordance with the trainees' needs or the trainer's preferences. We would, however, recommend that any audience that is new to research ethics cover the introductory material in Chapter 1 before progressing to the more applied topics, since this is intended both to motivate the enterprise of research ethics and to provide a framework for subsequent discussion. The book is also suitable for use as a self-study resource for those who are interested in research ethics – whether as professional researchers, research participants or interested citizens – but do not have access to or time to undertake a formal programme of study.

There is considerable flexibility in the way the book may be used in a teaching or training context. Many of the chapter topics could be covered in one or two teaching sessions, and the best configuration (for example a long session including an introduction to the material by the teacher and student discussion of case studies, or separate lecture and seminar sessions) may depend on student numbers, the level of the course and institutional requirements. Depending on the level of the course and the time available, several topics could easily be spread over a larger number of sessions to allow more thorough discussion of the case or to allow students to follow up the references and further readings. Similarly, while in the context of an academic course it may be appropriate for students to read the relevant chapters and think about the case studies before attending the corresponding class, for those encountering the material on a one-off short course the case studies provide a route into discussion of the ethical issues that does not depend upon prior reading.

Additional flexibility in the ways this textbook can be used is provided by the "Syllabus on Ethics in Research", which is made available as an addendum to the textbook. The syllabus contains an overview of the content of the textbook and ideally will be used in conjunction with it, but it may also be used independently, as a more succinct introduction to the issues and case studies discussed in the textbook.

Case studies

The textbook is structured around a series of case studies (between one and four in each chapter; twenty one in total), each with a set of questions for students or readers to consider, which are used to raise and illustrate the key ethical issues in research, and as a basis for discussion. The case studies are designed to illustrate and provoke reflection on particular practical and/or theoretical issues. In some instances they will be perceived as presenting difficult ethical dilemmas that motivate the reader to consider the arguments for and against the described piece of research and to think about how to weigh up the conflicting values. In other instances the case will elicit a certain intuitive response which the reader can then be challenged to defend.

Many of the case studies are based on real pieces of research, but all are adapted to serve a particular pedagogical purpose. The descriptions of the cases are kept relatively brief in order to maintain the reader's interest and to focus attention on the key ethical issues. One challenge for readers will be to identify what additional information they would need in order to reach a definitive conclusion in cases where the presented information does not allow them to do so, and to identify what is ethically significant about the additional information. This models the task that is faced by a research ethics committee in determining what questions to pose to a researcher, and by a researcher in deciding what information to include in a submission to a research ethics committee. Those using the book to teach a course may wish to encourage discussion of such issues by suggesting alternative ways in which the case descriptions might be elaborated and asking students what difference such elaborations would make to their ethical assessments of the research.

Similarly, another option open to research ethics committees is to request changes to the research protocol as a condition for granting ethical approval. Many of the case studies include a question asking readers to think about whether, if they consider the research unethical as it stands, there are modifications that could make it acceptable. As with requests for further information, this can help readers to think more broadly about the choices available to researchers to avoid ethical problems and ways in which ethical demands may compromise scientific quality.

Although the case studies can be used in various ways, ranging from teacher-led discussion to individual study, the approach that the authors have found most effective is for students to discuss the cases in small groups of between four and six, and then to report back to the larger group for a plenary discussion. This ensures that everybody gets the opportunity both to contribute to the discussion and to hear the wider range of views expressed in the larger group.

Disagreements within or between groups can provide valuable insight into contested principles. However, in order to ensure that such disagreements remain productive it can be useful to set appropriate expectations before beginning to discuss case studies in a group situation. Disagreement is to be expected but should not be considered personal. Rather, it should be welcomed as providing insight into the range of views that are likely to be encountered in a research ethics committee context and an opportunity to explore why other people hold the views that they do and to have one's own views challenged. Those who hold views that are unpopular within the group should not be made to feel uncomfortable in expressing them, and students should feel able to 'try out' controversial views that they do not necessarily want to be held to. Students should be encouraged to relate the discussion to examples from their own experience, but in some contexts it may be advisable to warn against discussing confidential cases in a way that could allow individuals to be recognised by others in the group.

Chapter 1 **Locating ethics in research**

Learning outcomes

In this chapter you will develop an understanding of the nature of ethical decision-making and its role in research ethics. You will also acquire an appreciation of the nature of research and its regulation. Specifically, you will gain the following:

- An understanding of the nature and definition of research and an appreciation of the importance of good research.
- An appreciation of the reasons for conducting ethical review of research and an awareness of some of the international codes of research ethics that have been developed in response to scandals and abuses in research.
- A critical understanding of the main theories and concepts that inform ethical decision-making, including consequentialism, deontology, respect, dignity, discourse ethics, communitarianism, liberalism, the ethics of care and the four principles approach.
- An ability to draw on these theories and concepts in order to analyse and evaluate particular examples of research.
- An appreciation of opposing views on the role of the research ethics committee, and of the implications of these views for the evaluation of research.

Introduction

This chapter introduces some central issues concerning the rationale and methods of ethical review, which will provide a context and framework for the discussion of more specific ethical issues in subsequent chapters. It begins with a consideration of the nature of research, its value, and some of the historical factors that have prompted the development of codes of research ethics and the system of ethical review. A single case study is used to illustrate the types of ethical consideration that commonly arise in relation to research. These are related to a range of key moral frameworks or theories which can provide a broader structure for moral deliberation. The final part of the chapter discusses the role and legitimacy of ethics committees.

Why research ethics review?

This part of the chapter focuses on the reasons for requiring research to be subjected to ethical review. It first explores what research is and why we might think it is valuable. Some historical cases of unethical research are introduced, along with the development of codes and laws governing research in response to these cases. These cases, along with a variety of other factors, provide a broad justification for the ethical regulation of research.

In most countries the majority of research involving human participants is now reviewed by a research ethics committee (REC) consisting of both professionals and lay people whose role is to assess the ethical acceptability of the research and to ensure adequate protections for research participants. Within the EU this is legally mandatory for all clinical trials, ([1]) and many countries require similar levels of scrutiny for all medical research. While there is much research involving human participants that falls outside these legal requirements, many institutions, such as universities, professional bodies and funders of research, have decided to regulate the research that they control by setting up institutional research ethics committees and/or codes of practice.

What is research?

Before we can identify the ethical issues that arise in research we need to have at least a working account of what research is. To readers who are engaged in research this question may seem too obvious to need an answer. It is simply what we do. However, such a definition is needed in order to distinguish research from related activities such as audit or journalism, which fall outside the scrutiny of research ethics committees, and it is surprisingly difficult to find a definition that distinguishes satisfactorily between these things. ([2]) Consider the following possible definitions of research:

- a systematic investigation to establish facts;
- an attempt to find out something in a systematic and scientific manner;
- a systematic investigation designed to develop generalisable knowledge;
- a focused systematic study undertaken to increase new knowledge and understanding;
- a systematic study directed toward fuller scientific knowledge or understanding;
- the collection of information about a particular subject;
- an inquiry that involves seeking evidence to increase knowledge.

Although these definitions capture elements that are common to many types of research, they fail to distinguish clearly between research and other activities. For example audit and journalism can also involve the attempt to generate new knowledge or to discover facts. On the other hand research conducted by students as part of their training may not generate new

1. *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use.* http://europa.eu/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf
2. What activities are scrutinised by research ethics committees varies of course from jurisdiction to jurisdiction and local regulations should always be followed.

knowledge but may nevertheless warrant ethical review. (This may depend on how 'new' is understood. Does it mean new to the investigator, to the public or to everyone?) Likewise many forms of study, such as university-based education, are focused and systematic, without being research.

This is further complicated by the array of different research areas and methodologies: there seems little in common between the research carried out by a historian and a biomedical scientist for example. This means that even notions that are shared between different research disciplines, such as the need for some methodology, will be interpreted in significantly different ways.

These considerations suggest that we should adopt an inclusive working definition of research, such as the following:

> *Research aims to generate (new) information, knowledge, understanding, or some other relevant cognitive good, and does so by means of a systematic investigation.*

While acknowledging that this doesn't distinguish all research from all other human activities, it nonetheless appears to describe most activities which are currently thought of as research. This working definition is used because it seems to capture the important elements of the partial definitions above. ([3]) It is important to note that a fundamental aspect of research is uncertainty, in relation to the outcome of the research, its potential benefits and the risks involved. Because research aims at generating new knowledge, uncertainty is unavoidable. It is also important to recognise that research involving human subjects is carried out in a wide range of fields ranging from social sciences, to applied technology and design, and of course the biomedical sciences. All of these areas of research can raise significant and specific ethical challenges.

Why is research important?

When the subject of research ethics arises, the first thing many people think of is various scandalous examples of unethical research. It is important to recognise that research is not intrinsically ethically dubious. Despite the problems that can occur there are still many reasons for holding that research is something to be encouraged. Several reasons might be given for viewing research as a valuable activity:

- Research has brought a better quality of life and increased welfare. We owe our present standard of living to the huge amount of research that has made it possible – huge improvements in economic efficiency, health care and wellbeing only exist because of research, and it is reasonable to expect that this will only continue.
- Huge numbers of lives have been saved. If we think about medical research in particular, huge numbers of lives have been saved by medical advances. Moreover, advances in our basic understanding of nutrition, sanitation and the environment have had a profound impact on life expectancy and the quality of life.
- Knowledge may be good for its own sake. Finally, even where new knowledge has no real world applications we may still think that we are in some way enriched by understanding more about ourselves, the universe we live in and our relationship to it.

These reasons support two different arguments in favour of doing research, based on different accounts of the value of new knowledge.

The first is an ethical argument that builds upon the idea of the knowledge generated by good science (or good research more generally) as *extrinsically valuable.*

3. Lisa Bortolotti and Bert Heinrichs, "Delimiting the concept of research: an ethical perspective", *Theoretical Medicine and Bioethics* 28, no. 3 (2007): 157-79.

On this view, research is valuable because of the benefits that the knowledge gained brings to society. This argument suggests that we ought to support and carry out research insofar as it has such benefits, and this should be weighed against the potential harms – intended or accidental – that might occur during research or as a result of the knowledge it generates.

The second argument appeals to the idea of knowledge as *intrinsically valuable*, that is, as being valuable in itself independently of any further benefits resulting from its application. This rests on the notion that there is something valuable about understanding ourselves and the world around us, even if there is no practical application of that knowledge. This second justification provides a reason why research without any anticipated applications or direct benefits may nonetheless be ethical.

It is worth considering how these arguments relate to the justification of research involving human subjects. All research involving human subjects involves costs, ranging from the use of participants' time to the risk of harm, and it would be hard to justify this unless the research was worthwhile in some way. This raises a question about whether research ethics committees should have a role in ensuring that research is not just ethically sound but also scientifically sound. There is some debate about this question, since the operating principles for many RECs discourage them from looking at methodology as it is felt that they are not well constituted to make this judgement in relation to the wide range of projects that they assess. ([4]) On the other hand, given that both of the arguments in favour of allowing research depend on the research having some chance of successfully reaching its objectives, it would seem that research needs to be methodologically sound to be ethical – especially when it involves risks to the participants. ([5]) It seems, therefore, that there is some reason for research ethics committees to ensure that research is methodologically rigorous, but this does not necessarily require them to review the quality of the science themselves, as they can rely on other methods of ensuring this, such as requiring independent peer review reports evaluating the methodology of the research project.

Research ethics scandals

In this section we will introduce some famous and less-well-known examples of research ethics 'scandals', and show how these have ultimately led to the establishment of the present system of independent ethics committees reviewing research. It should be noted that while the history of research ethics is often assumed to have begun with the scandals that took place in Nazi Germany, both unethical research and ethical regulation of research preceded those events.

Edward Jenner's smallpox vaccine, England, 1796

This research involved injecting an eight-year-old child with pus from a cowpox infection and then deliberately exposing the child to smallpox to establish their acquired immunity. While a great step forward in the fight against smallpox, the exposure to risk this involved for the child would be unlikely to be condoned today. ([6])

The Neisser case, Prussia, 1898

Albert Neisser conducted clinical trials on serum therapy in patients with syphilis. This was done by injecting serum from patients with syphilis into those who were admitted for other reasons, without either informing them of the experiment or seeking informed consent. When, subsequently, some of these patients contracted syphilis Neisser concluded that the vaccination had

4. David Hunter, "Bad science equals poor, not necessarily bad, ethics", in *Ethics, Law and Society* (Volume 3), Jennifer Gunning and Søren Holm, eds. (Aldershot: Ashgate Publishing Company, 2007): 61-70.
5. Angus Dawson and Steve Yentis, "Contesting the science/ethics distinction in the review of clinical research", *Journal of Medical Ethics* 33 (2007): 165-7.
6. Ernst Wynder, "A corner of history: Jenner and his smallpox vaccine", *Preventive Medicine* 3, no. 1 (1974): 173-5.

failed. This was picked up by newspapers, drawing public attention and ultimately leading to the minister for religious, educational, and medical affairs issuing a directive requiring that all non-therapeutic research must have unambiguous consent. This was followed in 1931 by the German minister of the interior issuing *Guidelines for New Therapy and Human Experimentation*, which further emphasised the necessity of considering the risks involved in research, and seeking informed consent, in particular for non-therapeutic research. ([7])

The Little Albert experiment, United States, 1920

This research aimed to demonstrate the phenomenon of human conditioning by conditioning an 11-month-old infant to fear rats by associating them with fear inducing circumstances such as a loud noise. The research was conducted without the knowledge or consent of Albert's parents. ([8])

Medical experimentation in Nazi Germany, 1939-45

Experiments carried out on concentration camp prisoners included involuntary sterilisation, subjection to radiation, freezing to induce hypothermia, infection of research subjects with malaria and tuberculosis (TB), and many other unethical experiments, conducted without the consent of the research subjects, and often leading predictably to extreme pain, mutilation and death. ([9]) One difficult and highly controversial question arising from this research is whether it is ethical to use the results of such experiments in those cases where they are considered to be scientifically valid. On the one hand not to do so does not help the victims and may deprive others who could benefit from the application of the knowledge generated. On the other hand to use the research seems in some ways to endorse the gathering of that data. This, however, is not an issue that research ethics committees normally have to deal with since they look at research prospectively rather than retrospectively.

These experiments led to the development of the *Nuremberg Code* in 1947, largely as a legal document to codify what was unethical about the Nazi research, but also as a code for future research. It also strongly influenced the development of the World Medical Association's *Declaration of Helsinki* in 1964, a code of ethics developed by physicians to self-regulate the conduct of medical experimentation.

The Milgram experiments, United States, 1961-63

In these experiments, designed to investigate people's obedience to authority, the research subjects were deceived about the nature of the research and led to believe that they (in the process of a different experiment) were administering electric shocks to other research participants. The aim of the research, which turned out to be very distressing for many of the subjects, was to see how far they would be willing to go in risking harm to the other research participants. ([10]) Surprisingly, the result was that most people (approximately 65 %) were willing to continue to the end of the experiment, even though had the electric shocks been real they would have been seriously endangering the other research participant. One observation that might be made about this research is that science that is ethically questionable is not always scientifically weak or unimportant, since from this research we learnt that people will often obey authorities even if this involves behaviour that they would normally judge to be unethical, which has important implications for psychology, sociology and governance.

7. Jochen Vollmann and Rolf Winau, "Informed consent in human experimentation before the Nuremberg code", *British Medical Journal* 313 (1996): 1445-7.
8. Ben Harris, "Whatever happened to Little Albert?", *American Psychologist* 34, no. 2 (1979): 151-60.
9. Vivien Spitz, *Doctors from Hell: The Horrific Account of Nazi Experiments on Humans* (Boulder, CO: Sentient Publications, 2005).
10. Stanley Milgram, "Behavioral study of obedience", *Journal of Abnormal and Social Psychology* 67 (1963): 371-8.

Tuskegee syphilis study, United States, 1932-72

This was a clinical study carried out between 1932 and 1972 in Tuskegee, Alabama, by the US Public Health Service. About 400 mostly illiterate African-Americans with syphilis were recruited into the study as well as two hundred healthy controls. The aim of the study was to observe the natural progression of the disease when left untreated, and in particular to compare the progression of the disease in African-Americans with the results of an earlier retrospective study of the disease in Europeans. The participants were not told that they were in a medical trial, and the tests were described as "special free treatments".

At the outset of the trial there was no effective treatment for syphilis. However, by 1947 penicillin had become the standard – effective – treatment for syphilis. The researchers blocked the study subjects from receiving effective treatment, going so far as to prevent the subjects from being conscripted into the armed forces since that would have necessitated them being treated. At the end of the study only 74 subjects remained alive, 40 of their wives had been infected and 19 children had been born with syphilis, some of which might have been prevented if these men had been given treatment. ([11]) The aftermath of Tuskegee led to the formalisation of ethics review in America, and was also influential on the 1975 revision of the *Declaration of Helsinki* which introduced the requirement for the independent review of all research.

This and the other well-known research ethics scandals listed above are clearly ethically troublesome, but it is important to realise that these high-profile cases form only a minority of cases of unethical research. Most countries have had public scandals regarding some breaches of ethical norms in research, and even in those that have not, it is likely that unethical research, at least by today's standards, has been carried out. Not all worries about research ethics are spectacular big scandals, nor is it always the case, even in the examples mentioned above, that unethical research involves researchers knowingly doing what they believe to be wrong. Often researchers are either unaware of the ethical implications of their research, or, being aware of them, believe that they are outweighed by the positive benefits of their research. Here are two examples recently submitted to research ethics committees.

Psychology of depression with eight-year-olds

In this case the researcher wanted to use a questionnaire, part of which consisted of the Becks Depression Index, with 30 eight-year-old children. The Becks Depression Index asks participants to express their agreement or disagreement on a scale of 1 to 5 with statements like:

- I feel like harming myself.
- If I died today no one would notice.
- I think about killing myself.
- There is no point growing up.
- I am useless.

The truly disturbing thing about this research was that the researcher was not actually interested in the children's responses to these questions, but included them in the questionnaire as a 'blind' to conceal the true nature of the research from the participants so as to avoid knowledge of the researcher's intentions from biasing the results.

Sports science muscle biopsy

For a piece of research on the oxidation of muscle tissue a sports scientist wanted to take pea-sized chunks of muscle out of the legs of athletes. The main piece of information on the participant information sheet was

11. Joseph Brady and Albert Jonsen, "The evolution of regulatory influences on research with human subjects", in *Human Subjects Research – A Handbook for Institutional Review Boards*, Robert A. Greenwald, Mary Kay Ryan and James E. Mulvihill, eds. (New York: Plenum Press, 1982): 3-5.

that this might hurt a bit. No information was given about ongoing pain, nor about the possible implications the removal of muscle might have for athletic performance.

In both of these cases the researchers declared that there were no ethical issues. Obviously in the first case there are clear risks involved in suggesting the notion of suicide to eight-year-old children. In the second case, while the research was not necessarily problematic, not nearly enough information was given to participants to allow them to decide for themselves.

All of these cases provide evidence of the abuses that can occur in unregulated research, and the more public scandals outlined above have been a dominant driving force behind the development of ethical codes and laws to govern research. [12]

Codes of Ethics and legal constraints

Ethical codes and guidelines are a means of establishing and articulating the values of a particular institution or society, and the obligations that it expects people engaged in certain practices to abide by. Some prominent examples of codes and laws which bear on researchers' conduct are listed below.

- *The Nuremberg Code.* [13]
- The World Medical Association's *Declaration of Helsinki.* [14]
- The Council for International Organizations of Medical Sciences' (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects.* [15]
- *The Charter of Fundamental Rights of the European Union.* [16]
- *The European Convention on Human Rights.* [17]
- *The European Union Good Clinical Practice Directive.* [18]
- *The Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine* (The Oviedo Convention). [19]
- *The European Union Clinical Trials Directive.* [20]

Research ethics as a separate area of concern arose with the increasing formalisation of medical research in order to address the ethical concerns arising from the conduct of research. Historically, the development of research ethics has been greatly influenced by examples of scandals and unethical research such as those described in the previous section.

12. Some further examples of unethical research can be found in the following: Henry Beecher, "Ethics and clinical research", *New England Journal of Medicine* 274, no. 24 (1966): 1354-60; Laud Humphreys, *Tearoom Trade: Impersonal Sex in Public Places* (New York: Aldine, 1975); Maurice Pappworth, "Human guinea pigs: a warning", *Twentieth Century* 171 (1962): 67-75; Udo Schüklenk, "Introduction to research ethics," *Developing World Bioethics* 5, no. 1 (2005): 1-13; Philip Zimbardo, *The Lucifer Effect: Understanding How Good People Turn Evil* (New York: Random House, 2007).
13. *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law* 10, no. 2 (1949): 181-2. http://ohsr.od.nih.gov/guidelines/nuremberg.html
14. World Medical Association, *Declaration of Helsinki: ethical principles for research involving human subjects* (2008). http://www.wma.net/en/30publications/10policies/b3/index.html
15. Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002).* http://www.cioms.ch/frame_guidelines_nov_2002.htm
16. European Union, *The Charter of Fundamental Rights of the European Union* (2000/C 364/01). http://www.europarl.europa.eu/charter/default_en.htm
17. *Convention for the Protection of Human Rights and Fundamental Freedoms* (Rome, 4.XI.1950). http://conventions.coe.int/Treaty/en/Treaties/Html/005.htm
18. *Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.* http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf
19. *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (Oviedo, 4.IV.1997). http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm
20. *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use.* http://europa.eu/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf

The norms of modern research ethics were codified by the N*uremberg Code* in 1947 in response to Nazi medical research and further developed by the World Medical Association's *Declaration of Helsinki* in 1964. Concerns about the effectiveness of the existing regulation arose when attention was drawn to various ethical concerns in ongoing research. ([21]) These concerns led to the 1975 revision of the *Declaration of Helsinki*, which introduced the requirement of a formal independent committee review of research protocols.

Following this pattern, a bewildering array of guidelines for research has now been put into place, some of which have a merely advisory status, such as CIOMS' *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Others, such as the World Medical Association's Declaration of Helsinki are binding on members of particular professions (and most professional bodies have published their own guidelines). Others have legislative status, for example national laws and European laws such as the *European Union Clinical Trials Directive*. ([22])

This array of documentation can be bewildering both to the researcher and to members of research ethics committees, since it can be unclear which documents apply to which research and what status each document has. This is particularly problematic in cross-jurisdictional research since local guidelines and laws can and do clash with international guidance. Most countries in the EU now have substantial guidance for the establishment and operation of research ethics committees, although there is still significant variation between countries. ([23]) Likewise funding bodies, including the European Commission, usually have their own requirements and guidance both for researchers and research ethics review. ([24])

The relationship between codes, ethical practice and the law is complex, however, and we should not assume that ethical evaluation can simply be a matter of 'applying' codes or laws. This is, firstly, because codes and laws are general and thus often fail to provide clear guidance in complex specific cases. Often judgement is required, and what is legal may depend on the judgement of a research ethics committee. Secondly, codes and the law are silent about many research practices, aiming to rule out certain very unethical behaviours but not to give comprehensive ethical advice. Thirdly, the contents of particular guidelines may be controversial and/or contradictory (internally or with other guidelines). Finally, of course, even where the law or code is clear it may not be ethically correct – for example research practices in Nazi Germany may have been legal but were clearly immoral.

It is sometimes argued that since unethical research is not widespread the present form of regulation constitutes an over-reaction to rare scandalous behaviour in the conduct of research. It is felt by some that the regulation of research treats all researchers as guilty of the crimes of a very few. Indeed, there is considerable complaint in the research community about the scrutiny their research undergoes and the resources that it costs. ([25]) There is a point here, given the positive benefits of research as discussed earlier. Preventing research

21. Henry Beecher, "Ethics and clinical research", *New England Journal of Medicine* 274, no. 24 (1966): 1354-60; Maurice Pappworth, "Human guinea pigs: a warning", *Twentieth Century* 171, (1962): 67-75.
22. A listing of legislation governing research can be found in: *Office for Human Research Protections, International Compilation of Human Subject Research Protections* (Washington: International Activities Program, Office for Human Research Protection, 2009). http://www.hhs.gov/ohrp/international/HSPCompilation.pdf. Likewise an outline of the regulation of research in the EU can be found in Michael Fuchs, *Provision of Support for Producing a European Directory of Local Ethics Committees (LECs)* (EC contract no. SAS5-CT-2002-30047, 2005). http://ec.europa.eu/research/conferences/2005/recs/pdf/lec_finalreport.pdf
23. European Forum for Good Clinical Practice, "The procedure for the ethical review of protocols for clinical research projects in the European Union: a report on the structure and function of research ethics committees across Europe", *International Journal of Pharmaceutical Medicine* 21, no. 1 (2007): 1-113. An updated version of this can be found on the EFGCP website: http://www.efgcp.be/html.asp?what=efgcpreport.htm&L1=5&L2=1#report
24. For example see http://ec.europa.eu/research/science-society/index.cfm?fuseaction=public.topic&id=36 for a guide to ethics review requirements for European Commission funded projects.
25. John Saunders, "Research ethics committees – time for change?", *Clinical Medicine* 2 (2002): 534-8.

from going ahead, or even delaying it, means foregoing some of these benefits. Nevertheless, in the light of the history of research described above it would be rash to think that regulation is now unnecessary. This is particularly the case because ethical decision-making is complex. Because of this complexity individual researchers may not be best placed to decide about the ethical issues a research project raises, and instead it may need a group of experts, both scientific and ethical, to make a good decision. Likewise given the plurality of ethical views that exist within any society, a committee decision can be representative in a fashion that an individual decision about the ethical legitimacy of a course of action cannot. This can be shown by considering the possible reactions to the following case.

Case Study 1.1
Testing of artificial blood product

Your ethics committee has been asked to review the following application. ([26]) Currently ambulances can only carry a partial range of blood of the various blood types, potentially significantly delaying the treatment of critically injured and ill individuals until they can be transported to the hospital. A replacement for human blood has been developed by a pharmaceutical company and now needs to be tested in the field. This artificial blood is blood-type neutral and initial testing with healthy volunteers seems to have shown that it is well tolerated with minimal adverse reactions. The researchers now propose further testing of the artificial blood by equipping five local ambulances with the artificial blood to be used in emergency care situations. In many cases it will not be possible to obtain consent from the patients to take part in the research because of the urgency of treatment and the fact that patients are often unconscious.

The researchers argue that given the extensive laboratory testing the product has already undergone the best way to test the usefulness of the artificial blood is in a 'real world' test. Furthermore they make the point that presently some people have to forego blood products until they reach the hospital in any case.

Questions

1. What arguments can the researchers put forward in support of their proposal?
2. What objections could be raised against the proposal?
3. In your opinion, should this research be allowed to proceed in its present form? If not, how might it be modified to make it more acceptable?

Discussion

This case study provides the basis for exploring a range of different ethical considerations relevant to research. In considering the questions attached to the case study we will identify some of the key ethical issues that arise in research. These will then be related to a range of moral theories and principles which will give a broader context to the moral considerations raised by the case, and will provide a framework for further consideration of this and other cases.

26. This case is based on the controversial trial of PolyHeme in the USA. A discussion of this research can be found in the *American Journal of Bioethics* 6, no. 3 (2006).

In support of their project the researchers are likely first to point out the benefits to future patients if the research goes ahead and is successful in demonstrating the effectiveness of the artificial blood product. This, after all, is the primary reason for carrying out the research and could lead to the saving of many lives. They may also point out that the research has potential benefits for the research subjects: the artificial product may be safer or more effective than standard donated blood. This is particularly the case for subjects who have the rarer blood types that are not standardly carried in ambulances, as it will enable them to receive a transfusion in the ambulance when they would otherwise have to wait until reaching hospital. It might also, although more controversially, be argued that patients have a duty to participate in research (at least if the risks are not too great) since they have benefited from the knowledge resulting from the contributions of previous research subjects. ([27])

Against this, opponents of the research might argue that the risks to research subjects are too great. What if the blood replacement product doesn't work or, worse still, some subjects have an allergic reaction to the product? Opponents of the research might also object to the fact that many participants will be unable to consent. This may in itself be taken as an objection to the research (perhaps because researching on people without their consent is considered a violation of their rights) and may also make it harder to justify subjecting research participants to risk. Even in the cases where consent can be obtained, there may be concerns about the quality of the consent, given that it takes place in an emergency situation where the potential subjects may not have a viable option other than to consent, given the limited range of blood products that ambulances presently carry, and where there is likely to be little time for explanations or deliberation. Concerns about the medical risks faced by participants and the absence of consent may be exacerbated by the thought that we are dealing with research participants who are vulnerable, as a result of their medical condition, and at risk of being exploited or used as means to other peoples' ends (for example those of the researchers or of future patients). Finally, some people may be concerned about the motivation of the pharmaceutical company involved in the research: are they just in it for the money, and if so, does this give us reason to be sceptical about the claimed benefits of the research and is it likely to affect the way in which the trial is conducted?

We have seen that there are plausible arguments for and against this particular piece of research. However, simply listing the arguments does not resolve whether the research should go ahead. One way of moving towards a decision is to examine the strength of the competing arguments. For example, in response to the concern about risks faced by the subjects it can be pointed out both that there may be counterbalancing benefits for the same subjects, and that, given the extensive lab testing and prior testing with healthy volunteers that the artificial blood product has undergone, we may have some reason to think that it will be relatively safe.

It may also be that relatively minor modifications to the design of the research could remove some of the objections. For example, if the ambulances could be modified to carry both artificial and donated blood this could enable patients to opt out of the research without being disadvantaged. Likewise, if allergic reactions are a possibility then the ambulance staff could be briefed and treatments for possible allergic reactions could be stocked in the ambulance.

In response to concerns about the absence of consent it might be pointed out that this is rarely sought for emergency treatment given the urgency of the situation, so maybe we could apply a similar practice to this research given its therapeutic aims. Perhaps also, as an alternative to individual consent, we could consult widely with the community, and adopt some form of community consent. If it is possible to carry both types

27. John Harris, "Scientific research is a moral duty", *Journal of Medical Ethics* 31 (2005): 242-8.

of blood in the ambulances we could insist that the artificial blood be given only to those who consent, or, if consent is not obtainable, to those who would normally receive no transfusion before reaching hospital due to having a rare blood type.

Even after critiquing the arguments in this way we may be left with plausible arguments on both sides and it may not be obvious how to weigh these up. In order to resolve the question of whether the research should go ahead we need to understand better the bases for the various arguments and how they fit within more general ethical frameworks. One way of doing this is to identify different types of argument that are characteristic of different approaches to ethics. In particular we might notice that many of the arguments for and against the research are about the *consequences*, or *effects*, of the research: the benefits or risks to participants or future patients, for example. Other arguments – mainly arguments against the research such as those concerned with consent and violations of rights – might better be seen as expressing *constraints* on research – limits to what it is permissible to do even in the successful pursuit of worthwhile aims. This distinction corresponds to the distinction between two of the most common types of ethical framework, to be examined alongside others in the following section.

Ethical frameworks

Consequentialism

In the discussion of the case study, several of the arguments focused on the expected or possible consequences of the research. These included potential benefits to the research participants and to the wider society, and risks to the participants. One way to assess this research would be to weigh up the potential benefits and risks, so as to determine whether, overall, the consequences are likely to be good or bad.

This approach to ethical decision-making is known as consequentialism.([28]) The key feature of all consequentialist theories is that they take the morality of an action to be determined entirely by its consequences. Different consequentialist theories have different accounts of what kinds of consequence we should seek to promote, but one of the most influential forms is utilitarianism. This holds that our sole duty is to maximise utility, where this is understood as the happiness or welfare of all the individuals affected by the action. Thus, in the artificial blood case, the research should go ahead if, taking account of all the risks and benefits, this is likely to produce more utility than not going ahead. Utilitarianism would also tell us that if there are steps that we can take to reduce the potential harms without foregoing equivalent benefits then we should do so.

However, the case study also illustrates some objections to a purely consequentialist approach to ethical decision-making. One objection is that while consequences do seem to be an important factor in ethical deliberation, consequentialist approaches treat them as the *only* relevant factor. One of the ethical concerns raised about this case was that individual consent would not be sought in all cases. To a consequentialist this would only matter if the absence of consent had bad consequences (for example if it led to a public outcry or if it resulted in participants who would have refused consent being included in the trial and suffering harm as a result). Many people think, however, that consent is important even if it does not have any such consequences.

Another objection to consequentialism is that the focus on overall consequences can lead to a neglect of the interests of individuals. Suppose we could be sure that the research would be successful and would lead to the saving of many lives in the future, but also that it would involve the deaths of ten participants. Leaving aside any secondary consequences (such as loss of public support for research) a consequentialist might think that the sacrifice is worth the benefits, whereas

28. For further introductory reading on consequentialism see James Rachels and Stuart Rachels, *The Elements of Moral Philosophy* (New York: McGraw-Hill, 2009), Chapters 7 & 8.

most people would consider that unconscionable. As with consent, there might be secondary consequences that would lead the consequentialist to a view more in line with most people's moral instincts, but to critics this would still show a failure to recognise the basic moral rights of individuals.

A common view of many critics is that consequentialism correctly identifies consequences as an important factor in determining whether an action (or piece of research) is ethically permissible, but that a concern with consequences needs to be supplemented by other principles and in particular by principles constraining what it is permissible to do even in pursuit of good consequences.

Duty-based ethics

In response to these concerns a rule-based or duty-based approach to ethics is often suggested as an alternative to consequentialism. In the case study, the ethical concerns that are not well accounted for by consequentialism might be better explained in terms of duties, for example to respect the wishes of individuals (by obtaining consent before involving them in research) or avoid harming them (by not sacrificing their lives or important interests for the good of others). These rules or duties can be thought of as placing constraints on the ways in which we may treat people.

There is a wide variety of duty-based approaches to ethics, but what they share is the view that the rightness or wrongness of actions is not determined solely by their consequences but instead is determined by the nature of the action itself. These are also referred to as 'deontological' approaches.([29]) An example of a deontological approach to ethics that will be familiar to many people is the Ten Commandments. This is a set of rules, identifying certain types of action as ones which we have a duty to perform or refrain from irrespective of their consequences. In this case the duties are usually seen as absolute, so that breaking them can never be morally justified regardless of the consequences. Other deontological approaches hold that we have *prima facie* or 'defeasible' duties, which can be overridden by sufficiently weighty considerations. What distinguishes these views from consequentialism, however, is that the rules or duties matter in themselves, so that deciding what we should do is not simply a matter of weighing up the consequences. A variety of duty-based approaches will be explored below.

One way of expressing the concerns raised about the research in the case study is that it involves using people as a means to an end. This can clearly be seen in the case where we imagined the lives of ten participants being sacrificed to save a larger number of future patients. The idea that we should not treat people solely as means is associated with the deontological theory of Kant.

Kant's primary insight was to associate reason and consistency with ethics. For the most part Kant thought we already knew the right things to do; we simply failed to do them. Kant thought of this as a kind of inconsistency: we expect the world to live by one rule, while we live by a less strict one. For example, it is easy to be annoyed by someone else behaving in a rude or inconsiderate fashion when driving, but it is also easy to do this ourselves, "just this once", or "because I'm in a *real* hurry". What Kant ultimately thought was that morality can be derived from reason via a requirement for consistency. This is important because, for morality to function as we expect it to, it needs to be based on claims that have universal appeal and motivation. Kant distinguished two different sorts of imperatives, hypothetical imperatives and categorical imperatives. Hypothetical imperatives have the form:

> if you want x then you need to do y.

For example:

> if you want your research to be ethical you need to obtain consent.

29. For further introductory reading on deontology see James Rachels and, Stuart Rachels, *The Elements of Moral Philosophy* (New York: McGraw-Hill, 2009), Chapter 9.

The problem with this type of claim as a basis for moral action is that it only motivates someone if they want x; so in our example if the researcher did not care about being ethical then the claim would fail to motivate them to seek consent.

Categorical imperatives, in contrast, are imperatives that all rational agents should recognise and be motivated by. Kant built his moral theory out of categorical imperatives, derived from reason, and in particular from the notion of consistency:

> *1st formulation of Kant's categorical imperative:* Act only according to that maxim whereby you can at the same time will that it should become a universal law.

From this notion of consistency Kant derived the idea of respecting people as persons or respecting their dignity. ([30])

> *2nd formulation of Kant's categorical imperative:* Act only in such a way that you always treat humanity, whether in your own person or in the person of any other, never simply as a means, but always at the same time as an end.

To treat someone as a mere means would be to behave towards them as if they were just a tool to you, a means to achieving your own goals. To treat them as an end is to treat their own goals as important and in general to treat them with the respect that is due to a rational, autonomous agent.

Another influential deontological approach is the human rights approach. ([31]) The basic idea here is that there is something special that ought to be respected and treated appropriately about every human being. Like dignity-based approaches, this approach is based on the notion that there is something morally important about being human, and that this moral importance gives rise both to certain claims on others and to certain freedoms, so each human has a set of rights that may not be violated. Rights can be based on claims about the nature of persons (natural rights) but they might also be established by agreement, laws or treaties (contractual rights). So, for example, many of the international treaties and EU laws we discussed earlier establish various rights for research participants.

Rights imply that other people have duties to respect those rights, and different types of rights establish different types of duties. A commonly drawn distinction is between positive and negative rights. If someone has a positive right to something then either all or some others have an obligation to ensure that the person gets the thing they have a right to. In contrast if someone has a negative right to something then others have no duty to provide it, only a duty not to interfere with the person getting their right fulfilled. For example, if someone has a positive right to life then the state might be obliged to do various things to protect this right such as providing food and shelter. However, if the right to life is conceptualised in negative terms then the state (at least as far as the right to life is concerned) does not have a duty to provide the person with the things that they need to continue living, but only to refrain from killing them. Rights are often related to the welfare of individuals and so can be linked to consequentialism, although in contrast to consequentialism they tend to protect the individual's interests against being sacrificed for the good of the group even if this produces less overall utility.

Deontological concerns could underwrite several of the arguments discussed in relation to the case study. For example, Kantian concerns for respect for persons might ground our concerns about the lack of consent. Similarly, dignity might arise as a concern in relation to using research participants as means to others' ends,

30. For further introductory reading on rights see Leif Wenar, "Rights", *The Stanford Encyclopedia of Philosophy* (Fall 2008 Edition), Edward N. Zalta, ed. http://plato.stanford.edu/archives/fall2008/entries/rights/
31. For further introductory reading on respect for persons see James Rachels and Stuart Rachels, *The Elements of Moral Philosophy* (New York: McGraw-Hill, 2009), Chapter 10.

particularly in view of the vulnerability of the research participants in this case and their inability to protect their own dignity through a standard consent process. Human rights might play a role if we think that people have a right not to be used as subjects of experimentation without consent.

A common objection to absolutist deontological approaches to ethics is that they are very inflexible. While informed consent, for example, is very important, given the possibility of very significant benefit to the participants, we might want to be more flexible than an absolutist approach would allow. Another problem with absolutist approaches is what to do when different rights or duties come into conflict. One response to these problems is to adopt a different type of deontological approach, where the rules can be traded off against each other (a *prima facie* or defeasibilist approach). This approach will be explored later in this chapter.

Some have argued that the general approach adopted by Kantian and consequentialist approaches of focusing on actions as the locus for moral evaluation is mistaken and that we need to view morality in a different way. Two such approaches will be briefly outlined below.

Virtue Ethics

Virtue ethics is an approach that addresses ethical issues in terms of the character of the agent carrying out the action. ([32]) Virtue ethical concerns might be raised if we think about the character of the researchers or the motive they have for carrying out the research. For example, the concern about the motivation of the company financing the research might be seen in these terms. But the other concerns could be captured in virtue terms by thinking about how a virtuous agent would act.

The essence of virtue ethics is that character is the primary object of ethical appraisal, and actions are judged according to what they tell us about the agent's character. We might, for example, think that respectfulness is a virtue, and this might underwrite several of the objections that were raised to the research in the case study. Likewise, we might think that beneficence is a virtue and this might provide a reason to support the research because of its potential benefits. Virtue is considered to be important because it leads to 'eudaimonia', or flourishing. So the basic idea is that the virtues are those character traits that lead to human flourishing, and the vices are those character traits that destroy human flourishing.

As with the previous two ethical frameworks, virtue ethics faces serious objections. One is that there can be competing accounts of what counts as human flourishing and thus competing accounts of virtue. Another objection is that virtue ethics does not provide us with a clear account of what we ought to do: it tells what sort of person we ought to be, but not how to act in particular situations. One response to this is that the complaint is unfair, since we should not expect an ethics of character to tell us about our actions. We might for example take the central insights of virtue ethics and incorporate them into another theory in order to evaluate both character and actions.

Others have defended virtue ethics from the charge that it is not action-guiding by appealing to the use of moral exemplars. If I am not fully virtuous I may be able to decide how to act by emulating someone I believe to be more virtuous than me; by trying to do what they would do in the situation. So, for example, we might think: "what would Gandhi do?"

This response might be too quick though. How do you know who is virtuous unless you yourself are virtuous?

32. For further introductory reading on virtue ethics see James Rachels and Stuart Rachels, *The Elements of Moral Philosophy* (New York: McGraw-Hill, 2009), Chapter 12.

And even those we think of as virtuous in some contexts may not be virtuous in others (for example, some people believe that the way Gandhi treated his wife was neglectful). Finally it is difficult to identify moral exemplars in the context of research ethics; to do this we would arguably need to have fairly settled intuitions about what the right actions would be.

Ethics of care

Another non-action-focused approach to ethics is known as the ethics of care.([33]) This starts from a criticism of views like consequentialism and deontology, which take ethical obligations to be impartial and universal, arguing that these rely on an unrealistic view of individuals as autonomous, self-sufficient beings, and that instead we ought to see people as social beings, nested within a complex set of relationships. The ethics of care concentrates on these relationships and the emotions such as sympathy and solidarity that tend to go with them. Because the ethics of care focuses on receptivity to the needs and desires of particular people to whom we stand in particular relationships it tends to see moral judgements as highly contextual rather than deriving from general rules. Historically, the ethics of care has been associated with feminist thinkers and has been said to reflect the ways in which women and girls think about ethical issues, but its focus is broader than simply gender relationships and some feminists have criticised this view as reinforcing stereotypes about women as the 'caring sex'.

Someone approaching research ethics from the perspective of the ethics of care might focus on the relationship between the researcher and the research participants (although in the research in the case study the relationship would be minimal). On the question of whether people taking part in research should be termed 'subjects' or 'participants', those with an ethics of care perspective might argue that 'participants' is a richer term that encourages the participants being seen by the researcher as people to be engaged with, not merely resources for research. Although a Kantian might make a similar point, their focus would be slightly different: the ethics of care theorist would focus on the researcher and research participant's relationship while the Kantian would focus on the researcher's action.

As with virtue ethics, though, we might be concerned about this as the basis for the entirety of our moral decision-making. While there is a strong case for thinking that both character and relationships are morally relevant, there appear to be equally strong grounds for thinking that actions and activities are morally relevant, and not just insofar as they affect character or relationships.

Dealing with moral difference

We have introduced four of the most common approaches to ethical decision-making, but it seems that in at least some cases they will lead us towards different answers. For example, in the case study it seems likely that a consequentialist will be inclined to approve the research because overall the benefits outweigh the risks, whereas a deontologist might reject it because enrolling research subjects without consent might either violate their rights or the researchers' duty to treat people with respect, and a virtue ethicist might go either way, depending on what they understand the relevant virtues to be. Given a population with diverse moral views this creates an obvious problem for ethical decision-making especially when, as in the context of research ethics, we are making ethical decisions on behalf of society. This is the problem of moral difference.

Moral differences exist not only between the major ethical frameworks described above, but within each of them. As we saw above, there are different accounts of the consequences we should promote, the rights and duties we should respect and the virtues we should cultivate. This raises a general question about the authority and mandate of research ethics committees:

33. For further introductory reading on the ethics of care see James Rachels and Stuart Rachels, *The Elements of Moral Philosophy* (New York: McGraw-Hill, 2009), Chapter 11.

what gives a committee the authority to decide what others can do and on what basis should it make its decision? We will return to this issue towards the end of this chapter and again in Chapter 7.

How should we respond to the problem of pluralism? We will quickly review and reject two initial responses before exploring some more promising options.

- We might adopt one ethical approach and reject the others. This might mean trying to develop a version of the preferred approach that can overcome the objections raised against it and providing arguments for its superiority over other approaches. However, given that all the approaches combine elements of plausibility with serious difficulties, and that philosophers have been grappling with these problems for hundreds of years, we are unlikely to reach a consensus in the near future. To impose one approach in the face of ongoing disagreement and in the absence of compelling arguments would arguably be both disrespectful to those taking a different view and harmful to the authority and legitimacy of the research governance process.
- Alternatively we might give up on a search for answers to ethical problems. If we are unable to come up with arguments that can command general agreement, perhaps that is because there are no answers to be found. One difficulty with this approach is that it conflicts with our sense that it matters what we think about ethical questions, that people can be mistaken about such questions and that it makes sense for us to protest when someone is doing something unethical.

Both of these responses to ethical pluralism seem difficult to defend in the context of research ethics, given the extent of moral disagreement in society and likely to be found around the table at an ethics committee meeting. The first approach is likely to end up with a deadlock between members of the committee holding different views, and if there happened to be consensus within the committee this would give rise to concerns about its representativeness and hence about the legitimacy of its decisions. The second approach threatens to undermine the rationale for having the ethical review of research in the first place.

Instead we need a coherent account of how to find an accommodation between several different ethical views, in essence a political approach to handling moral differences. We will return to this issue in Chapter 7, but for now we can identify some further moral frameworks which aim to explain how we can arrive at shared moral judgements in societies characterised by moral difference.

Discourse Ethics

Discourse ethics, at least as it was articulated by Habermas, claims to provide a universal account of our moral obligations that all ought to agree with. ([34]) It does this by focusing on the normative commitments that engaging in dialogue imposes on the participants in that dialogue. As such, the moral claims made by discourse ethics are situationally dependent and emerge as a consensus from discourse about the situation at hand.

Habermas claims that:

> *Only those norms can claim to be valid that meet (or could meet) with the approval of all affected in their capacity as participants in a practical discourse.* ([35])

On this account, the appropriate moral norms can only be established through dialogue under fair conditions in which all viewpoints are heard and taken seriously. The norms that govern this discourse discourage disingenuous debating techniques, irrelevancy and inappropriate claims of priority for particular

34. For further introductory reading on Discourse Ethics see James Bohman and William Rehg, "Jürgen Habermas", *The Stanford Encyclopedia of Philosophy* (Fall 2008 Edition), Edward N. Zalta, ed. http://plato.stanford.edu/archives/fall2008/entries/habermas/
35. Jürgen Habermas, "Discourse ethics: notes on a program of philosophical justification", in *The Communicative Ethics Controversy*, Seyla Benhabib and Fred Dallmayr, eds. (Cambridge, Massachusetts: MIT Press, 1990): 11-77.

viewpoints. This provides a means of coping with the plurality of moral views.

Two concerns might be raised for discourse ethics as a way forward for research ethics. The first is that we would need to establish what count as fair conditions of discourse, but this itself might be subject to disagreement. Habermas claims that the conditions of fair discourse emerge from the nature of communication itself, but there is still the possibility of disagreement about what this entails. The second is that discourse does not always come to a single clear resolution that is consistent with past decisions, so there still might be uncertainty in what the committee should decide, and researchers might find it hard to predict what kinds of research the ethics committee will approve.

It is difficult to know without actually having the discourse what practical conclusions would emerge regarding the research in the case study. However, since discourse ethicists believe that there are important norms within communicative transactions, and that these norms must be respected, it is likely that they would raise concerns about the consent process and the difficulties it faces.

Principlism

A framework that is very widely used in bioethics, and medical ethics in particular, is called 'principlism', or the 'four principles approach'. This approach, popularised by Tom Beauchamp and James F. Childress ([36]) developed out of the Belmont report, an American report on the ethical conduct of research published in 1979. ([37])

The four principles are:

- *respect for autonomy* (the obligation to respect decision-making capacities of autonomous persons);
- *non-maleficence* (the obligation to avoid causing harm);
- *beneficence* (the obligation to provide benefits and to balance benefits against risks);
- *justice* (the obligation of fairness in the distribution of benefits and risks).

These are to be viewed as defeasible, or *prima facie* principles. If only one principle applies in a situation then we should act on it but if two or more apply, and suggest different courses of action, then some will be overridden by others.

Principlism claims to provide a response to moral pluralism by basing moral decision-making on principles which can be supported by people with different ethical perspectives. For example, we have already seen how respect for autonomy is central to Kantian ethics and reflected in the requirement to treat others as ends in themselves. Many consequentialists would also endorse the principle of respect for autonomy. This is because, given that people have special insight into their own preferences, they are generally better judges of their own interests than other people are; thus, if you want to make people better off you should generally let them choose what to do rather than dictating to them.

The principles themselves are supposed to capture what is intuitively plausible about both consequentialist and deontological approaches, and to cover the full range of moral concerns. Sometimes these principles will come into conflict (for example, in the case study the principle of beneficence may support the proposed research while the principles of non-maleficence and respect for autonomy may oppose it in its current form). In some cases the conflict may be removed by a more careful 'specification' of the principles, which might lead us to conclude, for example, that the principle of respect for autonomy does not apply when the subjects lack competence (for more on competence see Chapter 3). When a conflict between principles cannot be avoided in this way we simply balance the principles against each other, using our judgement to

36. Tom L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics* (Oxford: Oxford University Press, 2009).
37. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (1979). http://ohsr.od.nih.gov/guidelines/belmont.html

assess which principle is most important in the particular circumstances under consideration.

However, critics allege that it is difficult to determine what answer the four principles approach gives to any particular ethical problem – making it a difficult approach to apply. To see the strength of this objection, consider that each of the arguments for and against the artificial blood research could be supported by one of the four principles; this still leaves us with the problem of how to weigh up the competing considerations. Lacking any particular formula for the resolution of such conflicts, different people may come to different judgements. It is therefore not clear that principlism solves the problem of pluralism. Likewise there is a question of whether the four principles really do capture the entirety of moral concerns, or whether they highlight a particular subset of concerns. ([38])

Liberalism

A popular view in the light of the plurality of different ethical concerns is to claim that the government ought to aim, as far as possible, to be neutral between different ethical views or 'conceptions of the good'. ([39]) This view generally leads to a focus on not interfering with the life choices of people unless their choices are liable to bring about harm to others. This is known as the 'harm principle' and is most famously formulated by John Stuart Mill as follows:

> *The sole end for which mankind are warranted, individually or collectively, in interfering with the liberty of action of any of their number, is self-protection. That the only purpose for which power can be rightfully exercised over any member of a civilized community, against his will, is to prevent harm to others. His own good, either physical or moral, is not sufficient warrant. He cannot rightfully be compelled to do or forbear because it will be better for him to do so, because it will make him happier, because, in the opinion of others, to do so would be wise, or even right… The only part of the conduct of anyone, for which he is amenable to society, is that which concerns others. In the part which merely concerns himself, his independence is, of right, absolute. Over himself, over his own body and mind, the individual is sovereign.* ([40])

This leads to a strong emphasis on individual autonomy and decision-making. In the context of research ethics this would lead the research ethics committee to adopt a strongly non-paternalistic role. The ethics committee would see its role as being to ensure that participants are fully informed, and after that it would be up to them to decide what risks they are prepared to take.

The research in the case study presents a difficulty here, in that many subjects are not in a position to decide for themselves whether to participate. In light of this they might insist that only participants who are in a position to consent can be enrolled in the trial. Note that for liberals an appeal to the potential benefit for the participant is not likely to be compelling because the harm principle (and more generally the liberal's anti-paternalistic stance) implies that people should not be forced to do things for their own good.

Communitarianism

Some authors have claimed that liberalism's emphasis on individual choice makes for an impoverished view of the individual which fails to recognise the extent to which people's values and sense of identity depend on the communities to which they belong. ([41]) Instead it is claimed that, due to the 'embeddedness' of people within culture and society, decisions should focus on what maintains the community rather than what serves

38. Tom Walker, "What principlism misses", *Journal of Medical Ethics* 35 (2009): 229-31.
39. For an excellent introduction to liberalism see Will Kymlicka, *Contemporary Political Philosophy: an introduction* (Oxford: Oxford University Press, 2001), Chapter 3.
40. John Stuart Mill, *On Liberty* (London: Longman, Roberts & Green, 1869; bartleby.com, 1999): 21-22. http://www.bartleby.com/130/
41. For a good introduction to communitarian thought see Will Kymlicka, *Contemporary Political Philosophy: an introduction* (Oxford: Oxford University Press, 2001), Chapter 6.

the wants of individuals. This position is known as communitarianism.

In contrast to liberalism, communitarians will allow consensual activities to be prohibited where they threaten the values of the community, even where there is no identifiable harm to individuals other than disapproval, offence or disgust. The justification for this interference is that once individuals are properly conceptualised as part of their community rather than separate objects, it becomes apparent that interfering with their liberty in these cases is actually in their best interests because their interests are dependent on the flourishing of the community.

In relation to research ethics, a communitarian is likely to question the view that individual consent is either necessary or sufficient to allow research to proceed. For example, if a piece of research might be thought of as undermining community values, a communitarian might think that it should be forbidden even if the individuals involved are consenting. In the case we are discussing, communitarians might insist on some form of community consultation and then allow the research to go ahead because of its potential benefits to the community despite the inability to seek individual consent.

As we have elaborated in this section, there are many different approaches to ethical issues generally and in research. Importantly, each of these approaches focuses on a different range of concerns and highlights different ethical issues. One conclusion we can draw from this is that sometimes important ethical issues may be missed or sidelined if we just stick to a single approach to ethical decision-making. When thinking about ethical issues in research it is useful to consider them from the perspective of several different ethical approaches. ([42]) This is one advantage of having a committee to review research, since inevitably different members of the committee will have different ethical approaches and so will focus on different ethical issues arising from the research that they are reviewing.

The role and legitimacy of research ethics committees

In the first section of this chapter a case was made for the regulation of research. Given the preceding discussion of moral decision-making it might now be asked what role research ethics committees ought to play in this regulation?

The European Union Clinical Trials Directive defines a research ethics committee as:

> *an independent body in a Member State, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.* ([43])

This of course only applies to committees governed by that directive, but many other committees follow similar lines. Nonetheless this remit is a broad one and a significant amount of discretion exists for research ethics committees to interpret their role.

There are three main models of a research ethics committee's role:

(i) To protect and support the autonomy of prospective and existing research subjects/participants. ([44]) As noted earlier this is a broadly liberal approach.

42. David Hunter, "Proportional ethical review and the identification of ethical issues", *Journal of Medical Ethics* 33 (2007): 241-5.
43. *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use.* http://europa.eu/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf
44. Sarah Edwards, Simon Kirchin and Richard Huxtable, "Research ethics committees and paternalism", *Journal of Medical Ethics* 30, (2004): 88-91.

(ii) To protect the welfare of prospective and existing research subjects/participants. This, in contrast, might be based on consequentialist grounds.
(iii) To balance a number of relevant moral considerations when considering research proposals, including that of respect for autonomy and the protection and advancement of welfare.([45]) The sort of approach exemplified by the four principles approach might support this view.

Each of these models will generate different sorts of conclusions about research proposals and different approaches to assessing them.

There are arguments for adopting any of these approaches, but in the light of the discussion above, the third position seems most defensible. As noted earlier, there is significant and widespread disagreement among reasonable people about moral claims. Given this, and the uncertainty that is necessarily involved in research, it is important to adopt a stance that allows at least the consideration of a wide range of arguments, even if some are ultimately rejected.

This is further buttressed by a consideration of the role of research ethics committees in society. Research ethics committees are not (typically) private organisations, they are instead public representatives. Their authority comes from the government, and they make ethical decisions on behalf of the public. As such, they need to be able to represent and take into account the different moral positions held by members of society. While the neutrality between moral positions that liberalism offers is tempting, it seems sometimes inappropriate for an ethics committee precisely because its mandate is to make moral decisions. While in principle neutrality between different moral claims is desirable in a public body, strict adherence to neutrality in cases of controversy would be likely to limit a committee too much. Given this, a pluralistic approach to moral decision-making is required.

A final challenge might be raised to the approach we have developed thus far in this chapter: what should a research ethics committee do if some of its members have a religious or personal moral objection to some aspect of the research under consideration? Suppose, for example, that in the case study the blood was derived from a process that relied on human embryos being destroyed to create stem cells. Or suppose the artificial blood was derived from pigs or cows. Many research ethics committees will have at least one member who would object to this on the grounds of their personal moral commitments, and in some contexts this may be the majority view. So should they present this as an objection to allowing the research to go ahead?

It is important that these objections are presented so that they can be considered by the committee. However, they should not be presented as trump cards ruling out the possibility of compromise and reasonable agreement. Part of the role of an ethics committee is to provide a forum for a compromise and reasonable debate between different viewpoints that a simple opinion poll cannot capture. This relies on members expressing their own views. It also requires a committee that functions in a deliberative fashion, and which welcomes discussion and consideration of potential ethical challenges.

So the role of a research ethics committee is to regulate the ethical conduct of research. Primarily this involves the review of research proposals before research is carried out, though it may also involve some role in monitoring the conduct of research and deciding what should be done if something goes wrong. Often the research ethics committee will require changes to projects or make recommendations before they allow them to proceed. In making such judgements committees should bear in mind that overburdensome and interventionist ethical review can itself be unethical insofar as it prevents or delays worthwhile and ethical research. RECs might also consider it part

45. Eve Garrard and Angus Dawson, "What is the role of the research ethics committee? Paternalism, inducements, and harm in research ethics", *Journal of Medical Ethics* 31, (2005): 419-23.

of their role to give constructive advice to researchers, promoting and encouraging good quality and ethical research.

For individual members of research ethics committees this means reading through the applications thoroughly and making sure that any potential ethical issues identified by them are raised in discussion with the full committee. It also means a commitment to approaching the process as one of discussion and deliberation.

Besides their primary duty of the ethical review of research, research ethics committees often have other responsibilities related to their role as regulators of research. As noted above this may involve monitoring research, which can be carried out in a variety of ways such as requiring reports at regular intervals or at the end of a project, or even in some cases by carrying out *ad hoc* inspections or audits of research. Likewise, they are typically notified of adverse reactions and may have the responsibility of deciding whether a trial ought to be terminated or continued in the light of these reactions. These roles are typically remit-dependent and vary from country to country.([46])

Research ethics committees might also have obligations to be vigilant for signs of fraud and scientific misconduct.([47]) However, their powers to detect departures from an approved protocol are likely to be limited and resource dependent. Often scientific misconduct occurs after research has been conducted, and it would be rare for a research ethics committee to have any powers to intervene at that stage.

Research ethics committees are constituted and operate in a variety of different ways. However, there are several principles that are generally followed to ensure that they can effectively do the task they are assigned. These principles include: some measure of independence so they can avoid serious conflicts of interest (this need not be institutional independence but might instead be achieved by the presence of lay members), some measure of both ethical and scientific expertise so that they can spot ethical issues and understand the protocols they are considering, and some degree of diversity so that they represent the public and can approach applications from different perspectives.

Conclusions

In this chapter we first explored the nature and value of research and the reasons why it is regulated in the way that it presently is. This led to a discussion of the case study and an introduction to ethical principles and theories. We did not conclude that any particular approach to moral decision-making was superior, but did recognise that there are significant challenges to taking any particular approach to moral decision-making as comprehensive, due to the existence of significantly different, plausible accounts of morality. In the face of this, and given the nature of a research ethics committee as a public decision-making body, a pluralistic approach that takes account of arguments from many different ethical perspectives was championed.

Further reading

- Beauchamp, Tom L. and James F. Childress. *Principles of Biomedical Ethics* (Oxford: Oxford University Press, 2009).
- Garrard, Eve and Angus Dawson. "What is the role of the research ethics committee? Paternalism, inducements, and harm in research ethics", *Journal of Medical Ethics* 31, (2005): 419-23.
- Rachels, James and Stuart Rachels. T*he Elements of Moral Philosophy* (New York: McGraw-Hill, 2009).
- World Medical Association. *Medical Ethics Manual* (2005). http://www.wma.net/en/30publications/30ethicsmanual/index.html

46. Micheal Fuchs, *Provision of Support for Producing a European Directory of Local Ethics Committees (LECs)*, (EC contract no. SAS5-CT-2002-30047, 2005). http://ec.europa.eu/research/conferences/2005/recs/pdf/lec_finalreport.pdf
47. Frank Wells and Michael Farthing, eds. *Fraud and Misconduct in Biomedical Research* (London: Royal Society of Medicine Press, 2008).

Chapter 2 **Consent**

Learning outcomes

In this chapter, you will develop your understanding of the nature and importance of valid consent in research ethics. Specifically, you will gain the following:

- An increased knowledge of the important role that consent plays in research ethics.
- An awareness of the ways in which the requirement for valid consent follows from other fundamental moral concepts such as autonomy, dignity, harm-avoidance, and respect for persons.
- An appreciation of the definition of valid consent: specifically the tripartite definition in terms of competence/capacity, adequate information, and voluntariness.
- An increased knowledge of key ethical issues relating to information-giving: e.g. how much should research participants routinely be told?
- An awareness of key ethical issues relating to voluntariness in research: e.g. when (if ever) do inducements render participation involuntary?
- An understanding of the issue of when, or whether, research without consent (on competent adults) is ethically acceptable: e.g. in cases where the methodology requires covert surveillance and/or deception.

Introduction

Central to this chapter is the consideration of three examples. However, before proceeding to look at these case studies, we need to provide some background information about consent. In particular, we will explain:

- the role of consent in some of the leading international documents on research ethics;
- the way in which the requirement for valid consent relates to some of the more fundamental ethical requirements outlined in Chapter 1; and
- the definition of valid consent.

The pre-eminence of consent in international codes and declarations

There is near universal agreement that informed consent is of the first importance in research ethics, especially (although by no means exclusively) in biomedical research. Here are some examples of official statements that support this view.

- Article Seven of the *International Covenant on Civil and Political Rights*, a United Nations treaty, states that: "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation." ([1])
- Article Three of the *Charter of Fundamental Rights of the European Union* (the 'right to the integrity of the person') states that: "In the fields of medicine and biology, the following must be respected… the free and informed consent of the person concerned, according to the procedures laid down by law…" (2)
- The World Medical Association's *Declaration of Helsinki* states that: "In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed." ([3])
- Article Five of the Council of Europe's *Convention for the Protection of Human Rights and Dignity with regard to the Application of Biology and Medicine* states that: "An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw consent at any time." ([4])
- The International Sociological Association's (ISA) *Code of Ethics* states that: "The consent of research subjects and informants should be obtained in advance. Covert research should be avoided in principle, unless it is the only method by which information can be gathered, and/or when access to the usual sources of information is obstructed by those in power." ([5])

1. United Nations, *International Covenant on Civil and Political Rights* (United Nations, 1966). http://www2.ohchr.org/english/law/ccpr.htm. Emphasis added.
2. European Union, *The Charter of Fundamental Rights of the European Union* (2000/C 364/01). http://www.europarl.europa.eu/charter/default_en.htm. Emphasis added.
3. World Medical Association, *Declaration of Helsinki: ethical principles for medical research involving human subjects* (2008). http://www.wma.net/en/30publications/10policies/b3/index.html. Emphasis added.
4. Council of Europe, *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (Oviedo, 4.IV.1997). http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm. Emphasis added.
5. International Sociological Association, *Code of Ethics* (Madrid: International Sociological Association, 2001). http://www.isa-sociology.org/about/isa_code_of_ethics.htm. Emphasis added.

This list of official statements about consent is by no means definitive or exhaustive, and the documents mentioned differ in status. For example, the *Declaration of Helsinki* and the ISA *Code of Ethics* are the statements of professional associations, whereas some of the other proclamations are treaties that many countries have signed up to and hence (at least in many states) these will have direct or indirect legal force. Our primary interest here, however, is in the *ethics* of research, not in the precise *legal* status of these statements, and they are mentioned here just to illustrate the pre-eminence of the idea of free and informed consent.

It should also be noted here that the International Sociological Association's statement about the need for consent appears rather more qualified than the earlier ones, suggesting perhaps that the requirement for consent in social research is rather less stringent than that in biomedical research, especially where the latter involves some form of experimentation.

How consent may follow from more fundamental moral principles

The practical principle that research on competent adults should only proceed with their informed consent arguably follows from several of the more fundamental principles introduced in Chapter 1. These include:

- respect for autonomy;
- respect for dignity;
- respect for persons.

Arguably, each of these three 'respect principles' generates a duty of non-interference, meaning that it would be wrong to do something to an autonomous person's body without his or her valid consent, whether this be for medical treatment, research, or any other purpose. This requirement may also apply (although perhaps less clearly and powerfully) to acquiring information about and/or observing an autonomous person. Similarly, one might claim that doing things to a person's body and/or observing the person without consent is (at least in some cases) a failure to respect the person's dignity.

The extension of non-interference rights to non-observation rights takes us to the idea of privacy, which is dealt with in Chapter 4. At this point, it is simply worth noting that there is a close connection between consent and privacy: that invasion of privacy is necessarily non-consensual. Thus, if I invited some people to observe me, then I could not (having validly consented) reasonably complain, when they did observe me, that my privacy had been invaded.

There is an interesting debate concerning whether the same is true of dignity and of respect for persons. One view is that any action at all could be consistent with these principles provided that a sufficiently robust valid consent had been obtained from the people affected. An alternative view is that some types of action are an affront to human dignity even if they are fully consensual: 'dwarf tossing' and 'sex work' are amongst the contested cases. ([6]) Consider, for example, the famous French case of Manuel Wackenheim. Wackenheim was a (so-called) dwarf who (until a ban was imposed, partly on the grounds that his job was contrary to human dignity) made a living from being 'tossed' by customers in bars and nightclubs. This 'tossing' formed part of a dwarf throwing competition – a sport "in which the aim of the competitors is to fling a dwarf over the furthest distance possible". ([7]) Wackenheim appeared keen to pursue his chosen career and did not welcome the ban on dwarf throwing, saying "this spectacle is my life; I want to be allowed to do what I want". So the question that this raises is: assuming that his consent to be 'tossed' is free and informed, ought we nonetheless to view the act of 'dwarf tossing' as inconsistent with human dignity? We should also bear in mind, though, that dignity is not the only possible moral

6. Stephen Wilkinson, *Bodies for Sale: ethics and exploitation in the human body trade* (London: Routledge, 2003): 42.
7. Susan Millns, "Dwarf-throwing and human dignity: a French perspective", *Journal of Social Welfare and Family Law* 18, no. 3 (1996): 375.

consideration in such cases (or indeed in research ethics) and that 'dwarf tossing' could be objectionable on grounds other than dignity. For example, it may be too dangerous, or it may incite other people to 'toss' short people against their wills.

Another interesting issue, one that will come up during the case study discussions, is the question of whether respect for autonomy creates an *absolute* requirement for consent, or rather one that can sometimes be overridden: for example, where there are strong grounds for undertaking covert surveillance. This could be for reasons of national security or crime prevention, or (more relevantly for our purposes) in order to gather important research data that could not otherwise be obtained. Similarly, there are interesting questions (again, ones that will come up during the case study discussions) about whether a person's autonomy creates duties that extend beyond death (for example, in relation to burial preferences or the desire to have one's body used in biomedical research or for organ transplantation). The latter are dealt with in Case Study 2.2.

As well as being justified by reference to respect for autonomy, the idea that valid consent is a requirement for ethical research is backed up by the principle of non-maleficence (introduced in Chapter 1). The thought here is that, since most prospective research subjects have an understandable concern to protect their own interests, requiring informed consent makes it less likely that they will be subjected to excessive risk by researchers. Furthermore, some of the harm and risk associated with research depends on people's preferences. For instance, some people might be scared of going into hospitals and, for these people, hospital-based research would be more harmful and unpleasant than for others; conversely, other people might find participating in hospital-based research interesting and rewarding and, for these people, the psychological risks would be correspondingly smaller. So, since people are generally well-acquainted with their own likes and dislikes, the informed consent process protects them from taking part in research that would be especially difficult or unpleasant for them, given their personal preferences.

The tripartite definition of 'valid consent'

In most cases (although perhaps not universally – see Case Study 2.3 below) getting consent from any human participants is a necessary part of conducting research ethically. However, just getting people to say 'yes' to participation is rarely enough. The consent must also be of a sufficiently high quality: it must be *valid*. Thus, consents based on inadequate or inaccurate information, or resulting from coercion, or made by people unable to understand what they are signing up to, will not suffice, and research utilising such consents will be ethically flawed.

While there are various different definitions of 'valid consent' (also known as 'free and informed consent') in circulation, most of these amount to the view that valid consent must include the following three elements:

- adequate information;
- voluntariness;
- competence.

Information

Valid consent requires adequate information. Thus, for each piece of research we need to ask what the prospective research subjects should be told and how they should be told it. As regards the *quantity of information*, one commonly appealed-to standard is what a reasonable person would need to know or want to know in order to decide whether to participate. Using this criterion, researchers would usually be obliged to disclose (amongst other things) any significant risks, the purpose of the research, any financial interests (e.g. do they receive a fee for each person recruited?), and the source of any external research funding (because people might, for example, object to helping certain companies or governments). But we would not necessarily be obliged to disclose everything about the research (if that is even a possibility). Indeed, excessive information provision can lead to what is sometimes called 'information overload', meaning that people are less likely to be able to absorb and understand the information provided.

There are also issues concerning the *quality of information* provided. Questions that arise here include the following:

- If participant information sheets are to be used, are these written in a style that the research subjects will understand or do they contain too much technical language?
- What if some prospective participants speak a different language from the majority population – will translations be on hand?
- Will prospective participants be given an opportunity to go away and think about the decision to take part and an opportunity to ask questions and to consult independent sources of information (perhaps third party books or websites)?

Clearly, there will be a lot of variation between different types of research. For example, whereas the decision to take part in a toxicity trial for a new drug may require considerable deliberation and information, answering a few survey questions about one's attitude to shopping usually will not. Similarly, whereas it is often appropriate to use a formal information sheet and to get participants to sign a consent form, this will not work (or would be excessively bureaucratic) for some kinds of research. In these cases, valid consent will still normally be required but it will need to be transacted and evidenced in ways other than documentation.

Voluntariness

Valid consent must be voluntary (or free). In practice, this means that the consent must not result from coercion, manipulation, or undue inducements.

Coercion is the use of threats. So consent would not be valid if the participants were threatened (or thought that they were being threatened) with violence or other substantial penalties for not taking part in the research. While there have been some extreme cases of this kind in the history of research (see Chapter 1), the coercion that we may encounter in contemporary European research is likely to take a more subtle form. It is also worth bearing in mind that people may believe that they are being coerced even when they are not; and that merely perceived coercion can be as much of a threat to voluntariness as the real thing. For example, people might believe that if they do not agree to take part in research carried out by their doctor, manager, nurse, lecturer, or supervisor, this will be disadvantageous in future dealings with this individual. So extra care needs to be taken when the researcher is in a position of power over the research participant. Such relationships can inadvertently create the impression of coercion; and indeed they can present researchers with opportunities for actually coercing people into taking part.

Ways of dealing with this include:

- not letting doctors/nurses/lecturers do research on their own patients/students (although this may prevent potentially valuable research from taking place, in some cases research that may benefit patients/students);
- ensuring that the consent process is done via an impartial intermediary, and avoiding situations in which the 'powerful' researcher directly asks the 'powerless' person to consent to be in a study;
- making clear in information leaflets that a decision not to participate will not adversely affect the prospective research subject's access to services, and that research subjects are free to leave the study at any time without penalty.

Manipulation sometimes, but not always, involves deception. Cases in which manipulation is deceptive are more properly considered under the previous subheading, 'Information', so we will focus here on *non-deceptive manipulation.*

What is it to manipulate without deceiving? This is a difficult question in philosophical psychology and we can only scratch the surface here. One important and relevant feature of manipulation (although not something that is unique to manipulation) is that it seeks to alter people's behaviour by influencing them in ways that somehow bypass rational agency; rather than influencing them through reason and argument, we (typically through some 'sleight of hand') seek to change their mind by appealing (consciously or otherwise) to non-autonomous and/or non-rational parts of the person.

Possible examples of (non-deceptive) manipulation are as follows:

- charity advertisements that use emotive music and imagery (e.g. pictures of sick children) and claim that "for *x* cents a day you could save little baby Olivia and thousands like her";
- graphic images on cigarette packets to discourage smoking;
- use of smells (e.g. coffee & fresh bread) to encourage purchasing;
- use of sexual attraction or desire to sell things or influence behaviour.

Note that (arguably at least) manipulation is not always wrong (e.g. using sexually explicit images to improve public health may be justifiable). It does, however, at least raise a question about the validity of any consent arising from it.

How does this apply to research? Well, one thing that can happen is that the benefits of the research are described (e.g. in information sheets) in factually correct but manipulative terms. For example, the researchers might claim that participation could help to save children's lives, that their research subjects are heroes, or they might use images of sexy young research assistants. While these methods may not involve lying, they do involve manipulating people and therefore reduce the quality of any consent given.

Inducements are monetary or other rewards for participation in research. These are not always wrong or problematic; however, they may invalidate a consent either if the rewards are excessively high, or if they target 'desperate' populations. In the former case, the worry is that, above a certain level, inducements to take part in research act rather like the manipulation outlined above and alter people's behaviour by influencing them in ways that somehow bypass rational agency. It is then almost as if the reward becomes too attractive for them to resist. In addition, in cases where the research is potentially dangerous or painful, there may be a worry about inducing people to do what would otherwise go against their better judgement. The concern about 'desperate' populations takes a fundamentally similar form. If, for example, we offer much needed (and otherwise unavailable) medical treatment to someone in exchange for research participation, it may be argued that this offer is too attractive for them to resist – and conversely that not participating is too awful for them to tolerate. ([8])

In defence of inducements, however, the following points are sometimes made: ([9])

- There are lots of areas of life (notably employment and shopping) where modifying people's behaviour through monetary reward is thought to be unproblematic. So why should research be any different?
- Researchers themselves normally get paid for doing the research so why should the research subjects remain unrewarded?
- There are many occupations where people get paid, or paid extra, for undertaking especially dangerous work (e.g. diving, military, mining). Why should research be any different?
- Rewarding research subjects is often good for them, especially if they really do need the money or the medical treatment that is on offer.
- If research participants are paid too little (or not paid at all) would this not be a form of exploitation, or a case of unjust underpayment?

Competence

The third element of valid consent is competence. Does the person giving the consent have sufficient mental competence or capacity to understand and retain relevant information about the research, and to

8. Nuffield Council on Bioethics, *The Ethics of Research Related to Healthcare in Developing Countries* (London: Nuffield Council on Bioethics, 2002). http://www.nuffieldbioethics.org/go/ourwork/developingcountries/publication_309.html
9. Martin Wilkinson and Andrew Moore, "Inducement in research", *Bioethics* 11, no. 5 (1997): 373-89; Martin Wilkinson and Andrew Moore, "Inducements revisited", *Bioethics* 13, no. 7 (1999): 114-30; Stephen Wilkinson, *Bodies for Sale: ethics and exploitation in the human body trade* (London: Routledge, 2003): 117.

communicate his or her views on the research? If not then the consent may not be valid. Competence, and research on people who are not competent, will not be discussed in detail in this chapter. These matters, along with the broader issue of vulnerability, are the subject of Chapter 3.

Before turning to the first case study, it is worth noting briefly that some people have criticised standard research ethics (and indeed bioethics generally) for being overly preoccupied by valid consent and by the underpinning principle of respect for autonomy. ([10])

Case Study 2.1 Spaceflight simulation study on healthy female volunteers

A proposed International Space Agency (ISA) research project aims to gather preliminary information about how women's bodies would cope with prolonged periods of time in spacecraft. Since most astronauts to date have been men, very little information on this exists and, given the prospect of long-range space missions involving both sexes, the ISA believes that this research is vitally important for the design of future spacecraft and space travel protocols.

In an experiment simulating certain aspects of weightlessness, 50 healthy female volunteers, recruited via advertisements in women's fashion and lifestyle magazines, will be paid EUR 200 per day (plus expenses and free food) to spend up to four months on a specially designed bed which is tilted backwards at a six degree angle. The volunteers will also be awarded a terminal bonus payment of EUR 20 000 provided that they manage to complete the study (i.e. if they stay for the full four months).

During the experiment (and afterwards, in follow up sessions) numerous medical checks will be carried out. Furthermore, subjects' behaviour will be continuously monitored by video feed. Participants will be largely isolated from the outside world and allowed only occasional contact with friends and family via email or telephone. No visits will be permitted. They will, however, be given access to personal entertainment devices.

Physical side-effects of participation are likely to include: swollen face, blocked nose, severe aches, muscle wastage, constipation, sores, and loss of bone mass. Participants are also likely to encounter psychological problems resulting from boredom and lack of exercise. All of the abovementioned restrictions and risks will be fully disclosed in advance to prospective volunteers, who will be provided with written information and individual counselling, and will undergo thorough psychological assessments. Counselling and psychological assessment will also be made available to the women during and after the experiment.

In order to enter the study, the women must be:

(a) competent adults aged between 20 and 40 (because this is the age group most likely to be recruited for space missions);
(b) in good general health, mentally and physically – and moderately, but not exceptionally, fit;
(c) not significantly over/under weight;

10. Charles Foster, *Choosing Life, Choosing Death: the tyranny of autonomy in medical ethics and law* (Oxford: Hart Publishing, 2009).

(d) non-smokers (because smoking is not possible in space and withdrawal symptoms may contaminate the results of the experiment if addicted smokers were used);
(e) childless (because of the welfare of the child, and possible psychological harm to mothers);
(f) single (because of the welfare of the partner, and because of possible psychological harm to women who are separated from their partners);
(g) not pregnant, and willing to undergo a pregnancy test before the start of the study (because of concerns about foetal damage).

They must also promise to do their best to avoid pregnancy for 3 years after participation in the experiment ends.

The experimental design has been subjected to extensive scientific peer review and graded 'excellent' for its methodology.

Questions

1. Is the research important enough to justify subjecting these women to the discomfort, inconvenience, and risk described?
2. Do you have any concerns about the quality of the women's consents? If so, what are these?
3. Is it possible for a woman validly to consent to be in this study?
4. Do you have any other ethical worries about, or objections to, this research (that is, apart from those to do with consent)?

Discussion

Before turning to the questions about consent that are the main concern of this chapter, we need first to ask whether the research described in the case study is important enough to justify subjecting these women to the discomfort, inconvenience and risk described. We must consider the various harms and risks involved, and think about whether the research is sufficiently good and important (both in terms of potential benefits and methodological reliability) to justify subjecting people to these harms and risks. We are told in this case study that the methodology is excellent and has been the subject of extensive scientific peer review, that there is a lack of information about women in space, and that this information may be very important for future space missions. It might be argued then that the Space Agency is trying to advance the long-term interests of humankind, and indeed contributing to sex equality, by conducting research that will help us safely to involve more women in the space programme. Thus there does seem to be a *prima facie* case for doing the research.

What about the harms and risks though? Are these excessive? One might have concerns about the physical side-effects of participation and about whether, psychologically, the experience of being in a space research centre for four months is too much to bear. We need to ask two questions at this point. First, given the potential benefits mentioned above, are the risks that participants are asked to undertake proportionate (relative to these benefits)? Second, has the research been designed such that the harms and risks have been minimised (so that they are as low as they can be without compromising the scientific quality of the project)?

As regards the first question, since the experimental design has been subjected to extensive scientific peer review and graded 'excellent' for its methodology, there are no (or few) methodological worries. The issue, then, is the level of expected benefit. In order to have a well-worked-out view on this we would need more information about some rather big questions such as the importance of space exploration to the future of humankind and human knowledge, for (other things being equal) the more important space exploration is, the more justifiable this research will be. So, given the case as described, we probably cannot say with any certainty what the likely benefits are. And this is often the case with research: it is hard to say what exactly the benefits of the project will be.

Turning to the question of whether the harms and risks have been minimised, the researchers would probably want to point us to the extensive medical testing involved and to the fact that counselling and psychological assessment is available during and after the experiment. Given that the experimental design has

been subjected to extensive scientific peer review and graded 'excellent', we must assume that the number of women involved is not excessive, but is sufficient to generate statistically significant results. And finally the researchers might draw our attention to the exclusion criteria for trial participation, which require entrants to have good mental and physical health. Overall then, there does seem to be good reason for thinking that the level of harm and risk has been minimised.

We can now move on to ask what concerns we might have about the quality of the women's consent. On the face of it at least, it appears that prospective participants will get a reasonable amount of information. The restrictions and risks will be fully disclosed in advance and people will be provided with written information and individual counselling. In addition, one of the criteria for inclusion in the experiment is that the person must be a competent adult aged 20-40. Hence (thinking back to the tripartite definition of valid consent offered above) it looks as if the *competence* and *information* requirements will be satisfied in this case.

That just leaves us with the question of *voluntariness* to consider, and one of the main concerns here will be the overall level of payment. Participants stand to gain over EUR 40 000 in total if they complete the study, which would be a lot of money for most people. Hence, we must ask whether this constitutes an undue inducement, whether such a reward would incite the women to take risks against their better judgement, and whether (for some women at least) a reward on this scale would be somehow 'irresistible'. In addition, there might be special worries about the fact that around half the total payment is a terminal bonus of EUR 20 000. As was suggested earlier, one important feature of voluntary research participation is that people are allowed to leave the study at any time without being penalised. But in this project, one might see the prospect of losing the terminal bonus as akin to a (coercive) threat, especially for women nearing the end of the study who feel that they cannot take any more, but who equally do not want to lose EUR 20 000 just because they have departed a few days early. So we need to ask whether the women are really free to leave the study at any time given that they stand to suffer very considerably financially if they do not stay for the whole time requested.

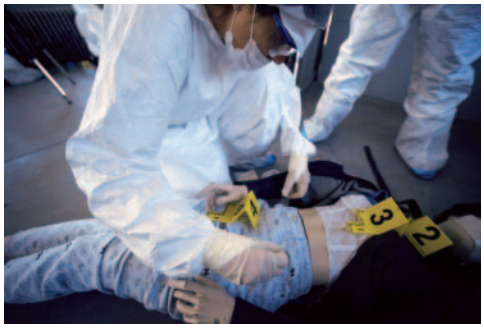
A further question relating to the payment is how the subjects are recruited and which populations are targeted. If, for example, the researchers were targeting economically disadvantaged countries or populations then we might ask whether such people are capable of freely consenting to take part, given their financial desperation and the extreme attractiveness to them of EUR 40 000. But, against this, one might argue that it would be perverse to exclude poor people, since these are the very people who need the money most, and excluding them would make them worse off financially than they could otherwise have been. Also, we would not generally be hostile to offering such people well-paid jobs, so (again) – why is research participation any different?

So how should we resolve the question of voluntariness in this case? The size of the terminal bonus is indeed an issue and one that may infringe the women's right to leave at any time, since the withholding of it may be seen as a *de facto* punishment for leaving. Against that, though, the researchers may argue two things. First, that it is an offer (of benefit) rather than a threat (of harm), and so not coercive. And second, that a strong financial incentive to stay until the end is justified in this case for scientific reasons; for if more than a handful of the women were to leave the experiment early then either the results would be invalidated (in which case vast amounts of effort and expense would have been squandered, including notably the efforts of the other research subjects) or it would be necessary to recruit even more women to the experiment, thus increasing the overall level of harm and risk to the research subject community.

Another aspect of the voluntariness issue concerns the target population. All we know based on the case description is that the study will be advertised in women's fashion and lifestyle magazines. If the core readership of those magazines in question were (for example) an economically disadvantaged group then it may be argued that a vulnerable population is being targeted: specifically one that would find financial inducements hard to resist. (See Chapter 3 for a more detailed discussion of vulnerability.) However, based on what is in the case description, there is no reason to think that this would be a problem here.

Question 4 asks us to consider whether we should have any other ethical worries about, or objections to, this research. One issue to consider is whether it is reasonable and proportionate to ask women to try to avoid pregnancy for three years after the study. Given that one of the inclusion criteria is childlessness, this could be a major sacrifice for a woman in her thirties. Also, are the inclusion/exclusion criteria fair? For example, married women (and their equivalents) and women with children are excluded. The researchers seek to justify this by reference to the interests of partners and children, but is this sufficient and are the interests of third parties any of the researchers' business? An additional issue is that we may (depending on our political views) regard women (or more plausibly *some* women) as a vulnerable research population on account of sex discrimination and of the oppression of women by men. Furthermore, it might be argued that the 'gender dimension' of this case means that a different perspective, such as the ethics of care discussed in Chapter 1, is appropriate. Rather than focusing mainly on consent, an ethics of care approach might, for example, place greater emphasis on the relationships between the researchers and the women, or indeed on the participants' attitudes and feelings towards those brave women who may in future undertake astronautical missions.

Case Study 2.2
Police and rescue research using cadavers



The European Institute of Police and Rescue Research has a long-running, internationally renowned research programme that seeks to discover which police and rescue training methods work best.

One part of this programme aims to discover whether training using real human cadavers is more effective than the alternatives in certain areas of police and rescue work. For instance, there is a growing (although still controversial) body of evidence suggesting that using real corpses (to represent the victims of terrorist bombings or other disasters) is the best way to teach people anti-terrorist and 'catastrophic situation' techniques.

One of the Institute's experiments is as follows. One group of trainees is instructed to search clothed corpses for objects such as diaries, mobile phones, jewellery and keys to ensure that they are properly documented. Trainees are then asked to strip the bodies to look for scarring and other distinctive marks that could aid identification. A second group of trainees goes through a similar process, but using realistic mannequins instead of actual bodies. A third receives classroom-based training only. The different groups' performances are later tested and comparatively evaluated using a well-established proprietary assessment tool. (The methodology of this experiment has been subjected to external peer review and accepted.)

Other similar experiments use corpses to assess different search training techniques. These involve, amongst other things, human body parts being buried and then searched for by trainees.

The corpses used by the Institute come from the nearby University Hospital. Prior to their deaths, all of the deceased persons involved gave general consent, in writing, for the use of their bodies for "research, training and education".

Questions

1. Ethically, does it matter that the consent given by the deceased persons was rather general and that they may not have known that their bodies would, or could, be used in the study described above? Would it have been morally better to give them more detail?

2. If valid consent was given by the deceased persons for their bodies to be used in this research would that allay all of your concerns about the research? Or would there be residual worries about using bodies in this way?
3. What sort of consent to take part in the trial (if any) ought the researchers to seek from the trainees?
4. Ought relatives of the deceased persons to be involved at all and, if so, at what stage and how?

Discussion

Although it concerns deceased persons, this case study raises a more general issue about valid consent (that posed in Question 1): how much information must the consenter be given and how specific must consent be in order for it to be valid? In this case, the worry is both that the consent given was not sufficiently specific and that the consenter may have been harbouring a false belief: namely, that his or her body would be used by the hospital for medical research (and not mutilated and used for rescue personnel training). So, one might argue that the consent given is invalid because it is insufficiently detailed and/or based on a false belief. Against that, would it have been morally better to ask the dying person if their body could be used in this particular trial, and risk causing distress? Again, this is not a point that applies just to the dead: especially in a medical setting, disclosure of information can be distressing even when it does not involve death. For example, describing in graphic detail what will happen during surgery could seriously distress some people and put them off having the surgery even if it would ultimately be beneficial.

Even if valid consent was given by the deceased persons for their bodies to be used in this research there may still be some ethical concerns. One such concern relates to the idea of dignity. Earlier on, we mentioned two views about the relationship between dignity and consent. One of these is that, provided that truly valid consent is in place, nothing falling under that consent can be an affront to human dignity. A reason for supporting this kind of view is that what really matters is *respecting the person*, and provided that we obtain the person's free and informed consent before doing what we do, then that is showing (sufficient) respect. On the other hand, some people deny this and assert that there are certain types of act that would be an affront to human dignity even if there was full consent. The mutilation of bodies could be an example of this.

Other concerns are that the community would be shocked and offended if it found out what was happening to the bodies. This may be bad both intrinsically and because it may erode the community's commitment to and trust in medicine and science (including their willingness to be involved in future research projects). Other concerns centre on people's religious sensibilities; some religious groups take very seriously the ways in which dead bodies are dealt with. Finally, we would need to be assured that the researchers were complying with any relevant national (and local) laws concerning the disposal of corpses (for example, environmental, and health and safety regulations).

A third set of issues concerns the consent of the trainees themselves. What is at issue here is not so much their consent to be trained (which presumably is implicit in their career choice), but rather whether an additional consent is required for participation in this educational experiment. In favour of the view that no additional consent is required, one might argue that what is happening to them in the research is, in practical terms, no different from what would (or could) have happened to them outside the context of research. In particular, they may have been randomly allocated to a particular training college with a certain training method without necessarily having much say in the matter. Also, it should be noted that there are some potential benefits here. There are possible collective benefits to members of the police service, whose training may become more evidence-based and more effective; and there are possible individual benefits to the trainees in this study who will be exposed to dead bodies for the first time in a controlled training situation rather than during an actual emergency (which could be much worse). Against this, it may be pointed out both that the research is likely to involve some additional observation of the trainees and that there is a difference between the randomness of everyday life and systematic randomisation as part of a controlled trial.

Finally, there is the question of whether relatives of the deceased persons should be involved and, if so, in what ways. We should start off by noting that this is something that will sometimes be determined by national laws: for example, there are some legal systems that give a lot of weight to relatives' wishes in relation to organ donation and the like, and others that put more emphasis either on the public good or on the known wishes of the deceased. While there is arguably a *prima facie* moral obligation to obey the law (or at least those laws that have been arrived at through a legitimate process) our concern here is with ethics rather than law as such, so what are the moral considerations? While, intuitively, people may think that relatives should have a role here, there are at least two important reasons *not* to consult them about the use to which the dead bodies are put. The first is a desire to avoid distressing and upsetting the relatives by making them confront the prospect of their loved ones' bodies being used in this way. That is not to say that there is necessarily anything wrong with the proposed use of the bodies; the point is rather that this is something that most of us (especially those recently bereaved) would prefer not to think about or to imagine in any detail. Secondly, one might argue that if valid consent from the dead person is in place (something that we have of course questioned in this particular case), then to allow a relative to override or veto this would be a failure to respect the autonomy of the deceased person. Very similar issues to this arise in the case of therapeutic organ donation from cadavers: i.e. where consent has been given by the dead person should we allow relatives to override this and to prevent donation from going ahead?

There are some parallels here with research on non-competent living adults (specifically the question of what the proper role of relatives in the consent process is). These issues are dealt with in more detail in Chapter 3.

Further related issues about biobanks and human tissue banking are dealt with during the discussion of Case Study 8.4, which concerns a large research project looking at the genetics of cardiovascular disease.

Case Study 2.3
Covert surveillance of health care professionals

Studies have shown that many health care professionals in hospital settings do not wash their hands correctly or as often as they should. This is believed to cause infection and illness in a number (possibly a very large number) of patients. A large international project is proposed to evaluate different methods of generating better hand hygiene. These methods include:

(a) warning health care professionals that they might be the subjects of covert video or other surveillance;
(b) sending health care professionals on a training course about hand washing;
(c) installing additional hand washing troughs;
(d) offering alcohol-based hand rub facilities as an alternative to conventional hand washing;
(e) installing 'extreme signage' in staff washing areas and toilets (e.g. comparing non-washers to murderers & showing ghastly images of infected wounds).

In general terms, the proposed study will proceed as follows:

- Covert surveillance will be used to establish hand-washing-frequency baselines for a large number of sites.
- (a) to (e) (above) will then be trialled at selected sites.

- Covert surveillance will be used to assess the effectiveness or otherwise of (a) to (e).
- At no point will the consent of health care professionals or patients be sought because this would, it is argued, invalidate the study.
- The researchers will seek to anonymise the data collected as far as possible by (e.g.) pixelising (digitally obscuring) name badges and faces, and by removing date and place information from video files. They will not feed back information about individual misconduct (e.g. inadequate hand washing) to hospital managers but do reserve the right to report serious criminal activity.

Questions

1. What are the arguments in favour of carrying out this research without the observed persons' consents? Are these arguments ultimately successful?
2. Can you think of any ways of modifying this research so that consent could be obtained?
3. Would it be ethically better or worse if the people observed were told about their unwitting 'participation' afterwards?

Discussion

Most of Chapter 2 so far has been about the nature and scope of valid consent. We have asked (for example) whether a particular form or type of consent is sufficient. Case Study 2.3, however, raises a very different issue: under what circumstances (if any) is non-consensual observational research on competent adults (specifically, in this case, that involving covert surveillance and/or deception) ethically acceptable?

Let us start to consider this by asking how the researchers in Case Study 2.3 might seek ethically to justify this research? Those arguing for covert or deceptive research generally claim that it is acceptable by appealing to the following considerations, or by saying that it is acceptable if the following conditions are met.

First, for non-consensual observational research to be justified, the research must be worth doing; it must be sufficiently important in its aims to justify overriding the usual requirement for valid consent. In Case Study 2.3, the researchers may claim that their research is potentially very good for public health and potentially life-saving, since many thousands of people become infected each year as a result of inadequate hand hygiene. If the research is successful, it could make a substantial contribution towards reducing these levels of infection, by providing hospital managers with information about the most effective ways of encouraging good hand washing practices. The research in Case Study 2.3 then appears to fare quite well in this respect; it does look like a potentially important and useful piece of research. If, however, the research was driven only by the curiosity of academics and had no (or very few) potential practical benefits then perhaps we would and should be more reluctant to see it as ethically justified.

The second important part of the researchers' justification will be that the project cannot, for methodological reasons, be done without covert observation. As discussed in Chapter 1, this is one of many instances in which methodological questions impact on the ethics of the research.

In Case Study 2.3, the researchers may say that if the health care professionals were aware that they were being observed then they would change their hand washing behaviour, thus invalidating the study. The researchers would need to make this case by convincing us both that their proposed methodology works and that there are no better alternatives (in particular, that there are no alternative methods that would allow us to obtain the same information without covert surveillance). When assessing research proposals it is important not to accept researchers' claims about such issues uncritically. Thus, in this case, we may (for example) want to think carefully about the extent to which knowing that they were being observed really would affect the health care professionals' behaviour (since there is some evidence that people become accustomed to being observed after a while and revert to their normal behaviour patterns). Thinking about this case from the perspective of a research ethics committee,

we should (where practicable) consider not just the researchers' testimony but also some form of expert independent scientific peer review, which would provide us with a judgement both on the overall quality of the research methodology and with a view on whether covert surveillance is really required in order to answer these research questions.

Thirdly, the researchers would need to convince us that their proposed surveillance will not substantially harm (or expose to risk) the research subjects. In Case Study 2.3, the researchers could claim that harm and risk will be minimal because: (i) the research subjects will not find out about the research, (ii) anonymisation will be used (as far as possible) thereby reducing the risk of personal information or embarrassing images being revealed, and (iii) (with the exception of serious criminal activity) there will be no reporting of bad behaviour to the management. In order to decide whether the research is ethically acceptable we would need to critically assess each of these claims (i) to (iii).

Regarding (i) we might raise the possibility of people finding out about the research by accident, or when it is published or reported. In addition, we might ask whether it is desirable to inform research subjects after the project has taken place: that is, to tell them, after the event, that they have been observed and possibly even to give them the opportunity retrospectively to consent (or to have their information withdrawn) at that stage. Debriefing in this way is sometimes thought to be morally preferable to trying to keep the research secret forever. But, against this, it may be argued that some research subjects will be angry and upset if they are told, and hence that there is a harm-based justification for not telling them at any stage. Perhaps there is also a distinction to be drawn here between experimental research that involves deception (for example, some psychology experiments involve misleading the subjects about what is being tested, because knowledge of the exact nature of the research would alter people's behaviour) and cases of covert surveillance in which the subjects have no idea that they are being observed. In the former case, some kind of debriefing may be beneficial and interesting and it will come as no surprise to the participants to hear that they were being observed, since they did after all sign up to be in an experiment of some sort. But observing people completely unawares raises different issues because in these cases people will often be shocked and upset on discovering that they have been observed.

Fourthly, the researchers would need to assure us that the extent to which personal data would be gathered and stored was kept to a minimum or was proportionate; what this means is that they should only be acquiring personal data inasmuch as this is necessary to answer the research questions that they have set themselves. Thus, the researchers might seek to justify their project in this respect by pointing out that they will seek to anonymise the data collected as far as possible by pixelising (digitally obscuring) name badges and faces, and by removing date and place information from video files.

Some other issues are raised by this case.

One is that researchers and those evaluating research need to be aware of any relevant national laws covering covert surveillance of other human beings. In some jurisdictions this may be outlawed. In others, it is licensed and controlled.

Another is – does it matter whether the place observed is regarded as a public space and whether it is somewhere where people would generally expect to be observed? Arguably, covert surveillance in places where people would reasonably expect to be observed routinely (for example, by passers-by) is less ethically problematic than similar forms of observation in places that people would normally expect to be private. This is explored later, in Case Study 4.1 (Observational research in an accident and emergency department).

Further reading

- British Psychological Society. *Code of Ethics and Conduct* (2006). http://www.bps.org.uk/the-society/code-of-conduct/code-of-conduct_home.cfm
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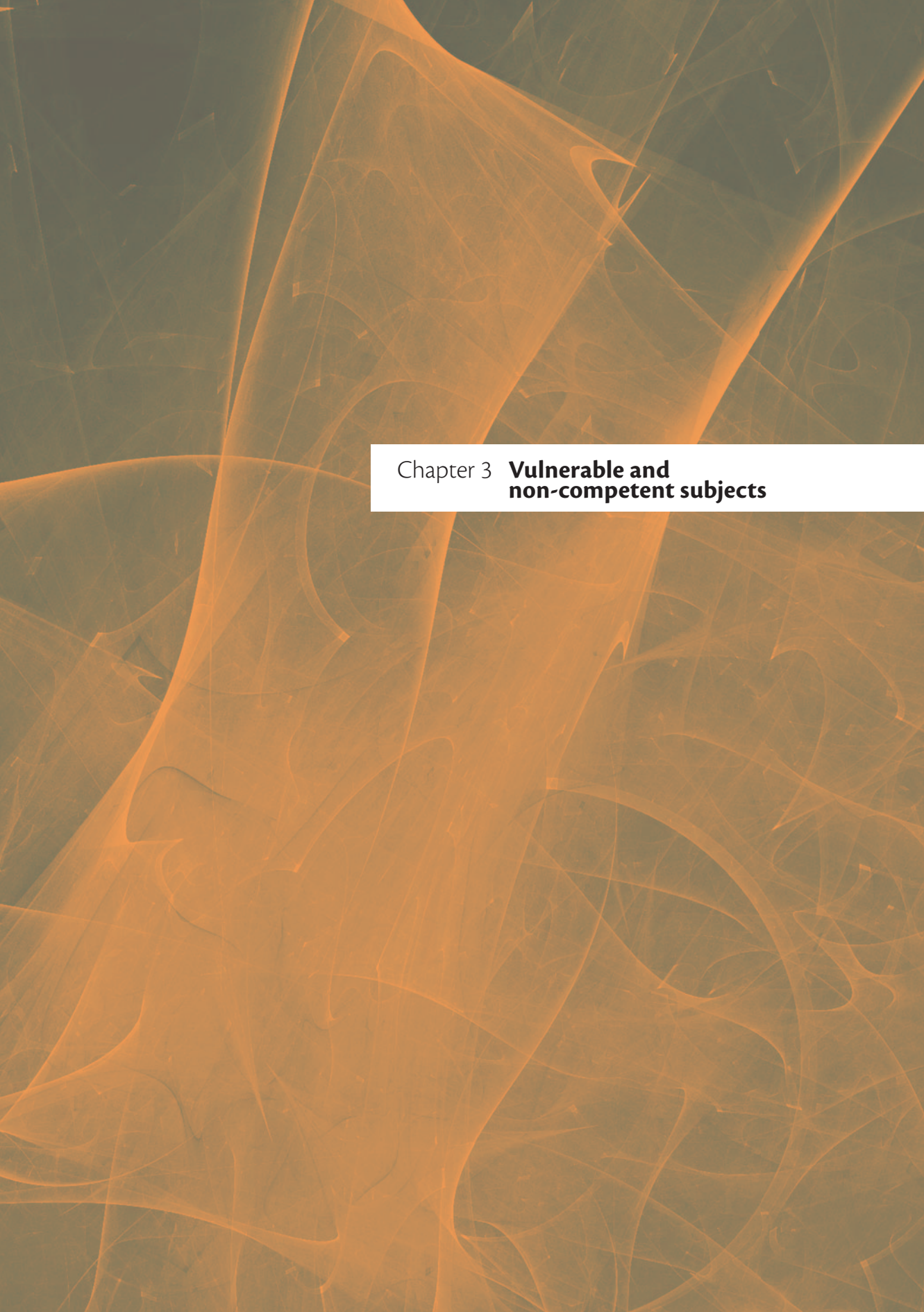

Chapter 3 **Vulnerable and non-competent subjects**

Learning outcomes

In this chapter you will develop an understanding of the ethical issues that are raised by research involving vulnerable and/or non-competent subjects. Specifically, you will gain the following:

- An understanding of what is meant by 'vulnerability' in a research ethics context, and why research involving vulnerable subjects may require special consideration by research ethics committees.
- An appreciation of the reasons for carrying out research on vulnerable and non-competent subjects.
- An awareness of the challenges involved in carrying out ethical research involving three main types of vulnerable subject: non-competent adults, the dying, and children.
- An understanding of the issues involved in assessing competence.
- An increased knowledge of how ethical issues relating to vulnerable subjects arise in research.
- An awareness of how issues concerning vulnerable subjects relate to other concepts and issues in research ethics, particularly consent.
- An understanding of what additional procedures and safeguards should be followed to protect the interests and welfare of subjects where the consent process is compromised.

Introduction

In the first two chapters of this book we have seen how research ethics has at its foundations an emphasis on protecting the welfare of research subjects (and also researchers) and on safeguarding other important concerns such as respect for autonomy, rights and personal dignity. In Chapter 2, discussion centred upon how obtaining valid consent from subjects to participate in research is one important way in which we can meet these ethical requirements. There will, however, be situations where researchers wish to carry out research on subjects who lack the competence needed to give valid consent or for whom additional safeguards may need to be taken to protect their welfare, dignity and rights. It is in cases such as these that research subjects are considered to be vulnerable and extra care needs to be taken if research involving them is to proceed ethically.

This chapter examines some of the specific ethical issues that are raised by research involving vulnerable subjects. These include the identification of subjects as vulnerable, the reasons that might justify carrying out research on vulnerable people, and (if we do allow such research to take place) the additional measures that might be needed for such research to be ethical. The case studies in this chapter highlight many of the key issues surrounding the use of both vulnerable adults and children in research. One area that will be a particular focus of concern is the status of subjects who are considered vulnerable because they are non-competent (or lack the capacity to consent), although, as we shall see, not all vulnerable subjects lack competence.

What is vulnerability?

Before we can examine the ethical challenges the issue of vulnerability raises in research, we need to give an account of what vulnerability is. For only when we have a good idea of what it is that makes someone vulnerable in research will we be in a position to properly consider what sorts of ethical problems this raises and how to address them. Although it seems that there should be a straightforward answer to this question, determining who counts as a vulnerable subject in research is not an easy task.

One way of addressing the meaning of 'vulnerability' is to examine the way it is used in research ethics codes and guidelines or in established literature. Many codes of conduct for research, such as the *Declaration of Helsinki*, refer to the need for researchers to consider and offer special protection to vulnerable subjects. ([1]) However, this does not help us to understand what vulnerability is. One of the most explicit accounts is that of the Council for International Organizations of Medical Sciences, which defines vulnerable persons as "those who are relatively (or absolutely) incapable of protecting their own interests". ([2]) Other authors on the topic, such as Goodin, see vulnerability in somewhat different terms involving power balance and responsibility. Goodin sees vulnerability as being "under threat of harm", ([3]) a threat that often arises because of a power imbalance between an individual and those who are able to cause them harm. Although there is no settled account in the literature, the frequent references to vulnerability establish this as an important – if challenging – issue in research ethics.

In our everyday language we use the term 'vulnerable' to describe people who are subject to an unusually high risk of harm. However, not all situations in which people are subject to increased risks of harm are cases of vulnerability, as the following example illustrates. Suppose I am visited by friends who have heavy colds and am therefore at increased risk, compared to the general population, of catching a cold myself. Although I would be exposed to a risk of harm by my friends' visit, this would not make me a vulnerable person in the

1. World Medical Association, *Declaration of Helsinki: ethical principles for research involving human subjects* (2008), paras. 9 & 17. http://www.wma.net/en/30publications/10policies/b3/index.html
2. Council for International Organizations of Medical Sciences and the World Health Organization, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002), Guideline 13. http://www.cioms.ch/frame_guidelines_nov_2002.htm
3. Robert E. Goodin, *Protecting the Vulnerable: A Re-Analysis of Our Social Responsibilities* (London and Chicago: The University of Chicago Press, 1985): 110.

substantial ethical sense intended when we speak of vulnerable research subjects. I am not vulnerable in this sense, because the risk I face is no greater than would be experienced by an average person in the same situation. I have freely chosen to see my friends, and having done so face the same risk as others making that choice. Now imagine that, instead of being in good health, I have been receiving chemotherapy as part of my cancer treatment and as a result have a compromised immune system. Under these circumstances I would certainly be vulnerable if visited by the same friends. I would require additional measures to protect myself because my weak immune system makes the risk of harm much greater. If I am also confined to a hospital bed, I may need someone else to intervene on my behalf to prevent the friends from visiting me, because I could not do so myself. In both cases the threat I am exposed to is the same – the cold virus – but in the second case the likelihood and severity of the harm I might receive are higher, and my ability to protect myself from the harm is lower, and it is this that makes me vulnerable.

It is also important when considering the nature of vulnerability not to lose sight of its ethical importance. This special ethical significance implies that certain ethical responsibilities arise out of the power imbalance that the vulnerable are often subject to, which leads Goodin to claim that, "If one party is in a position of particular vulnerability or dependency on another, the other has strong responsibilities to protect the dependent".([4]) This ethical responsibility to protect the vulnerable arises from a number of more fundamental ethical duties. For example, protecting the vulnerable can be seen as a particular application of the principle of respect for autonomy (for example in cases where people have difficulty in expressing or acting on their desires and preferences), the principle of non-maleficence (where the person is less able than others to protect themselves from harm), or the principle of justice. Exploitation (which will be considered in Chapter 6), is a form of injustice particularly closely connected with vulnerability in that it involves using another's weakness to further one's own goals. The key elements in all these cases are that the vulnerable person is at higher risk of harm or exploitation than others would be in a similar situation and/or is less able than others to protect themselves from harm or exploitation.([5])

While these elements can provide the basis for a satisfactory working definition of 'vulnerability', a further clarification is required for our purposes. The problem is that such a definition could include almost all research subjects simply in virtue of the risks of research participation and the imbalance of power between subjects and researchers (resulting from, amongst other things, differences in knowledge and access to information). There is a sense in which we might want to endorse this conclusion, seeing the general vulnerability of research subjects as the reason for having a system of ethical review of research. However, if we wish to use the concept of vulnerability to pick out a subset of research subjects for whom *additional* safeguards are required, its definition needs to be further qualified. To do this, we should view vulnerable subjects as those whose particular susceptibility to harm and exploitation and inability to protect their own interests results from factors *over and above* those resulting from the research setting itself.

Part of understanding and applying the concept of vulnerability will therefore be to consider what additional factors might make a research subject vulnerable. Three main areas stand out as indications of subjects' vulnerability:

4. Robert E. Goodin, *Protecting the Vulnerable: A Re-Analysis of Our Social Responsibilities* (London and Chicago: The University of Chicago Press, 1985): 39.
5. The definition of vulnerability remains contentious. However, the elements identified here are central to several other recent accounts of vulnerability, such as: Doris Schroeder and Eugenijus Gefenas, "Vulnerability: too vague and too broad", *Cambridge Quarterly of Healthcare Ethics* 18 (2009): 113-21; Ruth Macklin, "Bioethics, vulnerability and protection", *Bioethics* 17, no. 5-6 (2003): 472-86; George F. Tomossy, "Vulnerability in research", in *Disputes and Dilemmas in Health Law*, Ian Freckelton and Kerry Peterson, eds. (Sydney: The Federation Press, 2006): 534-59.

1. Subjects who lack competence will be unable to protect their interests by choosing to give or withhold consent (as discussed in Chapter 2).
2. If the voluntariness of the subjects' consent is compromised, this may similarly prevent them from choosing to give or withhold consent in a way that would protect their interests.
3. The physical (or psychological) condition of some subjects leaves them especially liable to harm, for example as a result of frailty through age, disability, or illness.

Members of different groups may be considered vulnerable for one or more of these reasons; for example, young children probably fall under all three headings due to their lack of physical, mental and emotional maturity. In other cases, it is less clear whether individuals or members of particular groups might be vulnerable for any of these reasons. For example, unconscious subjects such as comatose patients might be thought to lack competence and voluntariness because of their current condition but may also have indicated their willingness to participate in research through an advance statement made prior to their loss of consciousness, so making the ethical status of their inclusion in research more difficult to ascertain. Moreover, whilst these three areas are the most prominent concerns, people may be vulnerable for less obvious reasons. For example, vulnerability due to power imbalances can arise when research subjects belong to particular (especially minority or disadvantaged) social groups. Such subjects may in some circumstances feel threatened or coerced into taking part. This does not, of course, mean that every member of a minority group will be vulnerable in this way, but rather indicates that some factors can be less clear or easy to determine when assessing the vulnerability of a potential research subject.

Rather than trying to provide examples of all of the many possible factors that can make research subjects vulnerable, the rest of this chapter will use three case studies to explore key aspects of vulnerability in research. In thinking about these cases we should consider which groups or individuals might be considered vulnerable and why; whether there is sufficient justification for including vulnerable subjects in the types of research described; and, if it is acceptable to conduct the research using vulnerable subjects, what sorts of measures might be appropriate to protect these subjects from harm or exploitation. The ability of subjects to provide valid consent is an issue in all three cases, but each case also presents other reasons for thinking that some of the subjects might be vulnerable.

Case Study 3.1 Research involving adults with terminal illness

Dr Abbott, an oncologist at a major teaching hospital, has been asked to put forward a number of her patients for participation in a clinical trial of a new cancer treatment.

Mr Day is a terminally ill patient with a type of cancer suitable for participation in this trial. Mr Day is incredibly keen to participate and volunteers at the first opportunity. When asked to explain his eagerness during the recruitment process, he says that God has sent him this opportunity, that the treatment (which he's "read all about on the internet") is a "wonder drug", that it will save his life, and that (if entered into the trial) he expects to be "completely cured" in time for Christmas (less than 6 months away).

Mr Day's health carers all think that his views of the trial are extremely over-optimistic. What's more, his views persist in spite of the fact that he's been told on a number of occasions that:

(a) the experimental treatment isn't expected to prolong his life by more than a few months (although it may have quality of life benefits too);
(b) this expected benefit can't be predicted with any certainty;
(c) the chances of his being "completely cured" by it, or anything else, are close to zero.

When confronted with this information, Mr Day just says things like "you're just being cautious and covering your backs" or "you lack faith".

Dr Abbott thinks that participation in the trial might benefit Mr Day psychologically, alongside any direct clinical benefits, by sustaining his hopes and expectations, and (conversely) that not permitting him to take part would be psychologically damaging. She also thinks that the fact that he's very keen to take part should be taken seriously and that not to do so would be a failure to respect his autonomy. But, on the other hand, Dr Abbott is not sure whether Mr Day is capable of supplying valid consent, since he appears unable or unwilling to grasp the true nature of his situation and of the trial.

Questions

1. What are the main ethical issues that this research raises?
2. Is Mr Day in a position to give valid consent to take part in the trial?
3. Would denying Mr Day a chance to participate in the trial be a failure to respect his autonomy? What is the relationship between irrational beliefs and autonomous decision-making?
4. Should the fact that Mr Day's seemingly irrational beliefs have a religious basis be a matter for special attention in assessing his vulnerability?
5. Would entering Mr Day into the trial be exploiting his vulnerability?
6. Are there any alternatives to Mr Day offering consent or any additional safeguards that should be in place to protect his welfare?

Vulnerable adults in research

Question 1 draws attention to general ethical issues of harm and benefit raised by the case, but alongside them there are other features of the case which raise the question of whether Mr Day should be considered a vulnerable participant. Even if Mr Day is vulnerable, this does not necessarily mean that it is unethical to enter him into the research. Research into conditions which, by their nature, make the potential research subjects vulnerable can be extremely important (for example, research into dementia, childhood diseases, or terminal illness), and it may be permissible to recruit vulnerable subjects provided their interests can be adequately protected.

In this case study, it is proposed to test a new treatment for terminally ill cancer patients. Although the benefits cannot be predicted with any certainty and there is a negligible chance of the treatment effecting a complete cure, there is the potential for increased life span and better quality of life. Such improvements may make a substantial difference to the lives of terminally ill people. There are no anticipated harms associated with the treatment, although it is possible that some patients will see no or little benefit, which may have some psychological or emotional impact on them, and that some will experience unexpected side effects.

As with any proposed research involving human subjects, we need not only to weigh up benefits against risks, but also to ask whether the proposed research would violate ethical principles such as respect for autonomy and dignity. Consideration of these issues will draw our attention to aspects of the case that are connected with the question of vulnerability.

Competence to consent

In determining whether Mr Day is vulnerable in ways that should exclude him from participation in the research or require special protective measures, two issues in particular stand out. Firstly, there are the concerns of Dr Abbott, Mr Day's health care professional, regarding his competence to consent to participate in such a trial.

Secondly, there is the context of the trial itself, which necessarily involves terminally ill patients. Both of these potentially affect Mr Day's ability to give valid consent, and to determine for himself whether or not to participate in the trial, as raised by Questions 2 and 3.

The concerns voiced by Dr Abbot about Mr Day's capacity, or competence, to give valid consent arise from his seeming inability to grasp the nature of the trial. Competence is important in research ethics because, as discussed in Chapter 2, it is one of the three vital elements of valid consent (the others being adequate information and voluntariness). One reason consent is important is that it enables people to protect themselves by choosing whether or not to participate in a piece of research. If a person lacks competence, they are vulnerable because of their inability to protect themselves in this way. People who are incompetent may not make fully autonomous decisions and may not be able to judge whether participation is in their best interests. This means that additional care is needed to protect the welfare of non-competent individuals, because they cannot do so adequately themselves.

There is no universally accepted account of what competence is, but it is generally considered to involve a number of capacities or abilities. ([6]) For our purposes competence can be defined as the ability to understand relevant information, to evaluate that information and make a reasoned decision, to decide without undue influence, and to communicate consent or refusal.

Competence is generally taken to be decision-relative, so a person may be competent to make decisions about some aspects of their lives but not others. ([7]) For example, a person may be competent to decide what medical treatment they wish to undergo while at the same time not competent to manage their own financial affairs. Even within one area of decision-making, such as decisions about participation in research, there is an element of decision-relativity because a person may be capable of validly consenting to participation in some kinds of research but not others. This might depend, for example, upon the complexity of the facts about the research that the person needs to understand in order to make a reasoned decision about whether or not to participate. The thought behind this view is that because competence is primarily about understanding and evaluating information, the greater the complexity of information, the greater the cognitive capacities required to understand and evaluate it. Research that is straightforward and easy to understand can be validly consented to by a wide range of people, while fewer people will qualify as competent to consent to research that (for example) involves more complex procedures and greater requirements to weigh up probabilities of risk and benefit.

On the view just described, competence is 'complexity-relative'. ([8]) There is also a view (although this is more contentious) that competence is 'risk-relative'. On this view, the level of understanding required to qualify as competent to make a decision depends upon the level of risk involved, so that a decision that involves little risk will require a lower level of understanding than one that involves more serious risks. ([9])

6. There is a great deal of disagreement in the literature about the elements required for an assessment of competence. See, for example, Tom L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics* (Oxford: Oxford University Press, 2009); Allen E. Buchanan and Dan W. Brock, *Deciding for Others: the ethics of surrogate decision making* (Cambridge: Cambridge University Press, 1990); Charles M. Culver and Bernard Gert, "The inadequacy of incompetence", *Milbank Quarterly* 68 (1990): 619-43; James F. Drane "The many faces of competency", *Hastings Centre Report* 15, no. 2 (1985): 17-21; and Monique F. Jonas, "Competence to consent", in *Principles of Health Care Ethics*, Richard E. Ashcroft, Angus Dawson, Heather Draper and John R. McMillan, eds. (Chichester: John Wiley & Sons, 2007): 255-62.
7. This position contrasts with what is called a "fixed minimum threshold" conception of competence, where competence is not decision-relative. On this view, a person is considered to be competent as long as they possess a minimum standard of capacities, regardless of the kind of decision to be made. See Allen E. Buchanan and Dan W. Brock, *Deciding for Others: the ethics of surrogate decision making* (Cambridge: Cambridge University Press, 1990): 59-65.
8. See Tom Buller, "Competence and Risk-Relativity", *Bioethics* 15, no. 2 (2001): 93-109 and Monique F. Jonas, "Competence to consent", in *Principles of Health Care Ethics*, Richard E. Ashcroft, Angus Dawson, Heather Draper and John R. McMillan, eds. (Chichester: John Wiley & Sons, 2007): 255-62.
9. See Ian Wilks, "The debate over risk-related standards of competence", *Bioethics* 11, no. 5 (1997): 413-26.

Supporters of the risk-relative conception of competence argue that setting a low threshold of competence in cases where the level of risk is minimal allows significant respect for the autonomy of individuals, even if they are not fully autonomous; and if the competence assessment is faulty, little harm will be done. For cases that involve greater risk, the threshold level of competence should be set higher because the potential for harm is much greater. ([10])

Debate over these two conceptions of competence continues. Although it is not clear why the standard of competence itself should be related to risk rather than to the complexity of the decision, it is certainly the case that assessments of competence take on a greater importance for decisions involving greater risk. It would therefore be prudent to take the level of risk into account in deciding when and how to assess subjects' competence.

A wide range of factors can impair or prevent competence. It is therefore an essential part of any researcher's recruitment process to assess the competence of potential participants where there is reason to think that they may lack the capacity to give valid consent. That being said, it is usual to presume competence unless there is good reason to doubt it. To do otherwise could involve huge costs in assessing the competence of all potential research subjects, which could render much valuable research unviable, and could prove insulting to many subjects.

Irrational beliefs

Dr Abbot's concern about entering Mr Day into her trial relates directly to Question 2, because it raises the issue of whether Mr Day has the level of competence necessary to validly consent to participate in the trial. Mr Day's competence is placed in question by the strong belief he expresses that participation will result in him recovering from his terminal condition, a belief that seems almost certain to be false and to lack any rational basis.

Are Mr Day's apparently unreasonable beliefs and his unwillingness to engage with his health carers' advice about the likely outcomes of the trial indications of an inability to adequately understand and evaluate the information relating to the trial? They provide sufficient reason to *question* whether Mr Day is competent to consent to take part in the research. However, these indications do not necessarily mean that Mr Day actually is incompetent to consent.

One thing to bear in mind here is that the fact that certain beliefs are unusual or extreme is not necessarily inconsistent with their being autonomously and rationally held. What is at issue is whether the seemingly irrational or unusual views expressed by a potential subject are unreasonable due to a failure of understanding, or whether they are the entirely reasonable attitudes of an individual with a particular faith or belief system. It is crucial in order to answer Questions 3 and 4 that an attempt is made to distinguish between the two. Failure to respect the views of an individual where they are the result of strongly held sincere beliefs such as religious faith may be a failure to respect that person's autonomy and may result in the unfair exclusion of competent individuals from research. The possession of views considered unusual or eccentric by medical or research staff, or the wider population, is not necessarily a sign of irrationality or incompetence. The value judgements or religious beliefs of research subjects are not, in themselves, an issue for assessments of competence. One might indeed argue, in response to Question 4, that moral and religious views should be treated with special respect and tolerance, because of the importance that they have to individuals. However, it can be extremely difficult in cases such as Mr Day's, to disentangle such views from failures of understanding or reasoning about the research and its implications.

10. Allen E. Buchanan and Dan W. Brock, *Deciding for Others: the ethics of surrogate decision making* (Cambridge: Cambridge University Press, 1990): 41, 51-7.

Delusion, mania and other forms of mental illness can result in incompetence by interfering with beliefs about the information provided concerning the research or with the decisions that are associated with the evaluation of the information. This is the underlying concern of Dr Abbott in this case. What is at stake is whether Mr Day actually holds false beliefs about his prospects in the trial and, therefore, fails to properly understand the research. The difficulty is to determine whether what he says is, for example, an expression of his hopes, which have a religious foundation, a psychological mechanism to protect himself from what he really knows to be true in relation to his terminal illness, or a reflection of or an attempt to cover up the fact that he doesn't understand the nature of the trial. If it were either of the first two reasons – an expression of his hopes or a form of psychological protection – Mr Day should not be considered incompetent. If it is the third reason – that he lacks a genuine understanding of relevant aspects of the research – then no matter how sincere his beliefs, Mr Day cannot be said to have exhibited sufficient understanding of the trial for his consent to be valid.

Terminal illness and vulnerability

Having a terminal illness may not by itself make a person vulnerable as a research subject, but it does open up a number of ways in which they can become vulnerable. It is likely that diagnosis of a terminal illness will have a significant psychological effect on a person, leading to stress, depression, anxiety and other psychological conditions that may temporarily impact upon a person's ability to make clear and rational choices. Such conditions have to be taken into account alongside other concerns about a person's competence to consent. The inclusion of terminally ill people in research brings in other factors that can make such subjects vulnerable to exploitation, as suggested by Question 5. Given the psychological state a terminal diagnosis can create, such people may be more open to pressure than others. Alternatively, their desire for a cure or an increased lifespan may be so great that they jump at any perceived chance, without properly considering whether participation is in their interests. All of these elements need to be taken into account when seeking consent from terminally ill subjects.

An important issue that arises in relation to Question 5 is whether a lack of options – in terms of an available cure or further life-prolonging treatment – might compromise the voluntariness of a participant's consent. The concern here is that if a person's only possible hope for extending their life is an experimental treatment, this leaves them with no acceptable alternative other than to participate in the trial. The voluntariness of their consent may therefore be compromised. This makes the situation similar to one in which 'undue' inducements are offered – as discussed in Chapter 2 – with the inducement in this case being a seemingly irresistible offer of a chance to prolong life. We should, however, be cautious about concluding that voluntary consent is impossible in such circumstances as this would also make it impossible for patients to consent validly to life-saving treatment in many non-research settings. The question of how such concerns about voluntariness relate to exploitation will be discussed in Chapter 6.

There are many reasons why it might not be in someone's interests to participate in research, even if that research may prolong or improve their life. For example, the chances of success may be low whilst the nature of the intervention may be very unpleasant, such as intensive chemotherapy. A person diagnosed with a terminal illness may prefer the quality and length of life expected outside the trial to an extended but lower quality life. Alternatively, a person may wish to avoid any indignity they see as being part of a research trial in their dying days. However, the concern is that many subjects will simply see the rewards as so great that they will consent without giving due consideration to the disadvantages.

It is entirely possible for a person to choose voluntarily to participate in research in the context of terminal illness, despite the extremely strong incentive that the possibility of extension of life presents, not least because it is in many cases a rational choice that is strongly in the interest of the research participant. So the prospect of a life-prolonging treatment does not necessarily lead to vulnerability by compromising voluntariness, although it may do so where it exerts a 'controlling influence' (i.e. one that bypasses rational deliberation) over the patient's decision.

We also need to consider ways in which terminal illness could make a patient like Mr Day vulnerable even without undermining competence. Being terminally ill could make a research participant vulnerable by increasing the likelihood or potential severity of harms that they might suffer due to their physical condition. Even with the fully autonomous, valid consent of such a terminally ill patient, it is questionable whether they should be recruited into research that poses a significantly greater risk of harm to them than it would to other subjects who could be recruited. It should also be remembered that the risks of harm may need to be balanced against the potential benefits of participation in research. However, balancing harms and benefits may be significantly more difficult for terminally ill patients than for others. In particular, even if they are not at risk of greater physical harm than others, the harms that they are subject to may take on a more serious aspect, as they may blight a person's limited remaining time, with little opportunity for compensation or balancing benefits. Psychological and social side-effects of treatment, such as reduced cognitive function or disrupted ability to communicate may similarly take on a greater significance at the end of life.

Another aspect of terminal illness that may be associated with vulnerability concerns hope. For a person seeking full recovery, such as Mr Day, it may be very hard to keep hope of cure in check throughout the research process. For some research participants, their rational or public understanding of the likely outcomes that the research is working towards may be at odds with their secret and non-rational hopes of a cure. Mr Day may be vocalising the suppressed thoughts of many research participants for whom the options for successful treatment or cure have been exhausted. Regardless of whether or not it compromises their competence to consent, hope that a terminally ill person may feel despite their acceptance of facts that ought to undermine it, makes them vulnerable. Participants harbouring unrealistic hopes may feel devastated by the failure of a research intervention to effect cure, or they may feel cheated (perhaps by fate, rather than by the researchers themselves) if they are randomised to a placebo arm.([11]) These feelings may occur in spite of a participant's understanding and acceptance of the trial design and its stated expected outcomes. The difficulty that research participants may experience in aligning their expectations to the likely outcomes of the research should be clearly recognised by researchers, and factored into discussions with participants and their families.

These considerations do not vary in kind from those involved in ethical scrutiny of many types of research, but the potential vulnerability of research participants in this context makes it appropriate for researchers to be especially cognisant of these issues and to ensure that the interests of terminally ill research participants are safeguarded.

Concern that involvement in research may endanger vulnerable participants may lead some to doubt the ethical acceptability of all research involving potentially vulnerable individuals. But there are good reasons relating to the interests of vulnerable groups to support the execution of carefully constructed and ethically sound research involving vulnerable individuals. Some research questions can only be answered if tested in the context of conditions associated with vulnerability, and the opportunity to improve treatment and further the understanding of issues that arise in those contexts will be severely limited without research. Should a terminally ill patient expect to receive substantial benefit from participating in a trial then their inclusion might be warranted even if they are at more risk than other participants. It is also important to allow for the possibility of altruistic research participation in the context of terminal illness. For some people, participation in research from which they do not expect to benefit personally might present an opportunity to end their lives in a positive manner, expressing through their actions important values that provide for them a sense of meaning and hope. Although the potential for vulnerability makes it particularly important to present research sensitively and approach the information-giving and consent process with care, it is not in itself grounds for ruling research participation out.

11. Ethical issues surrounding the use of placebos in randomised controlled trials will be addressed in Chapter 5.

Question 6 raises the issue of what alternatives to consent or additional safeguards might be put in place to protect the welfare of Mr Day if he is judged to lack competence.

One possible response is to exclude him from the trial altogether. This response would resolve concerns about exploitation of Mr Day's vulnerability as well as avoiding harm that Mr Day may subsequently experience if enrolment in the trial does not lead to his cure. It is important to note that excluding Mr Day does not represent an ethically neutral response to concerns about his competence, but rather (given that Mr Day meets the clinical criteria for inclusion and the trial is not oversubscribed) expresses a view that Mr Day is not competent to give valid consent. Even if there are doubts about Mr Day's competence that are not able to be fully resolved by further discussions with him, exclusion may be unduly harsh. If participation in this research presents the best likelihood of improving the outcome for Mr Day, there are welfare-related reasons to include him in the trial. Although it is possible that Mr Day will experience trauma if the trial fails to deliver the fulfilment of his unrealistic hopes, it is at least equally likely that exclusion from the trial will traumatise Mr Day. So exclusion is not a costless option in terms of Mr Day's welfare or his autonomy.

One possible response in cases of borderline incompetence is to allow participation on the basis of consent, but with caveats designed to maximise participant understanding. This approach involves the provision of additional help to understand the issues that should inform their decision. This may take the form of one-on-one sessions between the researcher and the participant, the use of DVDs, web-based materials or written leaflets or exercise sheets. In this case, however, Mr Day may not be receptive to further efforts to ensure understanding, since he does not consider his understanding of the research to be problematic. The fact that Mr Day has disclosed unrealistic views of the research outcomes makes it appropriate for the researcher (or person overseeing the consent process) to invest time in building a constructive and frank dialogue with Mr Day which is aimed at ensuring that his understanding of the research is realistic. This is the case even if Mr Day does not recognise the importance of this process. Ultimately it is the researcher and not the participant who is responsible for ensuring that the participant has an appropriate understanding of the aims and design of the trial.

Another response to Mr Day's uncertain competence is to accord his decision the status of 'assent' rather than consent, and to make a decision about his inclusion on the basis of a discrete assessment of his welfare. The fact that Mr Day wants to participate is taken as a reason in favour of participation, but it does not have the decision-determining quality of a valid consent. The concept of assent and dissent is examined in the discussion of Case Study 3.2 below.

Including a participant like Mr Day in a trial despite unresolved concerns about the quality of his consent may be permissible on welfare grounds. How ought the interests of Mr Day to be assessed? One option would be to refer to a person or body of persons that is independent from the research (to ensure that the interests of the research or the researchers do not dominate the decision) such as an ethics committee. Another would be to refer to Mr Day's closest family (to gain further insight into Mr Day's belief structures, communication habits, and to find out about the support that he will have as the research progresses). If consultation of a third party is sought, it should be clear what its purpose is. Is the researcher seeking another opinion, which she will then weigh up along with her own views and those of Mr Day, or is she devolving decision-making authority to the consulted party? If it is the latter, it needs to be very clear why their decision is to be preferred to that of Mr Day or the researcher. It is also important to consider how a decision against inclusion would be presented to Mr Day.

Cases such as that of Mr Day engage many of our concerns about autonomy and welfare in the research context. In some cases, this sort of vulnerability concern will be adequately addressed through additional investment in communication between researchers and research participants. When research involves participants who are clearly not competent, good communication alone will not be sufficient. A case of this sort is considered next.

Case Study 3.2
Research into the role of carers for Alzheimer's patients

The increasing number of people diagnosed with Alzheimer's disease has led to a significant growth in the number of people needed to care for them. Researchers want to find out how people with Alzheimer's relate to their carers, and the impact this has on both patients and carers. The initial aim of the research is to identify the challenges that carers most often face as well as the aspects of care that do most to enhance or reduce the welfare of people with Alzheimer's. The researchers believe that answering these questions is vital if they are to develop better training and support systems for carers.

Researchers plan to carry out observational research on the daily activities of carers as they go about their normal duties caring for Alzheimer's patients. The observations will be carried out in a number of different institutions where people with Alzheimer's disease are cared for, such as nursing homes, psychiatric hospitals, and respite centres. Researchers also want to distribute questionnaires to carers and, where possible, patients to find out their responses to a number of central issues, such as:

- Which aspects of working with people with Alzheimer's disease do carers find easy and which aspects do they find difficult or stressful?

and:

- Which aspects of the carers' approach do most to enhance or harm the welfare of people with Alzheimer's?

The researchers are aware that the patients involved in the research will have varying levels of competence. Consent will be sought from all carers involved in the research, as well as the institutions in which the observations are taking place. Every effort will be made to gain consent from each patient. Where a patient is not competent to consent, proxy consent will be sought from the most appropriate third party.

Questions

1. What are the main benefits that might arise from this research proposal?
2. What are the ethical problems with this research proposal? In particular, is it ethical to conduct the research on those patients with Alzheimer's who are incompetent and cannot consent?
3. What additional efforts should be made to increase the understanding about the research for those with Alzheimer's? Do you think such efforts could have a negative effect on the patients?
4. Should any additional safeguards be put in place to protect the welfare of research subjects who are unable to give valid consent?

Vulnerability and cognitive impairment

The research proposed in the case study offers the prospect of significant benefits for both people with Alzheimer's disease and their carers. The carers stand to gain from better training and support in their roles, and this in turn will enhance the welfare of the patients they care for. Moreover, the research may have both immediate and longer term benefits. The identification of aspects of care that are beneficial or detrimental to the welfare of patients or carers will have an immediate impact upon their welfare if the results are made available to carers and to the organisations that provide the care, and used to improve training. If this knowledge is used more widely to develop and implement improved approaches to caring for people with Alzheimer's, future patients and future carers will also stand to benefit.

However, ethical concerns arise because of the inclusion of potentially vulnerable people with Alzheimer's disease in the research. In general, great care should be taken to determine the level of competence of subjects who have conditions that can cause cognitive impairment. These include not only Alzheimer's disease and other forms of dementia but also conditions such as stroke, brain tumour, mental illness, delusional states and head injury. People diagnosed with any of these conditions may be unable to understand, retain and evaluate the relevant information, or to make and communicate a decision based upon it. Within each condition there may be a wide variation in cognitive ability, so that although not everyone diagnosed with these conditions will be cognitively impaired to such a degree that they cannot consent, competence will have to be established in each case, and extra provision made in certain cases to assist their understanding.

There are also ethical concerns relating to the effects of the research on the carers. The Case Study does not specify whether the carers who will be involved in the research are employees of the institution in which the research will take place, members of the patients' families, volunteers, or a mixture of these. If they are paid carers then concerns might arise about the uses that their employer might make of information acquired through the research, for example to discipline staff or assess their performance. These concerns might be addressed by providing the employer with the results of the research only in the form of generalised findings and recommendations without reference to individual carers, ([12]) but whether or not this approach is taken it will be important for the researchers to define how the information they acquire will be communicated and used, and for the carers to be informed about this before consenting to participate. If the carers are members of patients' families, then they might themselves be vulnerable, for example psychologically and emotionally, due to the impact of the deterioration of a loved one or the stresses of being an unpaid carer. For carers in any of these groups the observation may give rise to privacy concerns, and this will be an issue to be addressed by the researchers. Participants should be informed about the circumstances in which information identifying individual carers will be supplied to the relevant authorities in the case of abusive, dangerous or criminal behaviour being observed or disclosed. Issues about privacy and disclosure will be addressed further in Chapter 4. The remaining discussion of this case, however, will focus on ethical issues relating to the involvement of Alzheimer's patients, and particularly on issues to do with competence and consent.

In the case study it is almost certain that some of the people with Alzheimer's disease whom the researchers propose to study will be unable to give valid consent, either because they lack competence due to impaired cognitive ability or because their condition undermines their ability to consent voluntarily. Although many Alzheimer's patients will also be elderly and therefore potentially physically vulnerable, the risk of harm to the vulnerable group is low, because the research is largely observational and involves no change to patients' daily care. There may, nevertheless, be some risk of patients becoming distressed or of the quality of care being adversely affected by the presence of observers.

12. This is similar to, and has similar limitations to, the use of anonymisation to avoid breaches of confidentiality, which will be discussed in Chapter 4.

(The carers may also feel uncomfortable about being observed and have concerns about how the observations and assessments of their practice might be used by their managers. A similar issue about observation in the workplace will be discussed in relation to privacy in Chapter 4.) There is also a serious concern about the privacy and the dignity of those being cared for. Observers in a care setting may witness behaviours and aspects of care that are of a deeply intimate nature and which the cared-for person would not have exposed to observational research prior to the onset of Alzheimer's.

Even where the risk of harm is low, we normally expect researchers to obtain the consent of participants. However, many of the patients in this study will be unable to give valid consent. As dementia in Alzheimer's patients is often progressive and results in a gradual decline of cognitive function, there will be many gradations of ability and understanding. Patients may range from still competent through borderline competent to non-competent. The likelihood of a gradual decline in competence makes lengthy studies more problematic, since consent given at the outset of the research may not endure if that person later becomes incompetent. Alzheimer's may also result in fluctuations of competence and episodic lucidity, where a person is fully autonomous and competent some of the time but not at other times. The concern here is that a subject may consent to participate in the research during a lucid phase but enter a non-competent phase before the research has ended.

In cases such as these, the loss of autonomy and competence, either permanently or periodically, generates a level of vulnerability for the subjects, as they may lose their ability to protect their own interests. It may therefore be appropriate for researchers to undertake periodic reassessments of subjects' competence, especially in longer studies. Once a subject has become incompetent, they require safeguards similar to subjects who lacked competence from the outset. Consent given before becoming incompetent is significant in that it provides an indication that the subject judged the trial not to involve excessive risk or exploitation. However, while a competent subject can continue to protect their interests by choosing to remain in or withdraw from the trial, a subject who has lost competence cannot be relied upon to make this judgement. Nevertheless, clear indications of distress and unwillingness to continue should be taken seriously, even if the subject initially consented.

Inclusion of non-competent subjects

A central ethical concern in this case, raised by Question 2, is whether it is ethical to include non-competent and other vulnerable subjects in research, and, if so, in what types of research?

When considering this question, it might seem that the simplest approach would be to adopt a blanket policy of excluding anyone judged to be vulnerable or unable to give valid consent from participating in research. Although this will be discussed in Chapter 6, it is worth noting that such wide-reaching policies of exclusion could have seriously detrimental consequences for society, and especially for those with conditions that result in vulnerability or loss of competence, by depriving us of important knowledge about those conditions.

This is reflected in the widespread recognition in relevant codes, guidelines and laws ([13]) that it is permissible to undertake research involving subjects who are

13. For example: World Medical Association, *Declaration of Helsinki: ethical principles for research involving human subjects* (2008), Articles 27-29. http://www.wma.net/en/30publications/10policies/b3/index.html. Council for International Organizations of Medical Sciences and the World Health Organization (CIOMS), *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002), Guidelines 9, 13, 14, 15. http://www.cioms.ch/frame_guidelines_nov_2002.htm. *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (Oviedo, 4.IV.1997), Article 17. http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm. *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use,* Articles 3-5. http://europa.eu/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf

unable to consent provided that it is methodologically necessary to use such subjects and that the research is likely either to benefit the subjects themselves or to benefit others with the same competence-undermining condition while imposing no more than minimal risk ([14]) on the subjects. (Other conditions frequently required are that assent should be sought and dissent respected, and that consent from a legally authorised representative of the subject should be sought – the latter will only be possible where legal provision for this exists within the relevant jurisdiction.)

We have seen that in the case study there is a likelihood of benefit both to the non-competent subjects and to future patients with the same condition. It might be questioned whether it is really necessary to include the Alzheimer's patients as research participants in order to obtain these benefits, given that the research is predominantly about the activities of the carers. However, since the activities in question involve interaction with patients it would be impossible to carry out the observational part of the research without also observing the patients, and, given that one of the key aims of the research is to ascertain the effects of the carers' actions on the patients, it is unlikely that similar results could be obtained without the involvement of the Alzheimer's patients.

Safeguards for vulnerable and non-competent subjects

Questions 3 and 4 prompt us to consider what measures might be taken to protect non-competent subjects who are to be included in a trial.

Improving the quality of consent

Question 3 raises the issue of how to deal with those subjects whose decline in health has placed them at or just below the threshold level of competence. Ascertaining why a person is not competent can facilitate attempts to improve the quality of consent that they can give, in particular in those cases where some additional help needs to be given to aid their understanding of the research. For example, those with early onset Alzheimer's may have difficulty concentrating, learning new facts, remembering and processing them. Attempts to improve their understanding and retention of the relevant information may lead to them being able to give valid consent, or, failing that, at least result in an improved standard of deliberation that would allow researchers to form a better picture of their wishes and preferences.

However, there are limitations on such an approach. Whilst attempting to enhance the autonomous decision-making ability of a dementia patient is important, care also needs to be taken that this does not lead to unnecessarily stressful and harmful interactions with the subjects. Forcing dementia patients to confront aspects of their mental state in an attempt to make them better understand the research may be extremely distressing to those involved. On the other hand, oversimplification of the proposed research may be taken by some as an affront to their dignity. This means that any attempt to improve the quality of consent through improving the patients' understanding should be handled sensitively so as to avoid harming them or failing to respect whatever degree of autonomy they retain before the research even begins.

Alternatives to consent

Another means of providing an additional safeguard for an incompetent subject's welfare is to consider alternatives to the standard consent processes. This might be through:

(i) gaining their assent or requiring the absence of dissent if the subject is capable;
(ii) the use of a proxy to make decisions on their behalf; or
(iii) relying on an advance statement, where one has been prepared.

14. Minimal risk is typically understood as risk not greater than that encountered in everyday activities. For a discussion, see Chapter 5.

The first of these, assent, was first raised as an issue in relation to the competence of Mr Day in Case Study 3.1, where his competence to provide valid consent was brought into question. Although assent is not meant as a substitute for valid consent, it is designed to support a range of ethical safeguards, from providing an additional layer of protection by indicating what a subject's interests are, to respecting the autonomy of an individual to the extent they possess it, to respecting their dignity as a human being rather than treating them purely as a means to the researcher's own ends. We can define assent and dissent as follows:

> *a form of agreement/disagreement that assumes a lower standard of information assimilation, voluntariness, and decision-making than that of consent. The purpose of assent/dissent is to respect a limited or developing autonomy.*

Assent (or dissent) can be given by a person whose competence is impaired in such a way that they cannot give valid consent (or refusal) but which is sufficient to allow them to grasp something of the nature of the proposed research and to communicate their preferences.

Assent is not a substitute for valid consent, but it does achieve a form of safeguard similar to valid consent, although to a lesser degree. Assent in response to the presentation of an opportunity to participate in research may provide the best possible indication of the desires and preferences of a person who is not competent to give valid consent. Seeking assent and, importantly, respecting dissent, is a way in which we can respect (limited) autonomy. Although a person may be unable to make fully autonomous decisions, that does not mean they have no level of autonomy to be respected. Engaging with subjects and obtaining assent or dissent is therefore a way to respect an element of autonomy and to help preserve something of the dignity that attaches to decision-making.

Assent or dissent can also inform assessments of best interests. The satisfaction of preferences is likely to form one element of best interests and so, to the extent that satisfying preferences does not conflict with other central interests (whatever those might be), we have a reason to respect assent or dissent. It is often thought that particular attention should be paid to any dissent that an incompetent participant exhibits to the research. As safeguarding the participant's welfare is paramount, any indications of dissent should be treated seriously in order to prevent them experiencing any further harm, perceived or actual.

There may be situations in which a non-competent person's assent or dissent to a piece of research appears to be at odds with their overall best interests. This may occur, for example, when a very young child refuses an injection that is part of a research intervention that represents the only chance of a cure for a serious condition. In a case such as this, it may be appropriate to override the child's dissent in pursuit of their overall best interests. But in many other cases, the extent to which the prospective participant's interests will be advanced by participation will be uncertain enough that their assent or dissent will carry great, and in some cases, determining, weight.

As with consent, assent is not achieved in a single instance but over the duration of the research. The episodic nature of conditions such as Alzheimer's makes it very likely that participants will respond differently to the research at different times. It is important to monitor signs of distress and unwillingness to continue throughout the research period. Such signs are clear indications of dissent, even in cases where the subject was initially able to provide valid consent to the research.

Let us consider the role of assent in relation to Case 3.2. The proposed research is likely to involve many people who are incompetent because of the degree of their dementia but who are still sufficiently able to grasp something about the proposed research to assent or dissent to participate. This research is unlikely to yield sufficiently tangible benefits to the particular individuals involved to provide interest-related grounds to override dissent. Therefore, the dissent of prospective participants should be respected. Dissent may be expressed when the research is initially presented, or at some point during the period of observation. If a participant who initially assented (or even consented) to involvement in the research later rescinds that, the

distress that is likely to follow from continued observation, along with the (partial) autonomy-respecting function of assent, dictate that observation should be discontinued. Because of the episodic nature of Alzheimer's, it may be appropriate to re-seek assent at a later time, but great care should be taken to avoid pestering or causing continued distress.

In this case, questions may arise about the status of the assent of some participants with respect to their likely pre-Alzheimer's wishes. The onset of Alzheimer's often brings quite radical changes to a person's behaviour and preferences and sometimes these are of a kind that loved ones believe the person would have previously disapproved or been ashamed of. People with Alzheimer's may also require help and care of a very revealing and intimate nature, and this may give rise to worries about the extent to which assent to an observational study can protect the ongoing interests in dignity and privacy that participants may possess. One response to these concerns would be to say that if the participants do not feel that their privacy is wrongly invaded by the research, their view should be respected, thus allowing participation. Another response is to hold that, even if participants do not currently feel motivated by a wish to protect their privacy, the likelihood that they would previously have refused to participate in research of this type should override current assent to participate. How much priority should prior wishes, or informed guesses about prior wishes, have when considering the participation of a person with Alzheimer's in research? This is a question that leads into complex philosophical debates about identity and autonomy, but it is one that should be afforded some consideration in the context of research of the type presented in Case 3.2.([15])

Family members are likely to have views about (a) whether a prospective participant would have given consent to participate in research of this type prior to the onset of Alzheimer's and (b) whether they should participate now. In the face of doubt about the moral weight of a participant's assent, or if no indication of assent or dissent can be obtained from the prospective participant, one option is to seek consent elsewhere.

An alternative where valid consent from the participant cannot be obtained is for a legally appointed representative, sometimes called a 'proxy', to make decisions on behalf of the incompetent subject. As a proxy is usually appointed by the subject prior to their becoming incompetent, or else is often someone with a close relationship to the subject, they can use their knowledge of the subject to promote any preferences and interests that they believe the subject has. Such proxy consent may be adequate to allow an incompetent subject to participate in certain elements of invasive research carrying more than a minimal risk (that is greater risk than would be experienced from performing day-to-day activities). The thought behind this is that the greater the risk, the greater the safeguards to protect a subject from research not in their interests. As a proxy is seen to provide a greater insight into what is in the best interests of the subject than the researchers can determine by themselves, proxy consent introduces an additional safeguard in cases where the subject faces more than a minimal risk.

However, there may be some concern with such an approach in Case Study 3.2, as the carers may be the ones best placed to provide proxy consent for the dementia sufferers. Although, on the face of it, carers are often highly aware of a patient's condition and preferences, making them a seemingly good choice as a proxy, in Case Study 3.2 this might be problematic. Given that the research aims to benefit the carers as much as the Alzheimer's patients, there might be a perceived conflict of interests between their caring role and their role as a proxy. A carer might be keen to have an opportunity to participate but might only be able

15. For readings relevant to these debates see the discussion of advance directives below.

to do so with the participation of the person they are caring for, making them potentially more likely to give proxy consent to participate. ([16])

Another possible way of dealing with consent issues is the use of advance directives (sometimes known as 'advance statements'). These are statements made by people when they are competent about how they wish to be treated in the future if they become incompetent. Such directives are seen as particularly useful for people with progressive conditions, such as dementia, where they are aware that their competence will become impaired in the future. A person, knowing they will eventually become incompetent, could decide whether or not they would like to be entered into research trials related to improving their condition and record that desire in an advance statement. As the statement is made when the person is competent, it may be seen as the next best thing to valid consent.

However, advance statements are still quite limited devices for recording a person's wishes. They may be limited in scope because they are vague or only cover specific situations. Moreover, unless they were constructed with a specific research trial in mind, where the still-competent subject had been able to review all of the relevant information and make a judgement about their future participation, an advance statement would fall far short of the normal standards of valid consent. Advance statements are therefore perhaps better understood as indicators of the wishes and preferences of an individual before they became incompetent. Whether such wishes are still considered accurate by the time they are acted upon is a question that is open to a great deal of debate. ([17])

Despite all of the alternatives available where valid consent cannot be obtained, there will be cases where none of them are applicable or where they are still not considered sufficient grounds to enter someone into a research trial. Given that consent as a means of protecting the welfare of a subject no longer has a central role, in order to include such vulnerable subjects in research other measures must also be taken into account to minimise risk and safeguard them from harm.

16. It should also be noted that the legal status of a proxy is not recognised universally, although the *European Clinical Trials Directive* gives Europe-wide recognition of proxies as legal representatives able to provide consent for an incompetent subject to participate in the kinds of research covered by the directive. (*Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use,* Articles 3.2 (b), (d) and Article 5 (a).
http://europa.eu/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf
Even where not legally recognised, however, a properly appointed proxy can give researchers valuable additional information about the interests of an incompetent subject. The same is also true of advance directives.
17. See, for example, Allen E. Buchanan and Dan W. Brock, *Deciding for Others: the ethics of surrogate decision making* (Cambridge: Cambridge University Press, 1990), Chapter 3; David DeGrazia, "Advance Directives, Dementia, and 'the Someone Else Problem'", *Bioethics* 13, no. 5 (1999): 373-91; Anthony Wrigley, "Personal Identity, Autonomy and Advance Statements", *Journal of Applied Philosophy* 26, no. 4 (2007): 381-96.

Case Study 3.3
Research into treatments for behavioural disorders in children

Professor Helsinki, a world famous psychiatrist specialising in the treatment of children, wants to comparatively evaluate four different treatments for a rare behavioural disorder called RBDC. RBDC, which involves occasional bouts of abusive and violent behaviour and episodes of severe paranoia, is most prevalent in children aged between 11 and 15, but 14% of cases occur in young adults, and a further 6% of cases are in people aged over 25.

All of the treatments that Professor Helsinki wants to test are 'standard' insofar as each has been used in clinical practice in the recent past. However, the evidential basis for each one is minimal (at least specifically in relation to RBDC) and none is proven to work.

In general terms, the options for trial are:

(a) a widely used pharmaceutical product;
(b) a programme of anger management and relaxation exercises;
(c) group therapy;
(d) cognitive behavioural therapy.

Professor Helsinki wants to enter almost all of his patients with RBDC (all of whom are younger than 16) into the study and to randomly allocate them into one of the above options. He proposes to do this without telling them or their parents/guardians and, hence, without prior consent for participation in the research (although the parents/guardians will be informed after the trial). Consent for the particular therapies offered will be obtained as normal, but the patients and their parents will not be told about the existence of the study or about the randomisation process.

Professor Helsinki's grounds for the non-disclosure policy include:

(i) that disclosure to patients or parents would undermine the scientific validity of the study by affecting the behaviour and mental states of the research subjects;
(ii) that disclosure would harm the research subjects by upsetting them and/or exacerbating their paranoia (e.g. the idea of being 'experimented on' and 'watched' would be highly disturbing to many of these young people);
(iii) that disclosure would make it impossible to recruit research subjects;
(iv) that most people with RBDC lack the capacity to validly consent owing to the nature of the illness;
(v) that this important research will benefit sufferers from RBDC and may even benefit the research subjects themselves;
(vi) that his patients could have ('randomly') received any of the treatment options in ordinary clinical practice depending on, for example, where they happen to live and that Helsinki's research is just a more systematic and scientifically valuable version of what would have happened anyway.

Questions

1. What are the possible benefits that this research proposal raises?
2. What are the ethical problems with this research proposal? In particular, is it ethical to conduct the research without obtaining the consent of either the children participating in the trial or that of their parents/guardians?
3. Do Professor Helsinki's grounds for non-disclosure justify him carrying out the trial without consent?

4. Are there any additional safeguards that should be put in place to protect the welfare of the research subjects if they are unable to give valid consent to participate?

The use of children in research

Up to this point, we have only considered vulnerable and incompetent adults in research. Case Study 3.3 prompts us to consider to what extent the ethical considerations applying to vulnerable and incompetent adults also apply to children, and whether any additional issues are raised by the participation of children in research. The use of children in research is a sensitive issue which has received special attention in several research ethics codes and regulations.([18]) Like some of the adults featured in the previous case studies, children may (depending on their age and maturity) be considered vulnerable because of limited understanding and a resulting incapacity to give valid consent, dependence on others (leading to possible lack of voluntariness in the making of certain decisions and susceptibility to exploitation and certain kinds of harm), and physical or psychological frailty leading to increased risk of harm from certain research activities. Factors that may require children to be treated differently from vulnerable and incompetent adults include the role of parents and guardians, and the fact that – in contrast to the participants with dementia in Case Study 3.2 – children can be generally be expected to develop rather than decline in maturity and understanding. Although children are commonly viewed as a vulnerable group in relation to research, the fact that they mature at different rates means that we cannot assume that someone who is legally a minor is necessarily incompetent or vulnerable; thus, even in a jurisdiction in which a minor's consent is not legally recognised or required, there may be a moral requirement to obtain consent from an older child who is capable of understanding the risks and benefits of participation.

As with adults who are unable to consent, one justification for including children in research is that they individually stand to benefit from participation, and another is that their participation is necessary in order to obtain knowledge that will benefit others in the same vulnerable group. In response to Question 1, we may note that the proposed research takes the form of a therapeutic study in which all of the participants will receive treatment for their condition. As all of the treatments being used are considered 'standard' and there is no obvious indication which one is best, all those in the study stand to benefit insofar as they are being treated.([19]) However, since the participants can expect to receive one of these treatments whether or not they participate in the trial, and given that they will be allocated to treatment arms randomly, it is not clear that there is any additional benefit resulting from their participation.

There are potential benefits for all those suffering from the behavioural disorder RBDC, because the results of the research should indicate which, if any, of the standard treatments is associated with the best outcome overall, and it may reveal further information about the effect of individual interventions on particular subgroups of the research population. The results of the research should mean that only treatments that do have a sound basis are provided in the future. Even if the results of the research indicate that there is no good basis for *any* of the 'standard' treatments, this will still allow specialists to seek alternative treatments rather than administering apparently useless treatments, which may be at best a waste of health care resources

18. For example, Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002), Guideline 14. http://www.cioms.ch/frame_guidelines_nov_2002.htm. See also: *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use*, Article 4. http://europa.eu/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf
19. This relates to the concept of 'equipoise', to be considered in Chapter 5.

or, at worst, harmful to patients. On the assumption that RBCD is a chronic condition and that Professor Helsinki is able to rapidly apply the results of the study to his own practice, the research participants may be able to benefit alongside others suffering from the condition. Again, however, this does not indicate any additional benefit resulting from participation in the study.

Question 2 asks us to consider whether the research raises any ethical problems. One immediate concern is whether the study actually requires minors as subjects or could be carried out using competent adults instead. The research proposed by Professor Helsinki concerns a behavioural disorder, which, we are told, is most prevalent in children aged between 11 and 15. However, this might not fully justify the research being carried out on children, since 14% of cases occur in young adults, and a further 6% in people aged over 25. So, although the condition occurs *predominantly* in children, perhaps there are enough adult cases for these to be the focus of the research. Thus, some additional justification is needed for carrying out the research on minors under the age of 16. The fact that all Professor Helsinki's patients are under 16 is not itself an adequate justification, as the research could be carried out at other clinics. Even if all those adults with the behavioural disorder were in some way vulnerable due to, for example, their competence being impaired, there might still be a preference for using them in the research on the grounds that their greater physical, mental and emotional development might make them less susceptible to harm. For a similar reason, older children are generally preferred to younger children as research subjects, as the younger the child, the less likely they are to be able to protect their own interests and the more susceptible they are likely to be to physical, mental and emotional harms.

There may, however, still be sufficient reason for the research to go ahead with children as subjects. In particular it is increasingly recognised that there is reason to include children when researching treatments for non-age-specific medical conditions, in order to understand how the treatments will function in children. As a child's developing mind might respond very differently to an adult's, a case might be made on methodological grounds for the use of child subjects.

Children and consent

Questions 2 and 3 also raise a specific concern about Professor Helsinki's proposal not to gain consent for participation in the research from either the children or their parents, nor to inform them in advance that they are involved in a trial.

Some of the reasons given by Professor Helsinki for not seeking consent are general arguments unrelated either to the age or the competence of the subjects. For example he puts forward a methodological justification of the kind discussed in Chapter 2 (see Case Study 2.3, Covert surveillance of health care professionals). The central argument is that, because this is a behavioural study, knowledge of the research would alter the behaviour of the subjects. In order to assess this argument we would have to weigh the plausibility of the methodological claim and the importance of the research against the absence of consent and the possibility of harm. In this case, as noted above, it is not clear that there are any direct benefits to research subjects to enter into the balance.

This methodological argument might in this case be supported by another of Professor Helsinki's general arguments: that because the research involves an investigation into the comparative merits of standard treatments it therefore is unlikely to expose the children to any greater risk than in the normal course of their treatment.

Some of the other reasons given by Professor Helsinki are more complex, however, and require a more detailed consideration of the involvement of children. In particular, the case raises the issue of the status of consent in relation to children in research. Although ethical concerns for obtaining consent where possible from children should be similar to adults (in line with the child's capacity to consent), a number of child-specific ethical concerns also arise. In general, it is worth remembering that when dealing with children in research, the following factors can influence the consent process markedly:

- a greater likelihood of deference and the existence of a power imbalance, making voluntariness an issue;
- the need to communicate in a manner comprehensible to the participants (for example, by providing child-oriented information sheets);
- the need to check comprehension, especially understanding the significance of longer-term risks;
- a child's varying level of understanding particularly over the course of a lengthy study.

Therefore, although obtaining consent from children in research can be challenging, there is still an expectation that provisions are made for it wherever possible. So, for the research to be ethical there would have to be good grounds for foregoing the consent process. Many of the reasons for allowing research to proceed without the valid consent of the subjects that were discussed in Chapter 2 are also applicable in this case as well.

Two major factors need consideration:

- the range of gradations of competence;
- the relationship of third parties, such as parents, in providing consent to participate in research on behalf of the child.

The first of these factors is illustrative of why not all children should be treated as having identical levels of autonomy even if they are the same age. Children tend to acquire competence gradually and at different rates so that some of the children in the study will be mature enough to meet the criteria for competence while others will not. Also, some of the child populations that research will seek to involve may, by virtue of their extensive experience of medical interventions and treatments for chronic or severe acute conditions, exhibit much greater levels of competence than would generally be associated with their age group. ([20]) Even where, as minors, competent children are not *legally* allowed to give consent to participate without the additional consent of a parent or guardian, ([21]) it is still an *ethical* requirement to ensure consent is obtained wherever possible. This means that all children would have to be assessed for their levels of competence before being recruited into a research trial. Even given that, in this case, Professor Helsinki has indicated that most people with the behavioural disorder being studied lack the capacity to consent, this does not necessarily mean that *all* those in the research trial will be incompetent. Furthermore, even where a subject is not competent to give fully valid consent, just as in the case of adults, other elements of consent, such as information provision, are still relevant. Hence (if this can be done without jeopardising the study methodologically) children should be informed of the risks and benefits of the research in a manner suitable to their capacity and maturity and, where possible, their assent sought.

Seeking the assent of a child to participate in research is a way of respecting their developing autonomy, as well as being a useful means of indicating whether a child will not cooperate with the research because of any fears the child may have. If fears do exist and can be uncovered as part of the process of explaining and exploring a research opportunity with a child, those fears can then be openly addressed and dealt with. Requiring assent therefore acts as another means to protecting the interests of the child.

However, many significant decisions involving children are often thought, with good reason, *also* to require the consent of a suitable third party. This is usually a parent or guardian of the child, who already has a number of rights and responsibilities towards the child. The less mature a child is in terms of their autonomy, the more important it is that those charged with safeguarding their best interests have the opportunity to do so. By not seeking the consent of – or even informing – the parents of the children about the research, the concern is raised that Professor Helsinki is disregarding the protective function that requiring parental consent has. He may also be violating the parents' moral rights regarding what happens to their own children.

20. See, for instance, Priscilla Alderson, Katy Sutcliffe and Katherine Curtis, "Children's Competence to Consent to Medical Treatment", *Hastings Centre Report* 36, no. 6: 25-34.
21. The legal requirements will vary depending upon the country in which the research is taking place.

However, if Professor Helsinki were to inform all parties – both children and parents – that research is taking place, not only would he place the results of the research in jeopardy by potentially altering the behaviour of the subjects and those who have a strong influence upon them, he may also encounter the following difficult ethical issue. A child, although not fully autonomous, who is mature enough to be able to comprehend the nature of the research and to express an opinion might indicate strong *dissent* to participation in the trial. Moreover, this might be the case even where the child's parents consent to the child's participation.

Cases in which parents support their child's enrolment in a piece of research that the child is unwilling to be involved in raise general issues about parental authority. In the discussion of Case Study 3.2, it was suggested that any expressions of dissent from participants ought to be taken seriously and result in the cessation of observation. But it is not at all uncommon for parents to cajole their children into activities, including research participation, from which they dissent. Not only is this practice widespread, but in some cases, it might be viewed as an essential part of the parental role. Parents who routinely accepted a small child's refusal to brush her teeth, for example, would generally be considered to be in breach of their duty of care. It is in a child's best interests to maintain the health of her teeth, even if she dissents from this view. Although there is a desire, where possible, to respect the wishes of all vulnerable subjects who are not fully autonomous, it is clear that the best interests of a child are not always served by simple capitulation to their dissent.

Can participation in research ever be so strongly in the interests of children that their dissent to participate should be overridden? In some instances of therapeutic research in which a potentially useful treatment is unavailable outside the trial and conventional treatment options are limited and/or ineffective, this may be the case. What about research that is not characterised by a likelihood of therapeutic benefit for the participants? It may be in the broader interests of children to learn what it is to contribute to an important project that one does not benefit from directly, even if this is at some cost, in terms of discomfort or inconvenience, to oneself. Parents may be keen to expose their children to such activity, even if it involves some overriding of their stated preferences. Should we accept that parents may sometimes have to coax, bribe or even force their children into participation in research? Can this be justified by reference to the children's best interests?

It is disputable whether children do have an interest in contributing to projects that do not benefit them directly, and, if they do, whether participating in research that they dissent from is an ethically legitimate way of advancing this interest. Given this, it is advisable that researchers defer to some extent to parents (or those with decision-making authority) to weigh up the interests of their children. Some forms of parental coaxing and encouragement are morally acceptable, especially when the children involved are young and not able to fully understand and evaluate the reasons in favour of participation. As children's ability to understand and evaluate this information increases, so does the moral weight that attaches to their assent and dissent. Thus parental coaxing and encouragement become more morally problematic when directed at a child who exhibits reasonably high levels of understanding.

If the only potential advancement of a child's interests that a research proposal offers relates to social interests in contributing to valuable projects, it will be particularly important that the risks associated with research participation are limited to 'no more than minimal' levels. If children express significant levels of distress during participation, it may be appropriate for their participation to be suspended, even if parents do not request this. It is always preferable to obtain assent from participants, and research involving children will typically require careful and ongoing attempts to secure the assent of children as well as the valid consent of someone with parental authority.

How do these thoughts play out in relation to Case Study 3.3? One of the reasons that Professor Helsinki cites for not seeking consent or assent for inclusion in the research is that consent or assent from either parents or children is unlikely to be forthcoming. Furthermore, he says that knowledge of inclusion in research (if not inclusion itself) would be likely to be against the interests of the participants, due to the tendency

of people with RBDC to experience paranoia and fear of observation. The difficulty that Professor Helsinki predicts in recruiting to the trial under conditions of full disclosure and consent reflects the fact that participation in this research is likely to be against participant's interests, if they are aware of it. The potential for harm to the participant and the destruction of trust that discovery of the research would involve are not, in this case, offset by benefits to the participant. Other potential benefits that may accrue from the research are not identifiable or certain enough to justify overriding the interests of the participants. Parental consent for participation in this trial appears to be a moral requirement, and given the slim chances that the research will serve the interests of the child, proceeding without the assent of minor participants would also be highly morally problematic.

There will also be cases of research involving children that raise the issue of whether the consent of a competent child by itself is sufficient to allow them to participate in the research or whether such consent always needs to be supplemented by the consent of the parent or legal guardian. One situation where this might arise is where the revealing of the research to third parties, such as parents, could exacerbate the potential harms and risks that a child subject might face. This may be the case, for example, in research into the sexual attitudes of teenage children. If participants, although able to understand the research and able to express an opinion, are not deemed able to provide valid consent by themselves solely on the grounds that they are legal minors, the parent or guardian's consent would have to be sought. But revealing the nature of the research to these third parties may be harmful if it reveals personal facts about the child's behaviour that they would not otherwise reveal to their parents. Here, the child's vulnerability to subsequent harms would be potentially greater if confidentiality was breached by seeking third party consent. This means there is an important ethical question as to whether such research may ever proceed. The two central ethical concerns of seeking consent and protecting the welfare of the subject seem to be in direct conflict. As research into such topics can be extremely important, exceptions are often made for more mature children who do not wish to involve their parents, provided they have sufficient maturity to understand the nature, purpose and likely outcome of the proposed research, and so long as the research is seen as directly beneficial to them or not deemed harmful.

Safeguarding children's welfare in research

Question 4 asks whether any additional safeguards are needed for the young research subjects. We have already considered the role of assent/dissent and parental decision-making in protecting the welfare of children.

In all cases of research involving vulnerable subjects, both adults and children, matters of privacy, anonymity and confidentiality are likely to be particularly important and sensitive. Although these issues are of general importance in research ethics, as will be discussed in more detail in Chapter 4, they take on a special importance when dealing with vulnerable subjects. If subjects are unable to protect their own interests adequately in the controlled environment of the research setting, then the possibility of the dissemination of information relating to them that might extend beyond the research context can have an even greater potential to cause harm.

Confidentiality is important and information-sharing should be proportionate to the risk of harm. However, the primary concern is still the safety of children and young people. Sometimes research can reveal facts about a child that would not have been known previously. Where reasonable concerns arise in the course of research that children are at risk of abuse or neglect, then an appropriate person or authority must be informed promptly when that is in the child's best interests.

In all cases of vulnerable subjects, safeguards to minimise any inconvenience, intrusion, embarrassment, coercion or distress should be written into the research protocol. In addition to these general safeguards, when dealing with children in research, additional measures are advisable to make allowance for their particular needs.

It is not only the welfare of the subjects that needs to be taken into account. The status of the researcher can also be an issue, both in terms of the child's needs and the protection of the researcher themselves. An example of concern for the child's needs would be to consider the sex of the interviewer carrying out the research in appropriate cases, such as research involving children who have been abused or suffered neglect at the hands of either men or women. An example of protecting the researchers themselves would be to ensure that interviewing of children is either undertaken by two researchers or in areas where the researcher and child are not entirely alone, to protect the researcher from false accusations as well as the child from inappropriate behaviour by the researcher.

Further issues

This chapter has focused on only a small number of cases of research involving vulnerable people and has not sought to cover all possible kinds of vulnerability. Vulnerability can be generated by a wide variety of factors including physical or mental disability, age (old or young), membership of a discriminated-against group, a relative lack of control over one's choices (as experienced, for instance, in the context of imprisonment) or being a victim of crime. It can also arise in cases where the power imbalance between researchers (or those encouraging the research) and the subjects is very great. In many of these cases, the general ethical concerns relating to vulnerability will be applicable. However, it is worth briefly discussing a few additional concerns that are raised by particular types of research on the vulnerable.

One important group of non-competent subjects (as seen in Case Study 1.1, Testing of artificial blood product) comprises patients requiring emergency treatment, particularly when such patients are unconscious or temporarily mentally incapacitated (for example, following a road traffic accident). The requirement to engage in research to improve emergency treatment is extremely compelling. However, these unconscious patients are extremely vulnerable (both by virtue of their inability to resist research and treatment, and their need of urgent intervention). Where emergency treatment is required, the very act of informing people about the research and asking for their agreement (even where this is possible) to participate could place people in danger by delaying treatment. Where the aim of the trial is therapeutic and the subjects stand to gain a great deal, their entry into such research trials appears to be both in their best interests and the interests of society at large. As consent is not possible because of the nature of the research, provided subjects are receiving treatment that is in their best interests then this kind of research (with appropriate hospital and research ethics committee approval) may be ethically acceptable.([22])

A final group for consideration consists of research subjects who are vulnerable because they are engaged in some form of illegal activity, where the purpose of the research itself is to investigate the illegal activity in question. This research could cover areas such as drug addiction, illegal immigration and prostitution. A better understanding of these sorts of issues can be extremely beneficial to society in terms of prevention and safety, as well as leading to improved services, conditions, and treatment of the subjects. However, it also raises welfare concerns for both subjects and researchers.

While confidentiality is important in research ethics and should normally be maintained, researchers need to be aware of their legal standing in relation to discovering or witnessing illegal activity. For, depending upon the specific laws of the country in question, the researcher may be required to reveal information they have gathered to a court if ordered to do so. Also (again depending on the relevant national laws) discovery of illegal activity that places a third party at risk of harm may place a legal duty upon the researcher to inform the authorities. Hence, being a purely impartial observer may not always be possible for the researcher. Should, for example, the case of an asylum seeker be officially

22. Although subjects should still be informed afterwards when they have recovered, in line with the requirements of non-consensual research discussed in Chapter 2.

investigated, researchers may find themselves having to testify against a subject who revealed their illegal immigration status to the researcher in good faith to assist with the research. The impact that simply carrying out research in these areas may have on individual subjects should be carefully scrutinised before the research takes place in order to minimise risks of these kinds, and research subjects should not be allowed to form (or persist with) the belief that strict confidentiality is in place unless the researcher is certain that this really can be maintained.

It should also be considered to what extent research into illegal activity encourages the illegal activity itself or places the researcher or the subject at risk of harm. For example, research might exacerbate an illegal activity if the researcher offered incentives, particularly financial inducements, to subjects. This may well lead to an increase in that activity in order to gain further incentives. Furthermore, the act of engaging with criminal activity and of recruiting subjects may itself place both the researcher and subjects in danger if, for example, the researcher is seen to be a potential informer to the authorities. Organised crime in areas such as prostitution (for example) could make this a real risk if something such as the health of sex workers was being researched.

Further reading

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Chapter 4 **Privacy and confidentiality**

Learning outcomes

In this chapter you will develop an understanding of the nature of privacy and confidentiality and their role in research ethics. Specifically, you will gain the following:

- An understanding of the definition of both concepts that will allow you to grasp what privacy is and what confidentiality is.
- An appreciation of the ethical importance of privacy and confidentiality in research.
- An awareness of the main challenges to maintaining privacy and confidentiality in research, including those imposed by methodological demands such as covert observation.
- An increased knowledge of how ethical issues relating to privacy and confidentiality may arise in research.
- An understanding of additional areas of concern in research where matters of privacy and confidentiality may be ethical issues, such as the use of databases and research relating to the deceased.
- An awareness of how issues of privacy and confidentiality relate to other concepts and issues in research ethics.

Introduction

This chapter explores two important and related issues in research ethics: privacy and confidentiality. These are often seen in legal terms, with researchers being subject to constraints under various pieces of national and international legislation, ([1]) as well as research ethics guidelines and professional codes. However, there are good reasons to take privacy and confidentiality seriously, independently of their legal status, and in some cases researchers may have ethical duties that go beyond what is legally required. In order to understand how we can make ethical judgements about privacy and confidentiality concerns when they arise in research, this chapter will draw on the ethical theories and principles covered in the previous chapters.

The first task will be to consider the definitions of these two key concepts and the reasons for their ethical significance. Subsequent discussion will relate to two case studies. The first is primarily concerned with privacy, in the context of observational research in a hospital Accident and Emergency unit. The second is about genetic research and also raises issues about both privacy but is primarily designed to focus attention on issues of confidentiality. Discussion of these case studies will consider the challenges to maintaining privacy and confidentiality in research, strategies for reconciling respect for privacy and confidentiality with the needs of research, and whether it is ever justified to override privacy and confidentiality because of other important considerations in research.

What are privacy and confidentiality?

Privacy and confidentiality are closely related, with privacy historically being considered the more basic interest. ([2]) Although, as we shall see, confidentiality is distinguished from privacy and has its own ethical justifications, its value stems primarily from the relation it has to privacy. This means that a good understanding of the nature of privacy is important not only in itself but also in order to adequately distinguish and understand confidentiality. There are, however, divergent views about what privacy is, its scope, and the circumstances under which it should be protected. ([3])

Privacy

The basic distinction between public actions for which one can be held accountable to society, and private actions where one is accountable only to oneself, has been maintained in liberal ethical and political thought as a fundamental right. The grounding for such a right is often based on the view that it promotes individual welfare and that society should only intervene in an individual's life in order to protect other people from harm. ([4]) This early liberal conception has formed the basis of much subsequent discussion, lending itself to a predominant view that privacy is based on some sort of 'right to be let alone', ([5]) so that privacy protection is frequently seen as a way of drawing a line defining how far society or government can intrude into a person's affairs. However, the extent of this 'right to be let alone', in terms of the various aspects of people's lives that it

1. For example, the Oveido Convention, Article 10, contains various protocols in relation to privacy and biomedical research. See: *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (Oviedo, 4.IV.1997). http://conventions.coe.int/Treaty/EN/Treaties/Html/164.htm
2. The classic early reference to privacy as being importantly demarked from other areas of life is found in Aristotle's *Politics*, c. 350 BCE. http://classics.mit.edu/Aristotle/politics.html
3. For example, the difficulty of defining privacy is explicitly stated at the outset in a number of key modern discussions, such as James Michael, *Privacy and Human Rights* (Dartmouth: UNESCO Publishing, 1994) and the Electronic Privacy Information Center (EPIC) and Privacy International, *Privacy and Human Rights Report 2006* (2007). http://www.worldlii.org/int/journals/EPICPrivHR/2006/
4. This view is often attributed to the great nineteenth century liberal philosopher John Stuart Mill in his essay *On Liberty*. (London: Longman, Roberts & Green, 1869; bartleby.com, 1999). http://www.bartleby.com/130/
5. This specific turn of phrase was used in the famous paper by Samuel Warren and Louis Brandeis, "The Right to Privacy", *Harvard Law Review* 4 (1890): 193-220.

applies to and the grounds that can justify third parties, such as government or media, in encroaching into these aspects, is highly contentious and can vary markedly across societies and cultures.

Another, more contemporary approach to the definition of privacy is that it is primarily about the protection of personal information. This view of privacy gives substantial weight to modern concerns such as data protection, whereby privacy is seen not only as preventing others from gaining information about ourselves that we would not wish them to have, but also as supporting a general desire to maintain control over information about ourselves that is stored elsewhere, such as on computer files. ([6])

Alongside these ethical and political debates about the nature of privacy there have also been attempts to formalise the concept and to create general agreement as to its nature and importance so that it can function as a legal concept. In this regard, the modern privacy benchmark at an international level can be found in the 1948 *Universal Declaration of Human Rights*, which specifically protects territorial and communications privacy. Article 12 states:

> *No one should be subjected to arbitrary interference with his privacy, family, home or correspondence, nor to attacks on his honour or reputation. Everyone has the right to the protection of the law against such interferences or attacks.* ([7])

This right has been further enshrined in the *European Convention on Human Rights,* Article 8:

1. Everybody has the right to respect for his private and family life, his home and his correspondence.
2. There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others. ([8])

However, although such documents serve as a useful reference point, identifying the areas of life to which the concept of privacy is typically applied (and in the case of the *European Convention* the kinds of consideration that might justify overriding the right to privacy) they do not fully define either the scope of the right or the kinds of intrusion that would constitute a violation of the right. The difficulty in constructing a comprehensive definition of privacy led the Calcutt Privacy Committee in the United Kingdom to report that: "nowhere have we found a wholly satisfactory statutory definition of privacy". The committee's own definition of privacy as "The right of the individual to be protected against intrusion into his personal life or affairs, or those of his family, by direct physical means or by publication of information" ([9]) acknowledges that privacy can relate both to physical interference and to the exposure of personal information, but leaves open the question of how precisely we might understand these. Given the difficulty of pinning down a precise definition of privacy that will be entirely uncontentious, it will be helpful instead to think of privacy as relating to a cluster of interests, allowing the following form of definition.

Privacy is the protection of:

- control over information about oneself;
- control over access to oneself, both physical and mental; and

6. This approach of control over information as primary to privacy has been argued for by e.g. William Parent, "Privacy, Morality and the Law", *Philosophy and Public Affairs* 12 (1983): 269-88 and as the central defining feature of privacy by James Rachels, "Why Privacy Is Important", *Philosophy and Public Affairs* 4, no. 4 (1975): 323-33.
7. United Nations, *The Universal Declaration of Human Rights* (1948). http://www.un.org/Overview/rights.html
8. *Convention for the Protection of Human Rights and Fundamental Freedoms* (Rome, 4.XI.1950). http://conventions.coe.int/Treaty/en/Treaties/Html/005.htm
9. *Report of the Committee on Privacy and Related Matters,* Chairman David Calcutt QC, 1990, Cmnd. 1102, London: HMSO, at 7.

- control over one's ability to make important decisions about family and lifestyle in order to be self expressive and to develop varied relationships. ([10])

These three elements are widely considered to be the most important aspects of privacy because of the way that breaches in these areas may affect us. Threats of information leaks, threats to our control over our bodies, and threats to our ability to make our own choices about our lifestyles and activities all make us vulnerable and fearful of being taken advantage of by others.

As well as these concerns about the effects that breaches of privacy may have on human welfare, the requirement to protect privacy also has a basis in principle-based and rights-based ethical theories. By protecting our control over these aspects of our lives, privacy provides the basis of certain fundamental aspects of autonomy and human dignity, for example, freedom from scrutiny, prejudice, pressure to conform, exploitation, and the judgement of others all help an individual to live their life freely in a manner of their own choosing.

There is more to understanding privacy than just having a definition. It is also necessary to consider what the scope of privacy is and to what areas of life can a right to privacy be extended. Amongst some of the more difficult assessments would be:

(i) whether appearing in public implies some forfeiture of privacy;
(ii) to what extent intrusion into the domestic or other environments such as the workplace might undermine privacy;
(iii) whether facts part of a 'public record' could still be private, given that the way in which these facts are disclosed could lead to embarrassment or harm;
(iv) whether a significant lapse of time affects the privacy of information;
(v) whether personal decisions about lifestyle and family, including birth control, marriage, domestic habits or practices, etc. are privacy issues.

For the researcher, the answers to questions such as these may determine whether their attempts to gather and collate information about research subjects constitute invasions of privacy.

As well as these questions about the scope of the concept of privacy we will also need to consider how strong the duty to protect privacy should be, and when, if at all, it may be overridden by pressing concerns of research.

Confidentiality

The concept of confidentiality is closely related to that of privacy, and in particular to the aspect of privacy concerning the protection of personal information. A basic definition of confidentiality can be given as follows.

A owes a *(prima facie)* duty of confidentiality to B when:

- B *(the subject)* discloses to A *(the researcher)* information which B regards as confidential or secret; and
- A undertakes (implicitly or explicitly) not to reveal this information to anyone who does not already possess it.

Because the duty of confidentiality rests on an *undertaking* (by A not to reveal B's secrets), respecting confidentiality can be considered as a kind of promise-keeping or contract. However, in many situations (particularly those involving interactions between professionals and their clients) there is a default assumption that the information provided by an individual will be treated as confidential and, as such, the researcher would need explicitly to 'opt out' of their presumed undertaking in advance of receiving the information in order not to be bound by a duty of confidentiality.

Confidentiality is a duty that arises when someone has been granted access to information that would

10. This kind of approach to privacy as being driven by a combination of factors is taken by Judith DeCew, *In Pursuit of Privacy: Law, Ethics, and the Rise of Technology* (Ithaca: Cornell University Press, 1997). See also Bernard Gert, Charles Culver, & K. Danner Clouser, *Bioethics: a return to fundamentals* (Oxford: Oxford University Press, 1997), Chapter 8.

otherwise be kept secret. In such circumstances maintaining confidentiality protects the subject's interest in maintaining control over their personal information. A breach of confidentiality will therefore also be a violation of this informational aspect of privacy. However, not every invasion of privacy is a breach of confidentiality, and there are some important differences between confidentiality and privacy that follow from the above definition:

(i) Confidentiality is related purely to information in a way that privacy is not. Only information can be confidential, but places (e.g. bedrooms) can be private.
(ii) The duty of confidentiality arises only within the context of special relationships or agreements. We only have duties of confidentiality where information has been given under an agreement or understanding that it will not be further disclosed without permission. This is not true of the duty to respect privacy. The duty to respect others' privacy is a more general duty than that of confidentiality because it extends to everyone. Ordinary members of the public who are unknown to me have a duty to respect my privacy but typically have no duty of confidentiality towards me.
(iii) Respect for privacy places constraints on the ways in which researchers (and others) acquire information about their subjects, whereas confidentiality is about how they may communicate information that they already have. Covert video surveillance is an example of a practice that arguably breaches privacy (although perhaps justifiably in some cases) but not confidentiality. Research that involves accessing existing confidential data from records may breach the record owner's duty of confidentiality to the provider of the information, and the user of the information may commit a breach of privacy if the information is of a personal nature.

As with privacy, there may be circumstances where the duty of confidentiality is overridden by other considerations. It is for this reason that confidentiality is characterised as a *prima facie* rather than an absolute duty in the definition above. The most common and widely accepted cases for revealing confidential information occur where the researcher acquires information that he or she has a legal obligation to disclose. These are often situations where there is a risk of serious harm to others, such as through criminal activity or contagious disease. There may also be cases not covered by legislation where there is still a strong ethical obligation to reveal information to protect others – or the subject – from harm. Judging these situations where there is a strong reason for a researcher to reveal information but not a strict legal obligation to do so can be extremely challenging, depending on the balance of benefits and harms as well as principles such as promise-keeping and respect for autonomy. Where possible the circumstances – when and to whom information will be disclosed – should be identified in advance and included in the arrangements to which participants consent.

Another factor is that because confidentiality is about respecting the wishes of the person who provides or grants access to their personal information, it really covers only information that a research subject *wishes* to be kept secret. Hence trivial and everyday information may not be subject to confidentiality requirements. Unfortunately, it is an extremely difficult task for any researcher to determine what information is trivial or likely to be damaging if revealed. The default position should therefore be that all information presented in the research setting is to be treated as if it were subject to the duty of confidentiality.

There is a further issue about the identity of the recipient of the information and the purposes for which it is given. Information may be given to an institution (such as a hospital), rather than to a specific individual, which would mean there would be no breach of confidentiality if the information were disseminated within the institution. However, if recipients of the information intend to disseminate it in this way then it is important that this is made clear to those supplying the information; otherwise a patient might, for example, reveal information that they *expect* only to be revealed to their health care team, not the whole hospital, or they might expect the information to be used only for therapeutic purposes and not for research, or for one specific research purpose and not for subsequent research projects. In these cases, and in the absence of clear information to the contrary, the expectations of those supplying the information would define the terms on

which the information was provided and hence determine the recipients' moral obligations concerning its dissemination.

Given the array of different factors that can give rise to concerns of privacy and confidentiality, we can now look at how they might arise in practical cases.

Case Study 4.1
Observational research in an Accident and Emergency Department

A psychology researcher wishes to investigate the ways in which individuals try to attract attention from authority figures. The researcher proposes to observe the waiting area in a city hospital Accident and Emergency (A & E) Department and record the actions of those who attend seeking treatment. The time that people first enter the reception area will be noted, as will the times at which people see relevant hospital employees (medical receptionist, triage nurse, attending doctor). Any attempts to bring attention to themselves in order to be seen before being officially called will be noted, as will the nature and outcome of the action. No attempt will be made to obtain individuals' consent to participate in this research project, as it is believed that the knowledge that they are being observed might alter their behaviour and lead to unrepresentative results. As it is only types of behaviour and people's responses to it that are under investigation, there will be no attempt to link behaviour to identifiable individuals and hence the research results will be entirely anonymous. Permission has been granted from the hospital in question to carry out the research, although the individual staff members have not been asked for their consent to participate. It is hoped that the information gathered will not only have implications for behavioural psychology but could also be used to train hospital staff to deal with potentially inflammatory situations in the A & E Department.

Questions

1. What are the main benefits and ethical problems that this research raises?
2. Does the research place anyone at risk?
3. Is it an invasion of privacy to observe the injured or ill whilst waiting for treatment in an A & E waiting room?
4. Do the methodological requirements of this observational study outweigh any concerns about privacy and the fact that subjects have not consented to be observed?
5. Does anonymous recording of data allay any concerns you may have about respect for privacy?
6. Should this research be allowed to proceed in its present form? If not, how might it be modified to make it more acceptable?

Privacy and the research environment

The research outlined in Case Study 4.1 draws attention to some of the major tensions that arise in research between the collation of information necessary for research and the maintenance of privacy for research subjects. In order to evaluate such a proposal, consideration should be given to the balance of benefits and harms that might arise and whether any non-consequentialist norms, such as respect for autonomy

or dignity, are violated. In this case, the methodology, the environment, and the status of the subjects all raise ethical issues that have a particular relevance to privacy concerns.

Questions 1 and 2 focus attention on the benefits and risks of the research. Its aims, although not specified in detail, involve both advancement of the academic field of behavioural psychology and direct benefits to staff and patients in hospital emergency departments by contributing to better means of dealing with difficult situations. These are significant benefits, but they need to be considered in the light of any ethical problems raised by the research. As the research is to be conducted by means of passive observation, the risk of direct harm to participants seems low. The main ethical concerns about this research are likely to be about the possible breach of privacy and the harms that might result from such a breach.

According to the account given in the previous section, privacy involves safeguarding the right of individuals to maintain control over physical and mental access to themselves and over information about themselves. This links the idea of privacy to the cluster of interests associated with autonomy and human dignity that it is designed to protect, and enables us to assess potential breaches of privacy by considering whether these interests are likely to be damaged.

Observing the activities of anyone for research purposes has the potential to invade their privacy. However, ascertaining whether there is actually a breach of privacy in this case is quite challenging. A key issue, highlighted by Question 3, is the environment in which the research is carried out. Arguably, people have less entitlement to privacy in a place such as a hospital A & E department than they would in their own homes. We therefore need to consider to what extent appearing in public places limits the individual's right to privacy, and whether the hospital A & E department constitutes a public place in the relevant sense.

The first of these questions has already been highlighted as a difficult issue in the application of the concept of privacy. It would be highly unrealistic for anyone to expect that they could go unobserved in the course of their everyday actions in public places, such as the streets, shops, and so forth. However, there are still elements of privacy that do remain intact even in public places, such as control over physical access to one's self, with commonly respected conventions such as allowing everyone a certain amount of 'personal space' around them that others do not move into uninvited being a widely held expectation. Certain public environments may change the scope and nature of this personal space, as anyone using crowded public transportation will be aware, although even here there are strongly expected norms of behaviour and restraint. However, the passive observation of someone's activity in a public place is unlikely to fall within the scope of privacy, as this is not something that one could reasonably expect to control.

The question of whether an A & E department is a public place in the relevant sense is more complicated, as not every environment that the public has access to is one where there is no reasonable expectation of control over information or access to one's self. For example, changing rooms in public facilities may be an example of a place where stronger elements of privacy are in force, albeit not as strongly as in an entirely private place such as one's home (there are, after all, other members of the public present who may happen to observe you during the course of their normal activity). In such a situation, the observing and recording of information that could be revealed to other people not present could be considered harmful, offensive or embarrassing to an individual. Feelings of vulnerability or being taken advantage of can easily arise in such situations. This is why greater limits and restrictions on access to information about people in such places is expected, such as a ban on filming in the area, even though it would be impossible to prevent other members of the public from observing you during the course of their normal activity. It is this sort of environment – one that the public has access to but which also has stronger expectations of privacy – which one can consider an A & E Department to be.

As hospital departments are not places that people typically make an unconstrained choice to visit, but do so because they are seeking medical aid, the expectation that one completely forfeits a right to privacy in

such an environment cannot be as strong as the expectation for an uncontroversially public place. Of course, it is certainly true that other people attending or working in the A & E department will be able to freely observe third parties whilst they wait for treatment, just as in any other public environment. The more difficult question to answer in this case is whether the presence of a researcher observing the behaviour of patients constitutes an unwarranted intrusion into people's private lives.

A way of explaining the difference between being observed by other patients or staff and being observed by a researcher is by appeal to the type of observation taking place. The observation by other patients can be considered incidental, meaning they are not there with the aim of observing other emergency patients but their inevitable presence does means that they cannot avoid observing behaviour. The expectation of anyone going to A & E will therefore include this form of incidental observation taking place under these circumstances. Although individuals may prefer not to be seen in this situation, where they may be in states of distress or in states that are publicly embarrassing, it is impossible to prevent on a practical level and unlikely to have any implications for the individual, particularly as all involved are in a similar position in seeking medical attention.

The observation by a researcher can be treated differently as it is something more than merely incidental. This form of observation only arises as a result of the research taking place with a specific purpose to collate information about the behaviour of individuals. However, whether this makes a substantial ethical difference in a way that violates those areas that privacy is designed to protect is less clear, as there are still many similarities to the incidental observation of other patients. For example, while there is no opportunity to opt out of being observed by the researchers (except by choosing to forego urgent medical treatment), it is also the case that one cannot avoid being observed by the other patients. Moreover, the observation by a researcher does not, arguably, change the nature of care that anyone will receive, so there are no immediate negative consequences of their presence.

There may be scope to ethically object to observation by researchers on non-consequentialist grounds. The importance people place on not allowing others to access intimate or important aspects of their lives is also a central part of privacy concerns, and granting access to people whose sole purpose is to observe these aspects of your life is something very different to casual observation. Such intense scrutiny can impact on one's freedom, make one feel threatened and place pressure on one to act in certain ways. Those with strong liberal inclinations therefore might well see this sort of observation as a breach of their privacy.

Alternatively, the ethical concerns in this case could be focused on the recording of information. The privacy concern is that the subject has no control over how the record of his or her actions is used, contrary to the interest in controlling information about oneself. This view, although plausible, is not uncontentious as the counter-argument can be put forward that there is nothing to prevent anyone in the A & E environment from memorising behaviour of others and making a record of their observations afterwards or even writing down observations at the time. Greater ethical concern might arise if observations were recorded through a medium such as video, where patients would be easily identifiable. Hence, the concern that arises in this case is the potential to link an individual's identity to particular observed behaviour in a specific environment.

Making such a link would place subjects at much greater risk of experiencing harm or negative consequences as a result of any link being made public, in cases where the research revealed potentially negative behaviour traits or even basic facts about their health and welfare. It could also be seen as an affront to people's dignity to be shown in states of distress and even seen as a failure to respect their autonomous wishes not to be part of any research that involves a connection to issues with their personal health. Ensuring anonymity of those observed therefore appears to be an important consideration if observational research is to respect privacy. The use and limitations of anonymisation will be addressed further in the discussion of confidentiality following Case Study 4.2.

Are there grounds for breaching privacy?

Question 4 invites us to consider whether the methodological requirements and benefits of the research in Case Study 4.1 might outweigh concerns about privacy. The basic means of ensuring that potentially privacy-breaching methods of data collection are ethically acceptable is to obtain the consent of those involved. In this way, subjects will stay in control of access to and information about themselves, by choosing whether to agree to the terms stipulated in the research protocol. However, as discussed in Chapter 2, obtaining consent is not always possible, particularly if – as in this case – there are methodological reasons why seeking consent would alter the results of the study. In such cases, invasion of privacy can often be one of the most significant ethical concerns. Where we draw the line between maintaining privacy and allowing it to be overridden by important concerns of research can depend upon how strong we consider our obligation to protect privacy to be, and this in turn may depend on the nature of the invasion of privacy and the measures that can be put in place to minimise its impact.

One of the most important justifications for breaching privacy is that the research cannot be carried out any other way. It might require, for example, entering a clearly private environment, such as the subject's home, in order to obtain information from them. Alternatively, there may be cases where breach of privacy is less clearly established, such as in the current case where people are observed in the A & E waiting area. What distinguishes such different cases is how our obligation to protect and maintain privacy would change depending upon the environment even if the methodological justification was the same in both cases. Observing someone in their private home for research purposes would be unjustified without their permission, regardless of the methodological requirements of the research, because of the very strong interests – supported by legal prohibitions and social conventions – we have in maintaining privacy in this environment. The same would be true of other intimate areas, such as in a medical treatment room. These are areas where the right to privacy is most strongly supported on ethical grounds. The stress, embarrassment and potential harms resulting from the revelation of intimate details gathered in such environments are potentially quite severe, as are violations of personal dignity and respect for autonomy. So even where there is a methodological reason for breaching privacy to access information about people, this is unlikely to be sufficient to justify it in such cases without the consent of the individuals concerned.

A greater ethical challenge comes from research such as that in Case Study 4.1, where the environment within which observation takes place is neither obviously a public place nor clearly a private place. In these settings, the obligation to respect privacy may not be as strong, given the underlying expectation that other people will be able to observe you, and this can influence whether we take a potential invasion of privacy to be ethically justified. Although the justification for observing without consent is presented as methodological, this sort of claim needs to be closely scrutinised in cases where access to potentially sensitive information about people might be obtained. It is important to consider whether the breach of privacy really is necessary for a methodologically sound study, or whether it would be possible to obtain consent for the necessary observation. In this case, a strong justification would have to be given as to why even the most basic attempts to inform the subjects and gain their consent would render the study ineffective.

As well as considering whether the absence of consent really is necessary for the study to succeed, it is necessary to consider the value of the proposed research. One approach would be to compare the value of the research with the amount of harm likely to result from a possible breach of privacy. This approach would appeal to consequentialists who, rather than seeing privacy as a basic *(prima facie)* principle, would see its ethical importance as relating directly to the level of harmful consequences that any breach might have, balanced against any potential benefits. The relevant kinds of consequence would depend upon the nature of the breach and of any subsequent information gathered by invading the privacy, as well as the attitudes of the subjects upon discovering the breach had taken place, together with any additional, subsequent harms that arise from failing to safeguard control over important aspects of one's life. A consequentialist might have no issues with breach of privacy if the subjects never

found out their privacy had been invaded and no harmful consequences resulted from the collection and dissemination of the information relating to them. Those who take privacy to be a fundamental right rather than a simple filter for consequences may, by contrast, still take potential breaches of privacy very seriously, even if they are likely to have no or limited harmful consequences.

One way of dealing with concerns about the consequences that breach of privacy may have in cases of valuable research is to consider what steps might be taken to minimise the effects of the intrusion. It has already been noted that preserving the anonymity of the research subjects (as proposed in the case study) may be an important way of doing this. However, it should also be remembered that one of the reasons that privacy is considered important is that people have an interest in controlling information about themselves. Anonymisation may help protect other privacy-related interests but it will not help people feel as if they are controlling access to themselves and their lives.

If obtaining consent prior to the research is impossible, then it may be desirable for subjects to be informed afterwards. This may allow subjects to choose whether or not to be part of the study and to allow the observations relating to them to be included. Doing so will help to limit harmful consequences and allow subjects to regain some element of control over how information about them is used. However, it will not prevent breach of privacy, which will already have taken place, and the impact of revealing that an invasion of privacy has taken place should be taken into account when assessing whether or not to permit the research with or without such a debriefing. In some cases obtaining consent even after the observations have taken place may alter the results by introducing a bias into the study (for example if people exhibiting certain kinds of behaviour are disproportionately likely to refuse consent). Moreover, in certain cases such consent will be impossible, for example where people are likely to leave the area before they can be approached, or when dealing with people who are unable to give valid consent. This might be significant in the A & E case, where people's capacity to consent may be affected by serious medical conditions or the influence of drugs or alcohol.

An additional aspect of the privacy concerns in this case is the fact that none of the hospital staff in the A & E department have been asked for their consent to be observed in the research, although their employer has agreed it can go ahead. This raises a number of interesting ethical concerns. Firstly, the aim of the research is to observe not only the behaviour of patients seeking to gain the attention of the staff, but also the responses of the staff. This makes the staff members who deal with patients in the A & E waiting area very much part of the research, so it becomes an important question as to whether their consent should be sought either before or after the observational study takes place, in addition to that of their employers.

The researchers may well feel that seeking the consent of staff would have a similar effect on their behaviour to that which it would have on the patients who are being observed. If staff were informed that they were being observed then this may change their normal behaviour, giving inaccurate results. Moreover, any one member of staff refusing consent could have a significant impact on the research, as it might be impossible to avoid observing their behaviour while at the same time observing that of other people. Also, because it is their place of work, staff may feel they have no real alternative to consent unless provision to work elsewhere or at an alternative time was made by the hospital. Even this could prove to be a significant burden both to the hospital, which might need to provide additional staff cover, and to the individual whose work patterns would be disrupted.

A further issue that arises in relation to the position of the staff as research subjects is whether observation in the workplace counts as an invasion of privacy. What has to be determined is whether a workplace, particularly one to which the public has constant access, should be considered as a public place. Even if it were considered public, there still may be some legitimate privacy concerns. Scrutinising the routine actions and behaviour of staff in any workplace might well lead to feelings of unease amongst staff and inhibit interactions, workplace relationships, and quality of service. Moreover, if the research were to take place, before commencing the observation a policy would have to be agreed about the circumstances in which information would be disclosed to the employer or other

authorities should any wrongful or illegal activity be observed.

Observing members of staff without seeking their consent has advantages for the research, but also raises ethical concerns. These concerns might be reduced by adopting provisions similar to those proposed for members of the public. Observations can be recorded anonymously (although it should be noted that this may be less effective in the case of staff than with members of the public at preventing observations being linked with particular individuals, as there are likely to be fewer of them and their behaviours may be recognisable to colleagues or managers). Consent to the use of data may be obtained after the observation has taken place (with the same limitations as in the case of members of the public). In addition, it may be advisable in cases such as this to seek agreement from a representative of staff members. This would enable any concerns about the effects of the research on the workforce to be fed into the design of the study, including such things as how the observations will be reported, and under what circumstances observations of wrongdoing will be disclosed to the management.

Case study 4.2
Genetic research into susceptibility to respiratory disease in smoky environments

A research team is trying to understand the genetic basis of respiratory diseases such as asthma, lung cancer and emphysema, which are attributed to environmental factors. One area they are particularly keen to explore is whether the presence of a particular genetic trait significantly increases the chances of people developing such a respiratory disease when exposed to tobacco smoke.

Researchers intend to identify families (through a clinical referral from children seeking treatment for asthma) with a significant incidence of respiratory disease, in which several relatives have died from asthma or lung cancer in the past. What is crucial for the success of this study is obtaining a sufficient number of related individuals with or without the condition who consent to be evaluated and to have blood tested for the genetic trait. A further important component is the testing of children and other family members who do not themselves smoke but who live or were raised in an environment containing second-hand smoke.

Suitable families for the study are rare so the researchers propose to study them one at a time as they find them over a period of time. One family in question is large enough to potentially provide sufficient data for the study to be a success. It is suspected that those family members who possess the genetic trait under scrutiny will be more likely to develop a respiratory disease than family members who do not possess the gene but who were raised in a similarly smoky environment. The first indications that a respiratory disease has developed usually appear in childhood asthmatic conditions, although this may develop later in life.

Questions

1. What are the main benefits and ethical problems that this research proposal raises?
2. Is it ethical to take blood samples from affected children? What about from the unaffected adults and children?
3. Is it appropriate to withhold results from the family on the ground that this is only one small part of a study of a complex genetic condition? If not, to whom should they be disclosed?

Privacy and confidentiality

The research described in Case Study 4.2 aims to explore a possible link between a genetic trait and serious respiratory disease. This gives it the potential to make an important contribution to genetics and medicine, but is also an area that has the potential to cause great distress amongst the research subjects. The discovery of a genetic predisposition to develop a serious disease could have a major impact on a research subject's welfare. The potential for causing distress is increased by the fact that the research also relates to family environments, children (especially those at increased risk of disease as indicated by the referral process), and bereavement.

The potential for causing distress arises primarily as a result of the information that the research is likely to reveal. This gives rise to concerns about both privacy and confidentiality. The privacy concerns are slightly different from those raised by the previous case, which involved observation of people in a (special kind of) public place. Here, the privacy concerns relate largely to matters of family life, with potential intrusions into subjects' privacy arising as a result of the researchers' enquiries into family relationships, matters of personal lifestyle (e.g. smoking habits) and perhaps obtaining direct access into subjects' homes (e.g. in order to obtain or verify information about environmental smoke levels).

What stands out in this case, however, is the focus on information about individuals and families, both in terms of the nature of information that is gathered that relates to individual subjects' genetic predisposition to develop serious medical conditions, and in terms of the implications that genetic information may have for other related family members.

The importance of maintaining confidentiality

We saw in the introduction to this chapter that, since confidentiality is predominantly about respecting undertakings given (perhaps implicitly) to providers of information about how that information will be used or disclosed, the obligation to respect confidentiality is a species of promise-keeping. As with any form of promise-keeping, this involves acting in accordance with expectations that have been created in another person. Even in the absence of an explicit undertaking, providers of information may have reasonable expectations that their information will be kept confidential, which researchers, as recipients of that information, should respect. This point is particularly relevant in health care contexts where there is a convention, backed up by professional codes of practice, that information given to heath care professionals will be treated in confidence. If researchers do not intend to act in accordance with the likely assumptions of information providers they can make clear how they will use any information before it is disclosed to them, but this will give rise to another obligation: to keep to the terms of the new agreement that the subject has consented to.

The ethical importance of promise-keeping is generally considered to stem from the way in which breaking promises undermines the autonomy of the person to whom the promise has been made. In the case of breaches of confidentiality, there is a failure to respect autonomy because the information was divulged by the subject on the basis of an agreement about how it would be used, so to break that agreement would also be to ignore the autonomous wishes of the subject. Promise-breaking can also be criticised on consequentialist grounds as it is liable to cause harm to the person to whom a promise is broken, and is damaging to the social institutions of promising and trust on which many social interactions depend.

The issue of trust is not only an important ethical principle to maintain in itself but also has a further significance in relation to research. Researchers often need access to the kinds of information that people are reluctant to disclose. People may be willing to disclose such information under conditions of confidentiality, but are less likely to do so if they become aware of previous breaches of confidentiality by researchers. This means that if the researchers in Case Study 4.2 deliberately or inadvertently revealed sensitive information about one family member to another, or to the wider public, the potential for researchers to conduct similar research in the future may be damaged. The impact

can be immediate, as further study with this family will be jeopardised and families like them will be considerably less likely to participate in further study in the future if it is apparent that the researchers are not to be trusted to maintain confidential information. Breaches of confidentiality can also lead to a more general public loss of trust in researchers. Fostering and maintaining trust by maintaining confidentiality therefore becomes important to the future viability of research itself.

The research in the case study will involve researchers discovering personal information about lifestyle choices, home environment and medical history. All of these are widely considered to be private matters. There is therefore likely to be a strong expectation by the research subjects that these intimate matters will be kept confidential and used only for the agreed research purpose. Breaching this confidentiality would be a significant betrayal of trust, regardless of any subsequent negative consequences it might have for the family. It is likely that the family would not only feel that their personal information had been divulged without permission, but also that the privacy of their family life and medical history had also been unfairly breached (on the basis of false expectations) in order to gain this information. The family should therefore be informed of the various ways that the information will be used, and to whom it might be communicated, so that consent is properly obtained for this use and trust and confidentiality are clearly perceived to be maintained.

In genetic studies, a wide range of information about an individual can be determined that could have a significant impact upon that person's life. In many cases it will be important to that person to control who else gains access to that information. For example, genetic testing may reveal information about the paternity of some family members which they or others might not have known about or may wish to keep secret, particularly from children. Also, if family members are found to carry a genetic trait indicating susceptibility to serious respiratory disease, this may cause distress both to the individual and to other family members. Grievances between family members might arise, for example, as a result of discovering that some with the genetic trait were raised in a household with smokers, so increasing their chances of developing respiratory disease. Alternatively, the discovery that the gene was inherited from one side of the family could lead to resentments or other strains on family relationships if members of that side of the family are perceived as being the cause of others' illnesses. If a genetic susceptibility to illness is discovered in the family then those affected may also be concerned about whether this information will be passed on to their physician. While this might be beneficial to them in facilitating early diagnosis in the future, it might also create problems for them if this meant that it would also be passed to insurance companies and mortgage lenders.

The genetic information revealed as a result of agreeing to participate in the research could therefore have a significant negative impact upon emotional states, family relations, and financial status. It is therefore important that it is made explicit to family members, before they consent to participate, what sorts of information might be revealed, what use will be made of the information, and to whom it will be communicated.

As indicated above, a basic ethical reason for maintaining confidentiality is to respect the autonomy of the person who has provided or allowed access to information on the basis of undertakings or expectations about how it will be used. The fact that a subject makes an autonomous decision to disclose information to the researcher on condition that it is kept confidential may provide at least a *prima facie* reason to maintain confidentiality regardless of the potential consequences breaching it.

The duty to maintain confidentiality can also be assessed on the seriousness of the harms that a breach of confidentiality might give rise to. Both consequentialists and principlists concerned with the duty of non-maleficence will view this as an important ethical consideration. In practice, however, it is unlikely in a case like this that researchers or members of research ethics committees would be in a position to judge the seriousness of a particular breach in this way, given the personal nature of the information and the effects of revealing it. It is therefore unlikely that a breach of confidentiality could be justified by an assessment of its consequences. Moreover, it should be recalled that

breaching confidentiality is likely to have negative consequences for society generally by undermining trust in researchers. Breaching confidentiality might also be considered a more serious violation of respect for autonomy than the covert observation proposed in Case Study 4.1 since in that case the research involved undertaking observation without consulting the subjects, whereas breach of confidentiality involves giving an undertaking to subjects in order to gain access to information and then violating its terms.

It should not be forgotten that many countries will also have legal requirements relating to confidentiality and the revealing of personal information. The provisions of data protection Acts can vary from country to country, ([11]) but typically concern the processing of any information relating to identifiable living individuals and the restriction of its use to specific purposes, agreed upon by the individual at the time the data was recorded. Although this is a legal rather than ethical concern, the growing emphasis on data protection should mean that it is a standard consideration for all researchers. National legislation may also include requirements to divulge information as well as to keep information confidential. This will be considered below.

Disclosure of confidential information

Although there are very strong reasons to preserve confidentiality, there are times when it is desirable to make confidential information available to people other than those to whom it was originally entrusted. This occurs, for example, when a piece of research requires the use of information that was originally provided confidentially for other purposes, and when information provided confidentially to researchers may be used to benefit the subject or to prevent a harm. In such cases there are two strategies that can be employed to preserve confidentiality:

1) the researcher can seek the consent of the subject, or:
2) the connection between the information and the individual is severed, such as by anonymising the information.

Consent and disclosure

As discussed previously, confidentiality can be seen as the result of a contract between the researcher and the subject. If the subject consents to a particular use of information that would, without consent, have been an unjustified breach, a new agreement is entered into that removes the obligation to maintain confidentiality in relation to that use of the information. Although the connection with the individual is maintained, a breach of confidentiality is avoided by obtaining permission from the individual who 'owns' the information. This strategy might be adopted in Case Study 4.2, if, for example, researchers believe that it is in the interests of a particular individual for information about their genetic status to be disclosed to relevant health care practitioners. The individual concerned can then weigh the benefits of disclosure against the disadvantages of having that information in their medical record, and can decide whether or not to agree to the disclosure. This strategy, however, cannot be applied in all cases.

The most basic impediment to seeking consent to the disclosure of information is that the subject concerned may not be competent (or may be for other reasons unable) to provide consent. This might apply in the case of the children in Case Study 4.2 (although older children who understand the concept of secrecy and the significance of the information may be competent to consent to its disclosure). However, where a child is not competent to consent to the release of information, then information can be disclosed to relevant third parties (e.g. to parents, social workers, etc.) where this is in the best interests of the child. The discovery

11. Europe-wide provisions for data protection are made in the EU Charter of Fundamental Rights: *The Charter of Fundamental Rights of the European Union* (2000), Article 8. http://www.europarl.europa.eu/charter/default_en.htm

of a genetic trait that increases the likelihood of developing a serious disease may be a case where release of information is warranted in a child's best interests, particularly if it is known that the child is being raised in a smoky environment.

Another difficulty relating to consent that can be seen in Case Study 4.2 is that, because it is a genetics study, the discovery and revealing of information about one person often means discovering or revealing information about others. The trouble with revealing this information is that there may have been no consent to access this information from the other family members affected by the disclosure, even if there is consent from those whose blood samples were taken for analysis. Thus an individual family member might find that other family members acquire knowledge of his genetic status (or that he acquires unwanted knowledge of his genetic status) without having consented to disclosure of his test results and without any formal breach of confidentially having occurred. In such cases we might conclude that it is unhelpful to think in terms of ownership and individual control of information, and that attention instead needs to be given to balancing the benefits and harms likely to result from particular disclosures. Researchers in this case would therefore need to be careful in the way they divulged genetic information in order to avoid providing additional, possible distressing, information to individual subjects (such as where paternity issues are raised) where it is not expected. Information that subjects wish to receive might therefore have to be limited in cases where it reveals significant information about other subjects in the study who have not agreed to share the information. ([12]) Given the potential for discovering such facts about subjects and the relative seriousness of the condition, post-research counselling services should be made available to family members for whom the results of the research have had an impact.

By carrying out research involving the revealing of important and intimate details about medical and family life, a good researcher will often develop a strong sense of trust between researcher and subject. Whilst this has many advantages for both researcher and subject, it can also give rise to problems if it leads to 'overdisclosure'. This is where the researcher is told more than is necessary for the purposes of their research. Although this might be a natural consequence of the development of trust, the consequences of revealing this information can be as damaging as (if not more damaging than) revealing information relating to the research. All information that is divulged during the research should therefore be considered confidential, even if it is not directly relevant to the research itself.

The researcher should also consider how the environment in which they collect the information can impact upon confidentiality issues. There may be a risk of some subjects disclosing other subjects' confidential information, such as in focus groups or, in the example of the genetics case, in family groups. The concern is that the other subjects involved in the research are not bound by professional obligations of confidentiality. Whether such group environments are appropriate will depend upon the nature of the research and the sensitivity of the information that may be revealed.

Case Study 4.2 also raises the possibility that researchers will want to study medical records of, or ask family members about, deceased relatives. Clearly, this is a case in which consent for the disclosure of confidential information cannot be obtained. However, this also raises a questions about the extent to which obligations of privacy and confidentiality extend to the dead. Although we cannot be physically harmed once we are dead, our reputations can still be damaged by disclosure of information, and we may think that the autonomous wishes of a former person still warrant respect

12. Arguments have been put forward that despite any loss of confidentiality, family members should be informed if they are discovered to be at serious risk of illness or disease. See Rosamond Rhodes, "Autonomy, respect, and genetic information policy: a reply to Tuija Takala and Matti Häyry", *Journal of Medicine and Philosophy* 25 (2000): 114-20.

(as discussed in Chapter 2 in relation to Case Study 2.2). This also raises an issue about the effect that disclosing information about the dead may have on living relatives, either as a result of revealing shared genetic properties or by giving rise to distressing memories or new knowledge relating to the deceased person.

More general difficulties with obtaining consent to divulge information might arise in different cases where, for example, contact details may not be available, especially where the data was gathered a long time ago. In some very large-scale studies, such as those in epidemiology, the number of subjects involved may be too large for contacting them to be practicable. There is still an expectation that reasonable efforts will be made to contact people whose information is to be used in research, but where this is impossible alternative measures to minimise any potential harms arising from the dissemination of this information should be taken.

Anonymisation and disclosure

This leads to the other major strategy for making confidential data available beyond its original recipients – anonymisation. Anonymisation is designed to sever the connection between the information and the individual, so that the information no longer reveals anything about that person. However, while there are often good reasons to apply anonymisation techniques to the collation and dissemination of information, in order to protect privacy even where confidentiality is not an issue, there are limits to the effectiveness of this strategy.

Initially, somebody has to access the raw data in order to perform the anonymisation and if that person is not entitled to access it under the terms of confidentiality agreed upon by the research subjects then at least a small breach will have occurred. Furthermore, even after anonymisation has been carried out, this will not always mean that the link between individuals and information is actually severed. In a localised study, or where dealing with rare conditions, individuals may be identifiable in published results even if the data is anonymised. If this is so, then confidentiality has been breached.

Anonymisation may also have implications for future uses of data. Total anonymisation makes it harder for results to be checked for errors or scientific fraud. It also gives rise to an ethical problem where information (e.g. that someone has a serious but treatable disease) could be used to save someone from serious harm. A compromise to avoid these potential pitfalls is to use coded data, where identifying information is removed from the raw data, but can be linked back to the identifying information via a 'key'. In this case it is important for researchers to consider in advance under what circumstances the key will be used to link the data back to the individual and how securely the key will be stored.

Ultimately, given the limits to what can be achieved by anonymisation and consent, the conflict between research objectives that rely on the use of confidential data and the principle of respect for autonomy may be inescapable. Consideration therefore needs to be given to the question of when, if ever, it is justifiable to breach confidentiality. Relevant factors might include the sensitivity of the confidential information and the level of harm liable to result from its disclosure, and the importance and quality of the research. The significance attached to these factors is likely to differ between adherents of the different moral theories discussed in Chapter 1.

Breaching confidentiality

Confidentiality is breached when information that a researcher has about a person or persons is revealed, without the subject's consent, to a third party who does not already have that information. However, there remain some situations that may arise in research where, despite the expectations of the subject and despite consent not having been obtained by the researcher to divulge the information, the researcher may be ethically required to breach confidentiality and pass on the information to relevant third parties. There are two types of situation where this occurs – those situations where the law requires the breach of confidentiality and those situations where breach of confidentiality is legally permissible although not obligatory.

Although legal obligations vary from country to country, most obligatory breaches occur where there is tension between confidentiality and public safety.

There are often legal requirements relating to health, safety and welfare – for example, public health (such as notifiable diseases), abortion, births and deaths, suspected child abuse and prevention of terrorism,([13]) all of which might require mandatory disclosure of information obtained through the research.

Non-obligatory but allowable breaches tend to be the cases that involve some weighing up of potential harms and interests, for example where there is a clear public interest, or where there is information that a subject or third parties are at risk of harm or committing a criminal act. More subtle cases of ethically permissible breaches may occur because of the practice of health care workers sharing information with colleagues from the same institution. This is most readily seen in therapeutic medical cases, where doctors have the discretion to share this information with other members of their health care team for the benefit of the patient. The reasons for sharing this information should usually be made clear to the subjects at the outset as part of good practice in adhering to the demands of confidentiality.

Some kinds of research pose particular problems with regard to maintaining confidentiality in relation to conflicting legal and ethical duties. For example, there is plenty of valuable research that may take place in relation to illegal activities. In these circumstances, researchers need to be absolutely clear as to their legal status in regard to reporting findings to the police and to giving evidence in court. The ethical requirement to respect confidentiality and to inform subjects of its limits should still be respected as far as possible. However, there may be complicating factors with such research. For example, telling a subject who might reveal information about criminal activity that this information might have to be disclosed to the police is likely to prevent them from discussing it. This may, in turn, be against the public interest in the longer term because the benefits of the research will be lost. As these benefits may be substantial, such as the prevention of serious harm, we might think that there is not necessarily an obligation to warn the subjects in such cases. Moreover, there may be a conflict between researchers' moral and legal duties if there is a perceived public interest in continuing to gather information where there is a legal requirement to disclose.

Further issues

Issues of privacy and confidentiality can arise in all forms of research involving human subjects and the gathering of information about them. This makes the scope for breaches and ethical conflict relating to these two areas potentially huge. Many research situations where privacy and confidentiality concerns arise can be dealt with adequately through appropriate considerations about access, consent, and the proper management of data. However, although discussion of the cases has covered many of the central concerns, there will remain many issues that space precludes from the discussion.

One further issue that is becoming increasingly important, which concerns privacy and confidentiality (as well as consent and data security), relates to the use of databases and biobanks for research. Potential breaches of privacy and confidentiality can arise on a large scale when databases containing information relating to individuals are set up for research purposes, or when researchers are given access to databases already set up.

13. For example, in the UK the notification of infectious diseases comes under two pieces of legislation: the *Public Health* (Control of Disease) Act (1984) (c.22), Part II. (http://www.opsi.gov.uk/RevisedStatutes/Acts/ukpga/1984/cukpga_19840022_en_1) and the *Public Health (Infectious Diseases)* Regulations (1988). (http://www.opsi.gov.uk/si/si1988/Uksi_19881546_en_1.htm); the notification of births and deaths comes under the *National Health Service Act* (1977), Section 124. (http://www.opsi.gov.uk/ACTS/acts1990/ukpga_19900019_en_20); the notification of abortions comes under *The Abortion Regulations* (1991), regulations 4-5. (http://www.opsi.gov.uk/si/si1991/Uksi_19910499_en_1.htm); and the legal requirement to volunteer information relating to suspected terrorist activity comes under the *Prevention of Terrorism (Temporary Provisions) Act* (1989), Section 18 (http://www.opsi.gov.uk/Acts/acts1989/ukpga_19890004_en_15).

The management of databases requires close and constant scrutiny if they are to be used ethically in research. The way in which information is collected, the kinds of information placed on databases, and the length of time information will remain on databases, all need to be carefully considered. Subsequent control over the access to this information is also crucial, with clear guidance for both subjects giving their details and researchers required to establish who can have access to this information and for what purposes.

As the number of databases and their scope continues to increase, their value as a research tool also increases. However, alongside this the potential for violations of confidentiality and privacy also increases, with potentially large numbers of people being affected. As databases and biobanks are at the forefront of new technologies in research, some of the issues relating to them will be explored in Chapter 8, Case Study 8.5.

Further reading

- Council for International Organizations of Medical Sciences. *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002), Guideline 18. http://www.cioms.ch/frame_guidelines_nov_2002.htm
- Council of Europe. *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (Oviedo, 4.IV.1997). http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm
- Frankel Paul, Ellen, Fred D. Miller and Jeffrey Paul, eds. *The Right to Privacy* (Cambridge, Cambridge University Press, 2000).
- Gert, Bernard; Culver, Charles M. and Clouser, K. Danner. *Bioethics: A Return to Fundamentals* (Oxford: Oxford University Press, 1997), Chapter 8.
- Manson, Neil. C. and Onora O'Neill, *Rethinking Informed Consent in Bioethics* (Cambridge: Cambridge University Press, 2007), Chapter 5.

Chapter 5 **Balancing harms and benefits: the case of randomised controlled trials**

Learning outcomes

In this chapter you will develop:

- An understanding of the main types of benefit that may arise from research involving human participants and an ability to reflect on their differing moral significance.
- An understanding of the main types of harm and risk that may arise from research involving human participants and an ability to reflect on their differing moral significance.
- An appreciation of the ethical issues involved in assessing and weighing up benefits, harms and risks, including questions about the distribution of harm and benefit and the significance of consent, and an ability to recognise the different approaches associated with different types of moral theory.
- An understanding of randomised controlled trial methodology and the ethical problems arising from the use of controls and placebo.
- An understanding of the principle of equipoise and its limitations.

Introduction

This chapter addresses two intersecting themes. Firstly, it invites readers to consider general ethical issues about the benefits and harms produced by research, for example what are the main kinds of benefit and harm that researchers and research ethics committees need to be aware of when designing and reviewing research proposals? How, if at all, should risks and potential benefits be traded off against each other when considering whether a piece of research is ethically permissible? Does research that is expected to have very practical (e.g. medical) benefits justify a higher level of risk than research that pursues knowledge for its own sake? How should very small risks, serious but improbable risks and risks with unknown probability be treated? How does the distribution of risk and benefit between participants, researchers, institutions and society at large, or the presence of a valid consent, affect the permissibility of research?

Secondly, the chapter examines particular ethical issues that arise within randomised controlled trials (RCTs). RCTs raise many of the same ethical issues as other kinds of research but also give rise to specific problems of harm and benefit arising from the use of placebos and controls, and from the way in which subjects are randomly assigned to treatments. These difficulties are compounded by problems of consent, arising from poor understanding of the randomisation process and the role of experimental treatment as an inducement. The principle of equipoise will be considered as a possible but controversial response to these problems.

A single case study involving a four-arm randomised controlled trial is used to explore both the general issues about harms and risks in research, and those specific to RCTs. The major issues raised in the case study and subsequent discussion have been encountered, though not analysed in detail, in previous chapters. Several of the earlier case studies were randomised controlled trials, though not explicitly identified as such, and important issues relating to the potential for harm to research participants have been discussed, for example in relation to breaches of privacy and confidentiality. However, whereas the principles of consent and respect for autonomy were central to the discussion in previous units, the focus here is on the kinds of harm that research can give rise to, and how these should be restricted and/or balanced against the benefits of research.

Case Study 5.1
Randomised placebo-controlled trial to investigate surgical treatments for Parkinson's disease

Parkinson's disease is a progressive neurodegenerative disorder affecting the patient's motor function and producing symptoms including tremor, rigidity and slowness of movement. ([1]) The impairment of motor function is caused by loss of dopamine-producing cells in the brain.

1. The case described here is a fictional one which includes elements of real pieces of research. See for example the trial described in T.B. Freeman *et al.*, "Use of placebo surgery in controlled trials of a cellular-based therapy for Parkinson's disease", *New England Journal of Medicine* 341, no. 13 (1999): 988-91.

Standard treatment for Parkinson's disease is levodopa, which converts to dopamine in the brain. However, this results in further suppression of endogenous dopamine production and so becomes less effective with prolonged use.

Experiments using rats and non-human primates have suggested that implanting fetal neural tissue into the brains of affected individuals can improve motor function. Several centres have consequently developed programmes of fetal tissue transplantation for the treatment of Parkinson's disease in humans. Some of these have reported significant and lasting benefits; however, the possibility that these result from a placebo effect or investigator bias cannot be ruled out. Moreover, fetal neural tissue used for this procedure is in limited supply, and the fact that it is derived from aborted human fetuses makes this therapy ethically controversial and vulnerable to changes in legal or regulatory regimes.

A randomised controlled trial is proposed to determine the effectiveness and safety of the fetal tissue procedure and to compare it to an alternative (xenotransplantation) therapy using tissue derived from pigs. If successful, the latter would provide an alternative that could be used by patients with a conscientious objection to the use of fetal tissue or in jurisdictions where the use of such material is not permitted.

All subjects recruited to this trial will be patients with a diagnosis of Parkinson's disease who are receiving the standard treatment. They will continue to receive standard treatment throughout the trial, but will in addition be randomly assigned to one of the four 'arms' of the trial.

1) Subjects in this arm will receive implants of human fetal tissue taken from a single donor. These will be administered by injection into the brain after drilling a hole in the skull under general anaesthetic.
2) Subjects in this arm will receive the same treatment as those in the first arm, except that in this case the implant will consist of material taken from multiple donors. Results of animal experimentation suggest that implants from multiple donors may have a better success rate than those from single donors.
3) Subjects in this arm will receive a similar implant, but one consisting of non-human tissue in the form of porcine neural cells.
4) Subjects in this arm will receive a placebo treatment designed to simulate the experience of subjects in the active arms of the trial. This will include magnetic resonance imaging, anaesthesia, a skin incision and partial drilling of the skull, but without penetration into the brain.

The trial will be 'double blinded' in that neither the subject nor those evaluating the results of the procedures will know which arm an individual is assigned to. The surgeon will know which treatment an individual receives but will have no contact with those evaluating the results.

Subjects will be provided with information about all four arms of the trial and will consent to being randomly allocated. They will be evaluated every three months for two years following the procedure. Subjects will have the right to withdraw from the trial at any point, except that those in the xenotransplantation arm will be subject to ongoing monitoring as a precaution against them becoming a vector for the transmission of porcine infections into the wider human population. The researchers think that this is extremely unlikely, as the cells will be taken from pigs raised in 'specified pathogen-free' herds and subject to close monitoring. However, the possibility cannot be conclusively ruled out and the researchers think that monitoring is necessary to allay public concerns. Provision for this will be included in the original consent.

Questions

1. Who are the potential beneficiaries of this piece of research and in what ways do they stand to benefit? What are the advantages of the proposed trial design?
2. What are the potential harms resulting from this trial and who is put at risk by it?

Which potential harms do you think are most important?

3. What ethical problems, if any, are raised by the use of the placebo control?
4. Are participants in a position to give valid consent? Why (or why not)? What difference does this make to your assessment of the trial?
5. Do you think the trial is ethically acceptable as described? Why (or why not)? If you need more information to decide, what questions would you ask the researcher and what answers would satisfy you that the trial was justified? Are there any other modifications that would make you more likely to approve the proposed trial?
6. What should happen if a preliminary analysis (while the trial is ongoing) gives some indication (although not conclusive) of differences in outcome between those on different arms of the trial?
7. Would a more limited trial consisting of the following arms be ethically preferable? If so, why?

    a. Arms (1), (2) and (4)
    b. Arms (3) and (4)
    c. Arms (1), (2) and (3).

Benefits of research

It has been noted in previous chapters that almost any research involving human subjects will involve some burden or cost to the participants, for example risk of physical or other harm, inconvenience, sacrifice of time or monetary expense. One of the ways in which we can seek to justify the imposition of such costs is by pointing to some corresponding benefit, and in order to do this we need to distinguish different types of benefits that research can produce and their differing moral significance.

The case study illustrates some of the key issues that need to be considered when assessing the benefits promised by a particular research proposal. One of those key issues, highlighted by Question 1, is the fact that different groups of people can benefit in different ways from research, and the benefits do not all go to the same people who bear the costs. This becomes important when we come to weigh up the potential benefits of research against its costs and potential harms since, as we will see, different ethical frameworks and guidelines can give rise to different views about the permissibility of trading off costs borne by one group of people against benefits to others.

Benefits to future patients

As with most medical research, the trial described in the case study is most obviously of benefit to future patients. If the research is successful then many future patients with Parkinson's disease should have their quality of life improved as a result of the treatments being investigated. The research may help practitioners by establishing whether the treatments are effective and safe, which categories of patient can benefit from them, and by providing data that will lead to further refinements of the treatments. The effectiveness and safety data may also be needed in order to allow regulators to approve the treatments for use and to allow funding bodies to justify allocating resources to them.

Of course the researchers cannot know the outcome of the trial in advance, and it could be that the research reveals the experimental treatments to be less effective or less safe than existing alternatives. Even if this is the case, the results may inform further research that will lead to the development of new treatments in the future. Moreover, a negative trial outcome of this kind will benefit future patients by ensuring that they are not subjected to dangerous or ineffective treatments. This kind of benefit is particularly significant where a treatment that is already in routine use is tested and found to be unsafe or ineffective; in such cases we may even be able to identify people who would have been subjected to the treatment if the research had not been carried out. However, even in the case of new treatments, rigorous testing is part of a system designed to ensure that patients only receive safe and effective drugs; the system as a whole is beneficial to future patients and negative trial results are a necessary part of the system.

While the research in the case study aims to enhance the quality of life of future patients by demonstrating the ability of the experimental treatments to reduce the symptoms of their disease, it also has a bearing on future patients' mortality inasmuch as it addresses the safety of the experimental treatments. Prevention of mortality is of course an even more central concern in those areas of medical research where the aim is to assess the effectiveness of life-saving or life-prolonging treatments. Although the anticipated benefits of medical research are often very clear, and their value may not be in question, quantifying them in order to compare the benefits of different pieces of research or to compare the benefits with the burdens and potential harms may be harder. This is partly because of uncertainty about the results of research that has yet to be carried out, and partly because of the difficulty of comparing quality of life to mortality and different aspects of quality of life to each other. There are tools designed to facilitate such comparisons: for example the Quality Adjusted Life Year or QALY is a unit of measurement of benefit according to which one year of healthy life counts as one unit and a unit of less than full health life counts as a fraction of a unit (with the fraction being determined by the degree of disability or distress according to a scale based on research into people's preferences). Thus both extension of life and enhancements in the quality of life can produce a gain in QALYs, and information about the number of QALYs produced by different treatments is used to inform decisions about resource allocation. In general, research ethics committees will not have the information needed to conduct a QALY analysis but it may nevertheless be useful for them to have some knowledge of the fundamental principles of a tool of this kind.

It should also be noted that medical research is not unique in having benefits of these kinds. Social, educational and criminological research, for example, can inform policy in ways which affect both quality of life and mortality. In some cases their benefit may be more diffuse, affecting broad sections of a population rather than individuals, but in other cases they can inform specific interventions which can benefit particular identifiable individuals in the same way that medical research can benefit particular identifiable patients. ([2])

The ability of any research to benefit future patients or society more generally depends on its results being known by those who can make use of it such as practitioners, policy makers and other researchers. This applies even to the results of trials that produce negative results and do not lead to new interventions. In general, the wider the availability of the results the more likely it is that the benefits of the study will be maximised. The case study gives no details of the researchers' publication and dissemination strategy, so a research ethics committee might wish to ask for information about this and to insist on a commitment to publicise and make available the results even if they are negative. The ethics of publication will be considered further in Chapter 7.

Benefits to trial participants

Although future patients are likely to be its main beneficiaries, the research in the case study also has the potential to benefit participants in the trial, who may similarly have their quality of life improved by the experimental treatments. However, the benefit to each participant is very uncertain, both because the treatments are as yet unproven and may be in need of refinement, and because a proportion of participants will be allocated to the placebo group and will therefore not receive either of the experimental treatments.

In addition to any benefits resulting from the experimental treatments themselves, there is a possibility that participants in the trial will benefit from other factors associated with participation in research. These might include more intensive monitoring and higher levels of medical expertise than would be present in an ordinary treatment setting – this relates to the so-called 'trial effect' which will be discussed further below. It is also

2. There are also cases in which the benefits to society may be controversial even where it is agreed what the likely outcomes of the research are. For example in relation to research with military aims, views may differ about the desirability of enhanced military capabilities. A question then arises about the relationship between the individual moral and political convictions of research ethics committee members and democratically determined social and political policies. This is also linked to the issue of dual use, discussed in Chapter 7.

worth noting that not all medical research offers the prospect of these kinds of benefits to participants: for example 'first-in-human' and Phase 1 drug trials aim to establish the toxicity and pharmacological properties of an experimental drug rather than to test a treatment regime, and are typically carried out on healthy volunteers who would not be expected to benefit either from the effects of the drugs or from any trial effect.

Participants may also obtain benefits from their involvement in a trial which are not directly connected either with the treatments being investigated or with their status as patients, although not all of these apply to the case study and some would be more likely to arise in other fields of research. These include economic benefits in the case of paid participation, and what may be termed a 'moral benefit' in the case of participants who enter into trials in order to help others and benefit from the knowledge that they are doing so. In some kinds of research (for example interview-based research involving prisoners, elderly people or others who may experience social isolation or boredom) the subjects may derive significant benefit from social contact with researchers, the opportunity to talk about their opinions and feelings on the matters being researched with someone who wants to listen, and engagement in an activity outside their normal routine.

Since these benefits are not directly connected to the subject matter of the research, at least some of them can be altered in order to achieve a more favourable balance of benefits and costs, without affecting its methodology. For example, levels of payment may be varied, and undertakings may be given to provide participants with experimental or other treatments post-trial. However, in order to avoid inadvertent deception it is important not to promise benefits that cannot be guaranteed, for example treatments that are dependent on funding or on the outcome of the trial.

Benefits to researchers and research organisations

As well as present and future patients, the research may provide intellectual, financial and reputational benefits for the researchers and the organisations for which they work. The research may also benefit employees and shareholders of companies that are involved in the research or in the supply of the treatments that may be adopted as a result of the research, and this in turn may provide social benefits through the taxation system and by contributing to economic growth.

The fact that researchers and others involved in the design and implementation of a study stand to benefit from it is sometimes viewed by members of research ethics committees as problematic. Often this is articulated in terms of the researchers' motives: for example that they are carrying out the research "for the money" or "to satisfy their own curiosity" or (in the case of student research) "to get a qualification", rather than for the sake of those that the results of the research might ultimately help. It is not clear that this should be considered a valid objection to a research proposal, since people often have a variety of motives for what they do, self-interested motives are not intrinsically bad, and we do not usually consider it morally problematic that those who provide important services through their jobs are at least partly motivated to provide them by the fact that they are paid to do so. However, these worries may reflect an underlying concern about possible conflicts of interests. The worry here is that the particular interests of researchers and their sponsors may lead to the research being designed and conducted in ways that do not best serve the interests of research participants or future patients. This could take various forms: some, such as methodological bias or fraudulent presentation of results would undermine the scientific validity of the study, while others might result in a scientifically robust study but one which gives inadequate protection to the welfare of research subjects or which answers questions of interest to the researcher rather than those of interest to society. These are ethical issues, but ones that are better addressed by research ethics committees and peer reviewers focusing on the substance of the research rather than the motivations of the researchers.

Uncertainty and research methodology

By asking about the trial design, Question 1 also prompts us to consider how confident we can be that the anticipated benefits will in fact be achieved. It has already been noted that the potential benefits to

research participants are uncertain. It is also uncertain whether the research will give rise to treatments that will benefit future patients since we cannot know what the results of the research will be until it has been conducted, and it might turn out that the experimental treatments are no better than placebo. However, if the research methodology is robust it should at least give us a reliable answer to the question of *whether* the experimental treatments are effective and safe, enabling clinicians and regulators to make an informed decision about whether they should be offered to patients.

The fact that the proposed research is a randomised controlled trial is important here, as well-conducted RCTs are (for reasons to be discussed below) widely perceived as providing the best possible evidence about the efficacy and safety of treatments. It may therefore be appropriate for a research ethics committee to give more weight to the anticipated benefits of an RCT than those of some other types of research. This does not mean, however, that other research methodologies should be rejected, since RCTs are not appropriate or practical for all research topics or questions, and even where they are technically possible they could be ethically unacceptable. This also leaves open the question of how well designed the RCT is. A poorly designed RCT (for example one with an inadequate sample size or which uses an inappropriate control) may fail to produce a definitive answer to the question it is addressing. It is worth noting that what matters here is not only whether the research produces results that are objectively reliable but also how the results are received by regulatory and funding authorities and practitioners: if regulators and funders are not persuaded by the research that the treatment should be approved and doctors are not persuaded to prescribe it (or to refrain from doing so in the case of a negative result) then the intended benefits will not be realised. Thus, although the terms of reference of research ethics committees often discourage them from directly engaging in assessment of the methodology of the proposals they are considering, it seems that they should at least ensure that such an assessment has taken place, for example by peer review.

Harm in research

Harm is often defined, following Joel Feinberg, as a setback to interests. ([3]) Since people have many kinds of interests this implies that there can be many kinds of harm. It is important to note, however, that not every setback to an individual's interests will constitute a moral wrong done to that person: there are some burdens or risks of harm that we think can legitimately be imposed on individuals for the benefit of society (consider for example the burdens and risks involved in the taxation and road transport systems); in other cases we may think that an individual's interest in something to which they have no legitimate expectation does not even create a *prima facie* objection to policies that set back that interest (consider the way in which the system of ethical review of research thwarts the interests of researchers intent on unethical research, but also to a lesser extent sets back the interests of well-intentioned and competent researchers).

Types of harm

In considering Question 2 we may identify several kinds of harm which potentially arise from the research described in the case study. Some of these arise from the experimental treatments themselves while others arise from particular features of the trial or wider social factors.

First and most obviously, there is a risk of *physical harm* to participants as a result of the procedures that they will undergo. In this case the possible harms include rejection of the transplant by the participant's immune system, increased risk of infection or malignancy due to the immunosuppressive drugs needed to prevent rejection, risk of post-operative infection or other complications, and risks associated with anaesthesia. Some of

3. Joel Feinberg, *Harm to Others: the moral limits of the criminal law* (New York: Oxford University Press, 1987): 33.

these risks are limited to participants in the active arms of the trial while others apply also to the placebo group.

One of the risks faced by the active treatment groups is that infections will be transmitted from the implanted tissue to the research subject. This risk is present for the groups receiving transplants of human tissue (and greater in the group receiving tissue from multiple donors), but is particularly problematic in the case of the porcine transplants. There are two reasons for this. Firstly, we know less about porcine infections than human ones and do not know which ones may survive and produce symptoms in humans, so are less able to assess the level of risk and to avoid infected sources. Secondly, we run the risk of transmitting infectious agents that have previously only affected pigs into the human population and cannot rule out the possibility that these will be transmissible between humans and will spread into the wider population. If this happens, not only might the aggregate harm be very large but it will potentially affect people who have nothing to do with the trial and have not consented to this risk.

A second kind of harm to which participants may be subject is *psychological or emotional harm.* For example, participants may feel anxiety at undergoing a risky experimental procedure. This would apply equally to participants in all arms of the trial since they do not know which procedure they will undergo. More specifically, it has been suggested that patients undergoing xenotransplantation may suffer psychological distress due to the effect on their sense of self of having tissues from another species implanted. ([4]) It should be noted that similar claims were made about human-to-human heart transplants when the procedure was first introduced and have more recently been made about face transplants, and that these sorts of worries often recede as the procedures become more established. However, the possibility of such effects cannot be ruled out, particularly where the sense that the procedure is in some way 'unnatural' is promoted by media commentary or social attitudes.

Related to this, participants may be at risk of *social harm;* that is, the way in which they relate to others or their position in society may be altered in a detrimental way. For example, participants might find themselves shunned by others due to a fear of zoonotic infection, or disapproval of treatment involving aborted fetuses. The loss of liberty resulting from monitoring and other restrictions imposed on those who have received xenografts in order to guard against the spread of infections may also be included in this category. More generally, social harms might include economic disadvantage (for example arising from difficulty in obtaining life insurance) or reduced employment prospects arising from participation in certain kinds of trial. It is often these kinds of harms that underpin requirements for confidentiality and anonymisation.

Harm to non-participants

It should be noted that, as with the benefits of research, each of the main types of harm identified here can affect people other than the research subjects. We have already noted the possibility that zoonotic infections could be transmitted from research subjects to others, resulting in a risk of physical harm first to people who come into contact with the research subjects and then to the wider public. Non-subjects, especially those who come into contact with subjects, may therefore also suffer psychological anxiety about the risk of such infection, and social harms resulting from the perception of such a risk by others (and may do so even if the level of fear is not justified by the objective level of risk). There is also a possibility of harm to non-subjects arising as a result of the diversion of resources away from other areas of medical research and provision; this issue of the relationship between research and broader social priorities will be explored in Chapter 7. Non-subjects could also suffer economic and reputational harms, and these sorts of harm could affect institutions as well as individuals. For example, both researchers and the institutions that employ them and fund or host their research may suffer reputational and economic loss if

4. Nuffield Council on Bioethics, *Animal-to-human Transplants: the ethics of xenotransplantation* (London: Nuffield Council on Bioethics, 1996): para. 9.12.

the research they carry out is judged by others (for example those who fund, regulate or employ them) to be dangerous and/or unethical.

Harm and risk

Harms, like benefits, are often difficult to predict with certainty. This is especially true in relation to research, where we are seeking to investigate patterns of cause and effect that are currently unknown. In such cases what we are dealing with is a *risk* of harm. When assessing risks of harm we generally take two things into account: the likelihood (or probability) that the harm will result, and the magnitude of the potential harm. The greater the likelihood of harm occurring as a result of some action, and the greater the size of that harm, the greater the risk of harm from acting in that way. Most of our decisions about how to act are based on predicted consequences, so most of the deliberations about risk that inform them are really deliberations about risk.

The statements that are found in many research ethics documents asserting primacy of research subjects' welfare over other interests suggest a strong commitment to the prevention of harm.([5]) Given, however, that almost any human activity involves *some* risk of harm, an unqualified commitment to its prevention would make almost all research impossible. Not only would this deprive society generally of the benefits of research, but it would also appear to be contrary to the interests of most research subjects, since in many cases the benefits of living in a system in which important research is able to take place will exceed the risks of participation in research. This would also be to apply a more restrictive standard to research than is applied to other activities. In order to avoid these consequences we need to give an account of what constitutes an acceptable level of risk.

There are three ways in which this might be done. First, a risk might be considered acceptable when it is consented to by the person or people that it affects. By permitting risks that are consented to we respect the autonomy of those giving the consent and also acknowledge that the acceptability of risk varies from person to person and so is best judged by the person affected. This view is supported by Mill's harm principle, which holds that the only legitimate ground for restricting a person's liberty is to prevent harm to others, and not to protect them from harming themselves.([6]) However, as we have seen in previous chapters, valid consent is not always possible (for example when dealing with non-competent subjects or covert research). Moreover, as the case study demonstrates, research that is consented to by its subjects may also involve risks to a wider population from whom it would be impractical to obtain consent. We might think that if the risks are small enough such research may still be acceptable, but if so, the acceptability of the risks must be based on something other than consent. Second, it might be considered that a risk can be acceptable (even without consent) if it falls below a certain threshold level. This gives rise to the concept of 'minimal risk', which will be discussed below. Third, it might be that the level of acceptable risk depends upon the balance between the risks and expected benefits of the research. This balancing of risks and benefits will be the initial focus of the following discussion.

Balancing risk and benefit

Although it is common to refer to the balancing of risk and benefit in relation to research ethics, this terminology is potentially misleading.([7]) A benefit is an actual outcome whereas a risk is a probability of a certain harm or cost. Benefits may be balanced against harms, while risks should be balanced against probabilities

5. See for example the very similar statements in the *Declaration of Helsinki* (World Medical Association, *Declaration of Helsinki: ethical principles for medical research involving human subjects* (2008), Article 6. http://www.wma.net/en/30publications/10policies/b3/index.html) and the Oviedo Convention (*Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (Oviedo, 4.IV.1997), Article 2. http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm).
6. John Stuart Mill, *On Liberty* (London: Longman, Roberts & Green, 1869; Bartleby.com, 1999. www.bartleby.com/130/), Chapter 1, para. 1.
7. Peter H. Van Ness, "The concept of risk in biomedical research involving human subjects", *Bioethics* 15, no. 4 (2001): 364-70.

of certain benefits. The balancing undertaken by a researcher or ethics committee therefore needs to take account of both the magnitude of the potential harms and benefits and their probabilities.

Consequentialism and expected utility

One approach to this balancing is suggested by consequentialism. It will be recalled from Chapter 1 that consequentialist moral theory in general holds that the right action is the one that produces the best available consequences and that utilitarianism combines this consequentialist principle with the view that all morally significant outcomes can be evaluated in terms of a single measure, referred to as utility and often equated with happiness or welfare. Utilitarianism therefore tells us to maximise utility. A more sophisticated utilitarianism will recognise that we do not know for certain what the utility of a particular action will be, and will tell us to maximise *expected utility*, where the expected utility of an action is understood as the sum of the utilities arising from each of its possible outcomes, each multiplied by the probability of that outcome.

In principle this approach offers a clear and determinate answer to the question of how we should balance risks against expected benefits in research. Applying this model to the case study we would estimate each of the potential benefits and costs mentioned in the previous sections (perhaps using a tool such as the QALY ([8])), multiply each by our estimate of its probability, and then add them together to obtain the overall expected utility of the trial. We would then compare this with the expected utility of not conducting the research at all or of conducting variants such as those mentioned in Question 7, and would choose the course of action with the greatest expected utility. In practice, however, this would be neither simple nor determinate, in part because we rarely have more than a rough idea of the probabilities of the relevant harms and benefits, but also because of the difficulty of measuring and comparing dissimilar benefits and because of the sheer number of possible consequences. Moreover, even if some of these difficulties could be reduced by making simplifying assumptions and adopting a standardised model for risk assessment, this approach is vulnerable to some standard philosophical objections to consequentialism and conflicts with some widely held moral intuitions as well as with the pronouncements of influential codes of research ethics.

Interpersonal and individual balancing

In particular, even if expected utility is considered a workable tool for comparing beneficial and harmful outcomes of research, the idea of trading off benefits to one person (or set of persons) against costs to another is morally problematic. This is reflected in the emphasis found in research ethics codes of practice and legislation on the primacy of the interests of the individual research subject.

The suggestion that such trade-offs may be *exploitative* will be explored in Chapter 6. For now, however, we can note (recalling the discussion in Chapter 1) that one of the features that distinguishes deontological approaches to ethics from consequentialism is their opposition to the general acceptance of such interpersonal trade-offs. Deontological approaches hold that we have duties to particular individuals that are not to be overridden simply because a greater aggregate good can be achieved by breaching them. Often this is articulated in terms of respect for persons and the corresponding idea that we should treat people as ends in themselves, and not solely as means to achieving the ends of others. According to one well-known formulation of this kind of view, in allowing interpersonal trade-offs "utilitarianism does not take seriously the separateness of persons". ([9]) In principlist approaches, such as that of Beauchamp and Childress, the principles of non-maleficence and respect for autonomy tend to be seen as more pressing than the principle of

8. The QALY, referred to above (p. 100), can be thought of as a measure of utility, albeit a restricted measure that only takes account of health-related elements of welfare.
9. John Rawls, *A Theory of Justice* (Cambridge, Mass.: Harvard University Press, 1971): 27.

beneficence (although officially there is no general ordering of the principles), so that requirements for consent and avoidance of harm will constrain what may permissibly be done to research subjects even when the expected benefits exceed the expected harms.

Some other, less individualistic, moral theories might appear more sympathetic to the idea that individuals should bear some risks or burdens for the sake of the common good. Communitarianism, for example, is perceived as promoting the common good of the community over the interests of individuals. Its emphasis, however, is not on a trade-off between individual and community but on the ways in which the flourishing of the individual may depend on, or be 'constituted' by, the flourishing of society; and this is perhaps more plausible in relation to social and cultural interests than in relation to risks to life and health.

It should also be noted that deontological and rights-based approaches need not be absolutist in their opposition to the balancing of benefits and risks across persons. They may hold that while there is a strong *prima facie* objection to imposing risks on some people for the benefit of others, which is not to be overridden for a marginal or modest benefit to the community as a whole, this objection can be overridden in order to prevent catastrophic harm. Thus, for example, they may accept the need for some compromise in the protection of individuals' interests in the event of an urgent need for testing of vaccines to prevent a serious global pandemic. However, while there may be debate about what would count as catastrophic circumstances, this would probably not apply to most cases of medical research, and still less to research in many other fields.

Even from a consequentialist perspective there might be reasons to reject or restrict trade-offs between risks to individuals and expected benefits to the wider society. Some argue that unless people's important interests are protected by a system of enforceable rights the resulting insecurity will undermine the possibility of achieving high levels of utility in society as a whole. If it was believed that researchers were in the habit of trading off risks to individuals against benefits to society this could cause significant insecurity, for example among those seeking medical treatment, and might lead to increased difficulty in recruiting research subjects in future.

There is thus a variety of reasons, reflected in research ethics codes of practice and legislation, for thinking that risks to individuals arising from research cannot be justified simply by balancing them against the expected benefits to society as a whole. This leaves open the possibility of balancing the risks and expected benefits for each individual. In this sort of trade-off no individual's overall interests are sacrificed for the good of others. In the case of competent individuals, however, we might think that rather than rely on a researcher's or ethics committee's judgement about how to weigh the potential harms and benefits in the light of their various probabilities, this is a decision that should be made by the person affected and exercised through the process of consent. One reason for thinking this is that it enables the weighing-up to take account not only of the importance that each potential harm or benefit has for the individual concerned, but also the individual's willingness to take risks in order to gain a chance of some benefit. However, as we have seen, consent is not always possible and in these cases it may be necessary for someone other than the individual concerned to assess the balance of risks and benefits. In the case of a non-competent subject this would amount to an assessment of whether participation in the research is, on balance, in their best interests; this is similar to the assessment that would typically be made before treating a non-competent patient in a clinical context.

Minimal risk

Further issues arise in determining how to handle particular categories of risk. One such category concerns very small risks. It has already been noted that an important element in the justification for exposing research subjects to risk is the consent of the subjects, but that this justification is not available in the case of research involving non-competent subjects, or where consent is impossible for methodological reasons. It may also be problematic in cases where there is a risk of coercion or undue pressure. The concept of minimal risk (and sometimes minimal burden) is used to

identify cases where it may be permissible to conduct research without valid consent, particularly where there are no benefits to the subjects that could offset more significant risks. ([10]) In some cases, depending on applicable regulations, it is also used to determine which cases may be subject to a process of expedited review (e.g. by Chair's action or by a subcommittee of a full ethics committee). A similar threshold may also be implicit in judgements about which risks need to be disclosed to subjects in order for their consents to be valid.

There is no universally agreed definition of minimal risk. Most accounts characterise minimal risk as a risk equivalent either to that encountered in everyday life, or to that encountered in routine medical examinations. These, of course, may not be the same. Moreover, each is susceptible to different interpretations. ([11]) For example, either account may be interpreted as an absolute standard applicable to all potential research subjects, or relative to the individual. A relative standard would allow quite significant risks to count as 'minimal' for individuals who are, perhaps for medical, social or occupational reasons, routinely exposed to above average levels of risk, and it would seem unjust to allow such individuals to be subjected to higher levels of risk as research subjects, without consent, just because of the higher risks that they already face. An absolute standard, on the other hand, would need to be further defined: it could refer to the level of risk that a typical or average member of the public would encounter in everyday life or routine medical examination, or it could, more restrictively, refer to a level of risk that every member of the public can routinely expect to encounter. Both of these standards also have the defect that, although they take as their reference point risks that are typically accepted without a requirement for consent (or at least for written consent), ([12]) these are risks that are often linked with benefits for the person undergoing the risk, so we cannot infer the acceptability of similar levels of risk in a research context where the subjects do not stand to benefit.

Another point worth noting is that by defining minimal risk in terms of equivalence to some other risk we are assuming that different risks can be compared in a straightforward quantitative way. This is problematic for two reasons. First, it is doubtful whether a researcher or research ethics committee could be in a position to quantify with any precision either the risks that define minimal risk or the risks arising from a proposed research project. Secondly, establishing equivalence between different risks presumes that the elements of the risks can be combined into a single measure. While this could in principle be done by multiplying the magnitude of each potential harm by the probability of its occurrence, as in calculations of expected utility, a further objection to this approach is that it may not correspond to the way in which we, collectively or as individuals, judge the acceptability of risk. We might, for example think that potential harm exceeding a certain level of seriousness makes a risk unacceptable even if its probability is extremely low.

10. For example, Article 17 of the *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (Oviedo, 4.IV.1997), http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm), and Article 15 of its *Additional Protocol Concerning Biomedical Research* (Strasbourg, 25.I.2005), http://www.coe.int/t/dg3/healthbioethic/Activities/02_Biomedical_research_en/195%20Protocole%20recherche%20biomedicale%20e.pdf, state that, exceptionally, and subject to various other conditions, research on a person without the capacity to consent which does not have the potential to produce results of direct benefit to the person concerned may be authorised provided that it "entails only minimal risk and minimal burden for the individual concerned". The additional protocol makes further use of the concept in relation to other cases involving vulnerable subjects including research during pregnancy or breastfeeding, research in emergency clinical situations, research on persons deprived of liberty.
11. For a discussion of this see Loretta M. Kopelman, "Minimal risk as an international ethical standard in research", *Journal of Medicine and Philosophy* 29, no. 3 (2004): 351-78.
12. The CIOMS guidelines use a version of the routine examination standard which explicitly refers to examinations involving procedures "for which signed consent forms are not customarily required outside the research context". (Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002), commentary on Guideline 4. http://www.cioms.ch/frame_guidelines_nov_2002.htm)

The *Oviedo Convention* offers definitions of minimal risk and burden that may avoid these problems. According to this account, a risk is deemed minimal if "having regard to the nature and scale of the intervention, it is to be expected that it will result, at the most, in a very slight and temporary negative impact on the health of the person concerned", and correspondingly a burden is deemed minimal "if it is to be expected that the discomfort will be, at the most, temporary and very slight for the person concerned".([13]) By basing its definition on a concrete description rather than an equivalence it avoids the immediate need for those trying to apply it to quantify and compare risks. It also seems to suggest that what matters is the maximum potential impact of an intervention, with probability having a relatively marginal role in determining which impacts count as minimal. However, this definition still leaves considerable scope for judgement by ethics committees: what counts as a 'very slight' impact and what is it for an outcome to be 'expected' – is this to be understood in terms of a threshold level of probability and if so what is the level?

Large risks

The concept of minimal risk is based on the supposition that some risks are small enough that people may be exposed to them without giving consent. Conversely it may be debated whether some risks are too large to expose people to even with their consent. We are unlikely to make this judgement where participation in the research has benefits for the individual that outweigh the risks. For example, in the case study one or more of the proposed treatments may have high risks because of their experimental nature, but they offer a prospect of significant improvements in quality of life which the treatments currently available to the subjects are not able to deliver. Other experimental procedures might have even higher risks but, as in medical practice outside the research context, still be acceptable if they offer the only hope for prolonging life or preventing very serious morbidity. However, many research ethics committees would hesitate to allow participants who do not stand to benefit in these ways to be subjected to very large risks, even with their consent.

There is a temptation in such cases to question the competence of a potential participant who wishes to consent to something that appears to be strongly contrary to their interests. However, as we saw in Chapter 3, it is possible for someone to have an unusual set of preferences, leading to decisions that seem strange to the majority, without being incompetent. Moreover, the reasons that motivate a person to participate in highly risky research need not be to do with their self-interest. Liberals and libertarians are likely to view it as unjustifiably paternalistic, and contrary to the value placed on autonomy in other contexts, for an ethics committee either to override an autonomous person's judgement that participation is in their best interests or to thwart their wish to participate for altruistic reasons.

However, there may be other reasons for holding that there is a limit to the level of risk that can be justified by a valid consent. If the same results could be obtained by less risky means then consequentialist considerations would oppose allowing the risky procedure. Even if the risky procedure does generate results that could not otherwise be obtained it may be thought that to impose high risks on another person, even with their consent, is contrary to the duties of the researcher, given that these include a duty not to harm as well as to respect autonomy. The researcher's duties might relate not only to the subject but to the research institution, whose reputation may be damaged by association with studies that are seen as having excessively high risk. The reputation of researchers in general (or in a particular discipline) may also be damaged, with consequences for the recruitment of participants in the future. Virtue ethicists might add that, even if there appears to be a justification for exposing a subject to high risks in a case where valid consent has been given, to expose the subject to such risks would be to act in opposition to the dispositions of character that we wish

13. *Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research* (Strasbourg, 25.I.2005), Article 17. http://www.coe.int/t/dg3/healthbioethic/Activities/02_Biomedical_research_en/195%20Protocole%20recherche%20biomedicale%20e.pdf

researchers to exhibit and nurture. This is an issue, then, on which different moral perspectives, and even different considerations arising within as single perspective, are likely to pull us in different directions.

High magnitude/low probability and uncertain risks

While we have considered risks that are very small or very large, a special problem is presented by risks that involve a low probability of very serious harm. In principle we could deal with such cases by calculating the expected costs and comparing them with the expected benefits of the procedure, either for each affected individual or in the aggregate. However, in many cases the probabilities are not known with any precision or are disputed, and we might think that some outcomes are so bad that we should seek to avoid them even if the chances of them happening are so remote as to make the expected harm quite low.

The third arm of the trial described in the case study presents such a scenario. One of the potential harms arising from xenotransplantation is the transmission of infectious agents from the 'donor' animal to humans, and in the worst case scenario such infections could prove to be both seriously harmful to humans and readily transmissible from human to human. As critics of xenotransplantation have pointed out, this could result in a new pandemic akin to AIDS or worse. This has led to calls for a precautionary approach to be followed, and for the adoption of a moratorium on xenotransplantation. ([14])

The precautionary principle originates in policies on environmental protection and in that context was introduced into the T*reaty Establishing the European Community* in 1992. However, the principle now informs policy on a much wider range of subjects: the European Commission's communication on the precautionary principle refers, in addition to the environment, to potentially dangerous effects on human, animal or plant health, ([15]) and the principle is invoked in relation to human health in the regulation on the general principles and requirements of food law. ([16]) The precise interpretation of the principle is a matter of some debate, to be discussed in Chapter 8, but broadly it asserts that where an activity introduces a risk of serious harm, appropriate steps should be taken to prevent or limit that harm even though the scientific data does not permit a precise assessment of the level of risk.

It should be noted, however, that precautionary action is not cost-free. Forgoing or even delaying the investigation of porcine neural implants in the case study may deprive many present and future patients of a valuable therapy, and more generally a moratorium on xenotransplantation might deprive many thousands of people of potentially life-saving treatments. Although the principle is designed to deal with cases where we lack scientifically rigorous evidence about the level of risk, it would be unethical to impose these sorts of costs merely on a suspicion of risk, without any evidence whatsoever. A plausible application of the precautionary principle must therefore take account not only of the magnitude of the postulated harm, but of the evidence that such a threat really exists and the costs

14. For example *Recommendation 1399 (1999) of the Parliamentary Assembly of the Council of Europe*, http://assembly.coe.int/Main.asp?link=/Documents/AdoptedText/ta99/EREC1399.htm, which called for the rapid introduction of a legally binding moratorium on xenotransplantation including clinical trials. Various European countries have at different times adopted moratoria or imposed special regulatory conditions on xenotransplantation. See *Council of Europe, Report on the State of the Art in the Field of Xenotransplantation* (Strasbourg, 21 February 2003), CDBI/CDSP-XENO (2003), Chapter 8. http://www.coe.int/t/dg3/healthbioethic/Activities/06_Xenotransplantation_en/XENO(2003)1_SAR.pdf
15. Commission of the European Communities, *Communication from the Commission on the Precautionary Principle*, COM(2000)1 final. http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexplus!prod!DocNumber&lg=en&type_doc=COMfinal&an_doc=2000&nu_doc=1
16. *Regulation (EC) No. 178/2002 of the European Parliament and of the Council of 28 January 2002 Laying Down the General Principles and Requirements of Food Law, Establishing the European Food Safety Authority and Laying Down Procedures in Matters of Food Safety.* http://eur-lex.europa.eu/pri/en/oj/dat/2002/l_031/l_03120020201en00010024.pdf

of the proposed precautionary action. In the case of xenotransplantation this might lead to the view that limited and carefully regulated trials should be allowed to proceed, so that evidence about the risks and benefits can be gathered while keeping the risk of disease transmission as low as possible.

Risks to researchers

In the discussion so far we have focused on risks to research subjects and to the general public. However, there is also a question about whether research ethics committees should seek to regulate risks that researchers impose on themselves, and whether they should give the same weight to these as to other risks. In the case study, the researchers may, because of their close proximity to the research subjects, be among the most at risk from zoonotic infections. In other cases researchers may more directly impose risks on themselves. For example, some kinds of social and criminological research may require researchers to associate with dangerous people or to participate in dangerous activities, and in medical research self-experimentation may offer the only prospect of advancing certain lines of research when experimentation on patients or volunteers would be considered too dangerous for ethics committee approval.([17]) One reason why research ethics committees might treat these risks differently from risks facing research subjects or the general public is that researchers may be assumed to have a good understanding of the risks involved and to have consented to their involvement. However, in a large project involving a number of staff with different levels of responsibility it may not be reasonable to assume understanding of the risks amongst all those involved, and the fact that they are participating as employees may lead to some doubt about whether their consent is fully voluntary. Similar considerations may apply in relation to researchers who are students.

Ethics and randomised controlled trials

As well as raising general issues about the relationship between harms, benefits and consent, this chapter's case study focuses attention on the specific ethical issues that arise in relation to randomised controlled trials.

Randomised controlled trials are a vitally important research tool. They are most widely used in clinical trials, but can also be used to assess interventions and practices in fields other than medicine, such as education, social services and the criminal justice system. RCTs can be used to test new or existing practices. They can provide evidence of an intervention's effectiveness (or ineffectiveness), safety, cost-effectiveness, and of the balance of benefits over harms in comparison with other treatments.

The last part of Question 1 prompts us to consider the nature of RCT methodology and the advantages of using this approach to investigate the experimental treatments for Parkinson's disease. The advantages in this case will be the same as those of RCTs in general. These lie primarily in the ability of RCTs to produce reliable results by controlling for 'confounding factors'. In many other kinds of research, the results that are obtained can be affected by factors other than the experimental intervention whose effects are being tested. For example, it may be difficult to separate the effects of an experimental treatment from the effects of factors such as the natural progression of the disease, changes in other treatments that patients may be receiving or changes in other aspects of their care, dietary or lifestyle changes, or the benefits of closer medical supervision resulting from trial participation.

Two factors that are particularly problematic are 'investigator bias' and the 'placebo effect'. Investigator bias occurs when a researcher consciously or unconsciously

17. For some examples, see Eleanor Harris, "Eight scientists who became their own guinea pigs", *New Scientist* (11 March 2009). http://www.newscientist.com/article/dn16735-eight-scientists-who-became-their-own-guinea-pigs.html

behaves in a way which favours a particular answer to the research question. For example, a researcher who expects or hopes for a positive outcome might, in the course of recruiting participants, apply the inclusion and exclusion criteria more or less rigorously such that they end up with a sample that is more likely than the relevant patient population in general to respond to the treatment. In measuring and interpreting the results of an intervention they may be more inclined to classify a patient's description of symptoms as an improvement, or in the case of a quantitative measurement may be more inclined to discard a disappointing result as an error and re-measure, in cases where they know that the patient has received the experimental treatment. The placebo effect occurs where a patient's belief that they are receiving an experimental treatment leads to an improvement in their condition independently of any direct pharmacological or similar effect.

The main features of RCTs, which enable them to control for these factors, are illustrated by Case Study 5.1:

- Participants are divided into one or more groups that will receive the experimental treatment(s), and a control group.
- Allocation of participants between these groups is determined by a random process, to ensure that the groups are statistically equivalent and are not affected by investigator bias.
- The control group typically receives either a placebo, or a standard treatment for the condition. In the case study, participants in all groups continue to receive a standard pharmaceutical treatment while those in the control group undergo a placebo procedure.
- Some RCTs are 'open' but the most rigorous are 'blinded'. Blinding means depriving one or more of the relevant actors of information about who is in which group. 'Single-blinding' means that the subject does not know to which group they have been assigned, so that any placebo effects will apply equally to all groups; 'double blinding' means that neither the subject nor the investigator knows. In this case the surgeon has to know which group his patient is in, but those who measure and assess the results are deprived of this knowledge, eliminating the possibility of investigator bias.

Given that the knowledge resulting from research and the benefits resulting from this form a vital part of the justification for carrying out research on human subjects, the ability of RCTs to provide reliable results, controlling for confounding factors is an important ethical consideration in their favour. It also counts in favour of RCTs that they are widely *perceived* as reliable, for example by clinicians or others who are expected to employ the techniques under investigation, and by the bodies that will licence and approve funding for them, making it likely that the results of well-designed and well-conducted RCTs will make a real difference in practice.

However, as we have seen, most moral theories do not view the production of benefits to society as sufficient to justify imposing risks of harm on individuals, and this is reflected in established codes of research ethics as well as in regulatory and legal provisions. The question therefore arises of whether, generally or in particular cases, the benefits of RCTs involve unacceptable costs for individual participants subjected to a regime of randomisation, controls and placebos.

Harm and the therapeutic obligation

Questions 2 and 3 invite reflection on whether being allocated to the placebo arm (or more generally the control arm) of a trial amounts to being harmed. The thought here is that receiving either the 'standard treatment' or a placebo may be a setback to the subject's interests relative to receiving the experimental treatment. The case for saying that the subject is harmed is stronger in the case of a placebo-controlled trial, since in that case the subject may also be disadvantaged relative to patients outside the trial who receive the standard treatment.

If there is a harm in either of these cases, the harm consists in an omission to provide the research subject with a treatment that could have benefited them. As noted above, some moral perspectives view a harm caused by omission as morally less significant than one caused by an active intervention. In this case, however, the fact that the harm results from an omission does not avoid the moral problem. This can most readily be seen in the case of medical RCTs, such as the one in the case study, where the treatment (or placebo) is provided by

a health care professional. It is generally held that members of the health care professions have a 'therapeutic obligation': a duty to provide what they believe to be the best available treatment for their patients. For example, the Word Medical Association's *Declaration of Geneva* requires physicians to affirm that "The health of my patient will be my first consideration", ([18]) while the International *Code of Medical Ethics* states that "A physician shall act in the patient's best interest when providing medical care". ([19]) Both of these inform the *Declaration of Helsinki*'s previously quoted assertion of the primacy of the individual research subject. ([20])

While these examples refer specifically to the medical profession, it is reasonable to suppose that similar obligations will apply to members of other 'caring professions', and even, in more qualified form, to those whose roles combine caring with public protection or social control. Thus, in any of these contexts, the question arises of whether a random assignment of research subjects to treatment regimes, including experimental treatments, controls and possibly placebos, can be compatible with the researcher's professional obligations.

Placebos

The concern about subjects being disadvantaged by random allocation among treatment options is strongest in the case of those assigned to a placebo group. A common response to this concern is that placebo-controlled trials are only justifiable where there is no well-established standard treatment, and that where an established treatment exists this should be used as the control. There are, however, difficulties with this rule.

One type of difficulty concerns the interpretation of the rule: what counts as a well-established standard treatment? The formulations given by the *Declaration of Helsinki* and the *Oviedo* Convention permit placebo controls to be used in the absence of any "current proven intervention" or "methods of proven effectiveness". ([21]) However, for many current treatments that pre-date the era of evidence-based medicine there will be significant evidence of effectiveness in the form of case histories and practitioner experience, which may be thought sufficient to generate obligations for practitioners providing treatments to patients, but which fall short of full scientific proof. Indeed one reason for conducting RCTs is to provide a definitive test of the effectiveness of such interventions.

There is also a question about how the rule should be applied when a treatment that is known to be effective is not available to the population from which the research subjects are drawn, for example for economic reasons. Where this is the case, a subject in the placebo group is no worse off than they would be outside the trial, but controversy exists as to whether researchers in this situation have an obligation to ensure that their subjects are provided with a level of treatment that would be regarded as standard elsewhere. This issue gives rise to intense controversy about the ethics of conducting placebo-controlled trials in developing countries and will be returned to in the following chapter. ([22])

18. World Medical Association, *Declaration of Geneva* (2006). http://www.wma.net/e/policy/c8.htm
19. World Medical Association, International Code of Medical Ethics (2006). http://www.wma.net/e/policy/c8.htm
20. World Medical Association, *Declaration of Helsinki: ethical principles for medical research involving human subjects* (2008), Article 4. http://www.wma.net/en/30publications/10policies/b3/index.html
21. World Medical Association, *Declaration of Helsinki: ethical principles for medical research involving human subjects* (2008), Article 32. http://www.wma.net/en/30publications/10policies/b3/index.html. *Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research* (Strasbourg, 25.I.2005), Article 23. http://www.coe.int/t/dg3/healthbioethic/Activities/02_Biomedical_research_en/195%20Protocole%20recherche%20biomedicale%20e.pdf
    Note, however, that both documents provide for other justifications of placebo, discussed below.
22. Nuffield Council on Bioethics, *The Ethics of Research Related to Healthcare in Developing Countries: a follow-up discussion paper* (London: Nuffield Council on Bioethics, 2005), Chapter 3. http://www.nuffieldbioethics.org/go/ourwork/developingcountries/publication_169.html. Charles Weijer and James A. Anderson, "The Ethics War: Disputes over International Research", *Hastings Center Report* 31, no. 3 (2001): 18-20.

Leaving aside these difficulties of interpretation, strict application of the established treatment rule has a number of disadvantages, which provide at least *prima facie* grounds for a more permissive approach to the use of placebos. Note that while three of the following relate to the interests of society in obtaining and utilising the results of research, the fourth relates to the interests of research subjects, although as a group rather than as individuals.

- In general, placebo-controlled trials are said to produce more reliable results than trials employing established treatments as 'active controls'. ([23]) The reliability and accuracy of the latter depends on the reliability and accuracy of our knowledge of the effectiveness and safety of the treatment that is being used as a control. Even if the trial shows us that the experimental treatment is better than the established treatment, in the worst case this could mean that both treatments are harmful to patients but the experimental treatment is less so.
- Regulatory bodies may insist upon or be more willing to accept placebo- controlled trials than those with active controls, making them necessary in order to achieve the intended benefits of the research.
- The results of non-placebo-controlled trials may be less convincing to practitioners, reducing the likelihood of the trial results translating into real benefits for patients.
- Placebo-controlled trials may be able to achieve statistically significant results with fewer participants, thus reducing the number of people subjected to the risks or burdens of research participation.

The circumstances in which placebo use is permissible have been a source of much controversy surrounding successive versions of the *Declaration of Helsinki*. The fifth revision (2000) appeared to prohibit placebo use where a proven treatment exists, but in 2002 a "note of clarification" was issued. This permitted the use of placebo controls even if a proven treatment exists, where "compelling and scientifically sound methodological reasons" make their use necessary, *or* the investigation concerns a "minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm". In the most recent revision (2008) a more moderate departure from the established treatment rule (with 'or' replaced by 'and') has been incorporated into the main text, permitting use of placebo controls where a proven intervention *does* exist but where "for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention *and* the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm". ([24]) The *Oviedo Convention* similarly permits placebos where there are methods of proven effectiveness but "withdrawal or withholding of such methods does not constitute an unacceptable risk or burden". ([25])

The effect of these provisions is to qualify the primacy of the research subject, allowing them to be allocated to treatments that are sub-optimal provided that this does not seriously disadvantage them. This allows some discretion in determining what counts as an acceptable level of sub-optimality. One factor that is potentially relevant to this judgement, although contentious, is the claimed tendency – often referred to as the 'trial effect' – of patients enrolled in RCTs to have better medical outcomes than those who are not, even if they are in the control arm. ([26]) There are also features in the design of certain trials that can reduce the disadvantage of

23. Although this view has been disputed: see Benjamin Freedman and Charles Weijer, "Placebo orthodoxy in clinical research I: Empirical and methodological myths", *Journal of Law, Medicine and Ethics* 24, no. 3 (1996): 243-51.
24. World Medical Association, *Declaration of Helsinki: ethical principles for medical research involving human subjects* (2008), Article 32. http://www.wma.net/en/30publications/10policies/b3/index.html. Emphasis added.
25. *Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research* (Strasbourg, 25.I.2005), Article 23. http://www.coe.int/t/dg3/healthbioethic/Activities/02_Biomedical_research_en/195%20Protocole%20recherche%20biomedicale%20e.pdf
26. David A. Braunholtz, Sarah J. L. Edwards and Richard J. Lilford, "Are randomized clinical trials good for us (in the short term)? Evidence for a 'trial effect'", *Journal of Clinical Epidemiology* 54, no. 3 (2001): 217-24.

those in the placebo arm. For example, in 'crossover trials' all participants receive a period of active therapy as well as a period on the placebo. However, this trial design is not possible in all cases and could result in *all* participants being disadvantaged relative to non-participants who receive uninterrupted access to an established treatment. Alternatively an undertaking may be given that those assigned to the placebo arm will be provided with whichever treatment proves most effective at the end of the trial. This, however, may not be possible or may not eliminate the disadvantage of being assigned to the placebo arm if the treatment is time-critical.

The research in Case Study 5.1 is less problematic than many placebo-controlled trials in that patients are *not* denied the standard (drug) treatment for Parkinson's disease but receive the placebo surgery in addition to it. In another respect, however, this trial is more problematic than typical placebo-controlled trials, because placebo surgery poses a greater risk to participants than the inactive placebo drugs used in pharmaceutical RCTs. It should be noted, however, that the general risks of surgery add to the consequentialist case for the trial, as without the effectiveness data that it generates we risk imposing the risks of surgery on patients unnecessarily.

Equipoise

Although much of the controversy about RCTs focuses on the use of placebos, concerns about the disadvantage that research subjects may suffer, and about possible violation of the therapeutic obligation, are also generated by the random allocation of subjects between experimental and control groups more generally. This has given rise to the doctrine of equipoise.

The question that the doctrine of equipoise attempts to address is whether it is possible to act in the best interests of a patient, or other research subject, while randomly allocating them between different arms of a trial. Consider a case in which a group of patients have consented to take part in a trial. Half of them (group A) will be given an experimental treatment. The other half (group B) will be given the established treatment, which is believed to be moderately effective. There are various beliefs that the doctor administering the treatments (and others involved in the research) might have about their relative merit, for example:

a) The experimental treatment is likely to be more effective than the established treatment.
b) The established treatment is likely to be more effective than the experimental treatment.
c) The prospects of success are equally good for both treatments.
d) I just don't have any view about which will be more effective.

If the doctor believes (c) or (d) then the problem does not arise, but if she believes (a) or (b) then we are confronted with the problem of treatment preference. If she believes (a) then it seems that the therapeutic obligation, or just the requirement to prioritise the interests of individual patients over those of society, requires her to give the experimental treatment to *all* the patients, not just those in group A. If she believes (b) then it seems that she has an obligation to provide the established treatment to *all* patients, not just those in group B. In the case of a multi-arm study such as the case study, it seems that unless the doctor is neutral between the treatments in all its arms she will have an obligation to provide whichever one she believes best to all the patients. This state of neutrality is what is referred to as 'equipoise'.([27])

The problem here is that it is not clear that researchers are ever neutral between the treatments provided in different arms of a trial. Although there will not be conclusive evidence in advance of a trial, in order to get to the RCT stage there will generally have to be *some* reasons to believe the experimental treatment to be superior to what is currently available (e.g. more

27. Charles Fried, *Medical Experimentation: Personal Integrity and Social Policy* (Amsterdam: North Holland Publishing, 1974); Lawrence W. Shaw and Thomas C. Chalmers, "Ethics in cooperative clinical trials", *Annals of the New York Academy of Sciences* 169 (1970): 487-95.

effective or less risky). And, as Question 6 invites us to consider, even if the researcher was in equipoise at the beginning of the trial, preliminary results are likely to give some indication that one of the treatments is superior before the trial is completed and before achieving the degree of statistical significance necessary for publication and regulatory approval. In cases where preliminary results give a very strong indication of the superiority of one of the treatment arms, trials are terminated. However, if this were to happen every time equipoise was lost then RCTs of more than a very short duration would become impossible.

In response to these problems an alternative view of equipoise has been proposed by some researchers, most notably Freedman.([28]) According to this view, instead of thinking of equipoise as a psychological state of an individual researcher, we should think of it as a state of uncertainty of the relevant *community*. An RCT can be justified when there is disagreement within the clinical community about which treatment is best, and it can be argued that a patient is not disadvantaged by random assignment to one of a range of treatments as long as each of the treatments is considered best by some section of the clinical community and would be selected by some clinicians when treating patients outside a clinical trial.

Equipoise in this sense is more likely to exist than a strict neutrality in the minds of individual researchers; indeed, it is the lack of consensus within the clinical community that creates the need to conduct a trial. Moreover, even if preliminary trial data gives some reason to prefer one treatment over another, it is unlikely that a trial will lead to consensus being reached (and therefore to equipoise being broken) until statistically significant results have been obtained and submitted to peer review.

There are, however, some difficulties with this version of the equipoise doctrine. It is not clear that the boundaries of the relevant community, or the extent of disagreement necessary for equipoise to exist, are well-defined. How many people need to reject a prevailing consensus in order for equipoise to exist, and does it matter whether they are researchers or clinicians, and the extent to which they are specialists in the relevant field? Even if we can agree about the criteria for clinical equipoise, does this justify a researcher subjecting patients to a treatment that he or she personally believes to be sub-optimal? More fundamentally, is equipoise necessary to justify RCTs, or is a more important consideration the willingness of subjects to consent to random allocation between treatment regimes?

RCTs and consent

The principle of equipoise attempts to identify circumstances in which trial participants can be assigned to a placebo or control treatment without being disadvantaged. However, the principle of respect for autonomy suggests that we should allow people to make this judgement for themselves. One reason for this is that what is best for an individual depends not only on clinical effectiveness and safety but on preferences and values of the individual concerned, so if the aim is to avoid subjecting people to disadvantage then arguably the best way to ensure this is to provide them with sufficient information (including information about differences of opinion within the clinical community) and allow them to decide for themselves. Another reason is that, in accordance with Mill's harm principle, respecting people's autonomy may involve allowing them to act on their own decisions even when this goes against their best interests. Thus, if someone wishes to enter a trial that could disadvantage them, either for altruistic reasons, or because the values they place on the various possible outcomes make it attractive to them to gamble on a particular outcome, then it may be objectionably paternalistic to prevent them from doing so. Arguably, therefore, what matters in assessing an RCT is not the indifference between the arms of the trial of a clinician or the clinical community, but the willingness of the subject to consent to being randomly allocated.([29])

28. Benjamin Freedman "Equipoise and the ethics of clinical research", *New England Journal of Medicine* 317, no. 3 (1987): 141-5.
29. Robert M. Veatch, "Indifference of subjects: an alternative to equipoise in randomized clinical trials", Social Philosophy and Policy 19, no. 2 (2002): 295-323.

There are, however, practical limits to the ability of consent to justify use of controls and placebos. First, as in other contexts, consent cannot be used to justify risks or burdens borne by people who lack the capacity to give valid consent, for example young children, incompetent adults, or those who are excessively vulnerable to manipulation or coercion. Thus, even if it is the case that consent is the preferred mode of justification when exposing competent subjects to risks, it remains necessary to consider the questions of harm and disadvantage raised by the equipoise debate when considering the justifiability of entering non-competent subjects into RCTs.

Second, there are features of RCTs that can undermine the validity of a consent even when it is given by a generally competent subject. For example, RCTs often involve experimental treatments that are not available except through the trial. In some cases, the prospect of receiving such a treatment might act as an inducement that could undermine the voluntariness of the participants' consent. As with other inducements, however, it should not be assumed that having a strong reason to consent makes it impossible to do so voluntarily, but rather we would have to consider whether the incentive provided by the treatment interfered with the process of rational deliberation.

A more pervasive factor affecting the ability of otherwise competent subjects to consent to participation in an RCT is the difficulty that many have in understanding the nature and implications of RCT methodology. Studies have shown that many patients fail to understand a crucial aspect of RCT methodology, believing, even after the process of randomisation has been explained to them, that they will be assigned a treatment on the basis of their individual therapeutic needs. This misunderstanding, known as the 'therapeutic misconception', appears to be persistent in the face of efforts to develop new ways of explaining randomisation to subjects, and also casts doubt on the possibility of obtaining valid consent. ([30])

Further issues

Question 7 invites consideration of ethical issues relating to particular arms of the trial. Some of these are issues that have already been discussed above, in connection with the balancing of risks and benefits, while others relate to the particular therapies being investigated rather than the means used to investigate them.

A trial involving only arms 1, 2 and 3 would avoid the ethical concerns associated with use of placebo but, for reasons discussed above, might undermine the actual or perceived methodological validity of the trial, leading to the loss of some or all of its intended benefits. Although trials with active controls can sometimes be effective, and can avoid the difficulties associated with placebos, this depends on the level of effectiveness and safety of the control treatment being well-established so that it can be used as a reference point for assessing the experimental treatments. In the present case, however, all of the remaining arms of the trial involve experimental treatments whose efficacy and safety are unknown. It therefore seems unlikely that such a trial could produce useful results. Moreover, in this case the argument for avoiding placebo is weakened by the fact that patients receiving the placebo will not be deprived of treatment but will receive the standard drug treatment as well as the sham surgery. Whether the placebo arm is objectionable is likely to depend on how much risk is introduced by the sham surgery.

A trial involving only arms 1, 2 and 4 would avoid the particular risks arising from xenotransplantation and in particular the risk of zoonosis. This is an important

30. Edward Fried, "The therapeutic misconception, beneficence, and respect", *Accountability in Research* 8, issue 4 (2001): 331-48; Angus Dawson, "What should we do about it? Implications of the empirical evidence in relation to comprehension and acceptability of randomisation", in *Engaging the World: The Use of Empirical Research in Bioethics and the Regulation of Biotechnology*, Søren Holm and Monique F. Jonas, eds. (Netherlands: IOS Press, 2004): 41-52.

consideration since the risk of zoonosis potentially affects a large population from whom it would be impracticable to obtain consent. Therefore, if the risks to the population at large are considered to be above the minimal level that can be justified without consent, dropping the xenotransplantation arm might shift the trial from being unacceptable to being acceptable. It would, however, mean that the trial was investigating only one, rather than two types of treatment, reducing the potential benefits to future patients. A trial without the xenotransplantation arm could also be more acceptable to people who object to the harming or killing of animals in the course of medical research and treatments. Animal welfare is an issue that is not usually within the remit of committees that conduct ethical review of research involving human participants, since it is often subject to separate legal and regulatory provision. However, it raises an interesting question about the extent to which members' personal views on such matters should influence the decisions made by research ethics committees.

A similar issue arises in relation to the use of fetal tissue in arms 1 and 2 of the trial. The moral status of the human fetus, like that of non-human animals, is a matter on which research ethics committee members may have strongly divergent views. One difference between the two cases is that opposition to the use of fetal tissue often has a religious basis, while opposition to the use of animals in xenotransplantation typically does not. ([31]) This raises the question of whether religion-based views on bioethical issues should be accorded any special status different from the status accorded to the secular judgements of individuals. The significance of different views on the moral status of the fetus will be considered further in Chapter 8, alongside other ethical issues arising from the content of what is being researched rather than the research process itself.

Further reading

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31. The Council of Europe report found that although there is some divergence of opinion within the major religions, only Buddhism is consistently opposed to xenotransplantation. *Report on the State of the Art in the Field of Xenotransplantation* (Strasbourg, 21 February 2003). http://www.coe.int/t/dg3/healthbioethic/Activities/06_Xenotransplantation_en/XENO(2003)1_SAR.pdf

Chapter 6 **Justice in research**

Learning outcomes

You will develop an understanding of ethical issues about justice and the related concepts of exploitation and discrimination in research. Specifically you will acquire:

- Knowledge of the definition and ethical significance of exploitation.
- An understanding of the relation of exploitation to other phenomena such as inequality, vulnerability and consent.
- An ability to reflect on the ethical significance of background inequalities which form the context for research but are beyond the control of the researchers.
- An understanding of the ethical problems associated with exclusion from research participation.
- An understanding of the definition and ethical significance of discrimination, including the distinction between direct and indirect discrimination.
- An ability to assess and distinguish between justifiable and discriminatory inclusion and exclusion criteria.

Introduction

This chapter examines concerns about justice and injustice as they relate to research. The principle of justice was identified in Chapter 1 as one of the 'four principles' that are commonly taken to cover the range of ethical issues arising in biomedical contexts, and is the only one of the four principles not yet to have been explored in this textbook. The issues to be addressed in this chapter fall into two broad categories:

- concerns about researchers unfairly taking advantage of research subjects and imposing unfair burdens on them for the sake of benefits to themselves or others; and
- concerns about unfair exclusion of particular groups from participation in research and the benefits that may attach to research participation.

The former is broadly about the exploitation of research subjects while the latter is broadly about discrimination.

Exploitation is a common theme in criticisms of particular research projects, particularly those that involve paying inducements to participants, and research conducted in developing countries. However, since there is no agreed definition of 'exploitation', it is not always clear what these criticisms amount to. Hence, in order to assess both the general usefulness of the concept of exploitation and its application to particular cases, we need to consider what exploitation is and what is wrong with it.

Although exploitation of research participants continues to be a concern for researchers and research ethics committees, there has in recent years been an increasing awareness that excluding groups of people from participation in research, even when this is done out of a wish to avoid exploiting or harming members of vulnerable groups, can itself lead to injustice and harm.([1]) Such exclusions may harm members of the excluded groups both by depriving them of the direct benefits of research participation and by reducing the evidence base relating to the treatment of those groups.

The issues addressed in this chapter connect in various ways with the major themes previously discussed in this textbook. Justice, in the sense addressed here, is about the distribution of benefits and burdens, and so relates to issues discussed in Chapter 5. Consent arises in relation both to exploitation and to exclusion from trials. And the analysis of exploitation will show that it is closely related to the notion of vulnerability.

To avoid confusion it should be noted that the term 'justice' is used in different ways. In a wide sense, it is used to refer to that part of ethics that concerns rights or obligations (or is enforceable), while narrower senses include distributive justice (which relates to fairness in the distribution of benefits and burdens), retributive justice (the infliction of punishment), rectificatory and restorative justice (compensating or otherwise making amends for previous injustices) and procedural justice (use of fair procedures for decision-making). This chapter is concerned with distributive, and, to a lesser extent, procedural justice.

The chapter includes three case studies. Two of these are intended primarily to focus discussion on issues of exploitation while the third is intended to focus discussion on the issues of exclusion and discrimination in relation to access to trials.

1. Anna Mastroianni and Jeffrey Kahn, "Swinging on the pendulum", *Hastings Center Report* 31, no. 3 (2001): 21-8.

Case Study 6.1
Recruiting homeless participants to Phase 1 trials

A large pharmaceutical company conducts Phase 1 trials of its products at a specialist trials unit in a major European city.([2]) These are trials conducted using 'healthy volunteer' subjects and designed to test the safety and pharmacological effects of new drugs, and to establish maximum tolerated dose levels. The products being tested have all undergone prior testing on animals, and in some cases there will have been previous trials in humans.

Volunteers typically spend between a few days and several weeks in the unit. After completing a questionnaire and undergoing initial health checks and baseline measurements, they will receive one or more doses of the product under investigation, while being subject to regular monitoring and assessment. Volunteers are required to report any adverse effects, and medical staff are on hand in case treatment is needed.

Because subjects participating in Phase 1 trials receive no therapeutic benefit it is usual for them to be paid. The unit's recruitment materials (leaflets and posters, which volunteers are encouraged to take away and distribute) state that "compensation for time and inconvenience" will be paid "according to the length and nature of the trial". In addition, the leaflets highlight the fact that meals and accommodation are provided free for the duration of the trial, and that entertainment and recreational facilities are provided.

In the past the company has had little difficulty in getting its trials approved by the research ethics committee, and it has a good safety record. However a new REC member has questioned the level of payments offered to volunteers and discovered that these are much lower than those typically offered by other pharmaceutical companies. Further investigation reveals that a large proportion of the volunteers are long-term unemployed and homeless (most of the addresses supplied on the initial questionnaire are for local hostels for the homeless or other temporary accommodation). Many are thought to be alcoholics or drug addicts, although they have to declare themselves 'clean' at the time of registering for a trial and will be unable to consume alcohol or drugs (other than the investigational product) while in the unit. It is also evident that, despite an absence of high-profile advertising, the unit is widely known, with many volunteers travelling long distances to participate in trials. Many have participated in trials for this or other companies on several previous occasions, and although the eligibility criteria specify a minimum of three months between trials there is some evidence of volunteers falsifying their identity to overcome this restriction.

The company is unapologetic about its low payment levels or the socioeconomic groups from which its subjects are drawn. It argues that the ease with which it recruits volunteers demonstrates that the benefits to participants are substantial, and that higher payments might amount to undue inducement. It also points out that the number of participants withdrawing from trials is very low, as is the number of complaints received.

2. This case shares some features with the recruitment practices reported in Laurie P Cohen, "To screen new drugs for safety, Lilly pays homeless alcoholics: it's 'quick cash' to habitues of Indianapolis shelters; it vanishes quickly, too", *Wall Street Journal* (Eastern Ed.) (November 14, 1996): A1, A10.

Questions

1. What advantages does the pharmaceutical company gain by recruiting from a disadvantaged sector of society, and what benefits do the volunteers gain from participation in the trials?
2. What disadvantages or risks does this method of recruitment have for the company and for the volunteers?
3. Are there grounds for considering the company's recruitment practice to be exploitative? If so what are they, and do you agree that it is exploitative?
4. What changes, if any, would the company need to make in order to persuade you that its recruitment practice was morally acceptable?

Benefit and risk

The first two questions in this case study relate to the discussion of harm and benefit in the previous chapter, but also have a bearing on the questions of whether the research described in the case study is exploitative, and if so what the moral force of this fact is.

Although the real case on which this case study is loosely based has generated a large amount of hostile comment, that hostility may be difficult to justify if the way in which participants are recruited benefits all parties. In the case study it appears that the company's recruitment practices do have the potential to benefit both the company and the participants. Benefits to the company include:

- the lower level of payment necessary to attract volunteers;
- the fact that recruitment by word of mouth avoids the need for expensive advertising;
- the fact that participants for whom the payment is an important consideration and who hope to participate in future trials may be less likely than more affluent volunteers to withdraw part way through a trial, and, if adverse events occur, less inclined to seek legal redress and more willing to accept lower levels of compensation.

Benefits to the participants include:

- payment (which even if relatively low may be very significant to individuals with few economic resources to draw on);
- food and accommodation (which may be an important benefit for impoverished and homeless volunteers);
- recreational and entertainment facilities;
- the opportunity to be in a safe, medically supervised environment free from alcohol and illicit drugs.

The fact that both parties stand to gain from the arrangement suggests that there may be a consequentialist case in favour of it, although to establish this it would be necessary to compare the effects of the recruitment practices described in the case study with alternative practices in which, for example, the company had greater costs, but the participants (drawn from a less disadvantaged population) received higher payments and, when necessary, higher compensation for adverse outcomes.

One reason for thinking that recruitment from the disadvantaged group would be supported by consequentialism (or more specifically utilitarianism) is that although utilitarianism tells us simply to maximise the amount of welfare resulting from our choices and is neutral about how that welfare is distributed, in practice it tends to favour redistribution of resources towards the more disadvantaged because of the phenomenon of diminishing marginal returns. This refers to the fact that a given amount of resources made available to someone who has very little will tend to produce more benefit for that person than the same amount of resources made available to someone who is better off to start with. In relation to the case study, this means that even though the company benefits by paying less to its recruits than other pharmaceutical companies do, the recruits themselves may gain as much or more benefit than better-off recruits would gain from larger payments.

This, however, does not establish a conclusive utilitarian case for the company's recruitment practices. Utilitarianism tells us to compare *all* the available

alternatives and choose the one that produces the most welfare. The available alternatives in this case would include arrangements in which disadvantaged people were recruited as subjects but paid (and if necessary compensated for adverse outcomes) at a much higher rate than the company is choosing to pay. This might be worse for the company but would be better for the recruits, and might plausibly produce more overall benefit.

Perhaps more importantly, given the discussion in the previous chapter, the fact that both parties stand to gain from the company's recruitment policy will tend to undermine deontological objections to the recruitment policy, based on the wrongness of sacrificing one party's interests for the benefit of another. If the arrangement is mutually beneficial, then no such sacrifice occurs.

These arguments, however, ignore the risks arising from way in which participants are recruited. Risks to the company include reputational damage arising from the fact that it appears to be acting exploitatively (the appearance matters here since reputational damage may be suffered even if the company's practices are not *actually* exploitative). The company may also be harmed (as may future patients treated with its products) if the scientific quality of its trials is compromised by participants lying about their drug use or medical history in order to get into the trials, or concealing adverse reactions for fear of being removed from the trials. This may be a significant risk, given that recruits are already motivated to accept lower than normal levels of payment, and in some cases to falsify their identity in order to evade the waiting period between trials. The fact that such falsification has been found to occur may suggest that the company's procedures for verification of claims made by its recruits are inadequate.

The concealment of relevant information may also put the participants at increased risk of harm, and, while the risks to the company (and to future patients) may undermine the utilitarian case for its recruitment practices, risks to the participants may undermine both the utilitarian case and the claim that nobody's interests are sacrificed for the benefit of others by the company's decision to recruit from a disadvantaged section of society. These counterarguments, however, depend on how the risks weigh up against the benefits. The fact that the participants choose, apparently with some enthusiasm, to participate indicates that they themselves believe the risks to be outweighed by the benefits. There may, however, be concerns about the validity of their consent, especially in cases where they conceal risk factors and therefore cannot be fully informed about the level of risk that they face, or where alcohol or drug addiction interfere with their ability to make autonomous choices.

Exploitation

Question 3 invites us to identify the features of the company's practice in virtue of which it could be considered exploitative, and to assess whether in fact it is a case of exploitation. 'Exploitation' has both a moral and a non-moral sense. We employ the term in the non-moral sense when we speak of exploiting a natural resource, an opportunity, or our own talents, locutions which imply no moral condemnation. When we speak of exploiting a person, however, we typically employ the term in its moral sense. In both cases, to exploit something or someone means, roughly, to use or take advantage of it or them, but in the moral case it implies using or taking advantage in a way that is at least *prima facie* morally wrong. Exploitation in the moral sense is also thought of as a form of injustice: to exploit someone is, amongst other things, to treat them unfairly. These elements are captured by Wertheimer's working definition of exploitation as taking unfair advantage of someone.([3])

The concept of exploitation is often employed in economic contexts, particularly in relation to the exploitation of workers by employers. Economic exploitation

3. Alan Wertheimer, *Exploitation* (Princeton University Press, 1996): 12.

is often characterised in terms of an *unequal exchange*, in which "the exploited party gets less than the exploiting party, who does better at the exploited party's expense". ([4]) Unequal exchange cannot, however, be a sufficient condition for exploitation, since we would not normally consider a freely given gift, a discount offered to a friend by a tradesperson, or an altruistic decision to participate in research, to be a case of exploitation. There must, therefore, be some other defining feature(s) present in those cases of unequal exchange that we do consider to be exploitative. However, even if we assume (for now) that the additional feature(s) necessary for exploitation are present in the case study, the account of exploitation as unequal exchange does not provide grounds for thinking that the research described in the case study is exploitative.

The most obvious cases of unequal exchange would be transactions from which the exploiter benefits while the exploited person is harmed. This relates to a distinction made by Wertheimer between *harmful* and *mutually beneficial* exploitation. ([5]) Mutually beneficial exploitation is, as Wertheimer notes, the more interesting category, because transactions that impose harm on one party will usually be unethical independently of whether they are judged to be exploitative. ([6]) From a research ethics perspective the interesting question is whether being exploitative can make a piece of research unethical in cases that are not already rendered unethical by other principles such as non-maleficence or non-violation of basic rights.

Relating this distinction to the case study, it appears that the transaction between the company and the volunteers may well be mutually beneficial. There are risks to participants (particularly if they conceal risk factors when being admitted to a trial), but the potential benefits are quite considerable and appear to be judged so by the participants themselves. Moreover, it is not clear that the gains to the research participants are smaller than those to the company. In monetary terms the benefits to the participants (payments plus cost of accommodation, food, etc.) may be smaller than the benefits to the company (proportion of expected profits attributable to the contribution of the participants), but in terms of effects on welfare, and taking into account the phenomenon of diminishing marginal returns, the participants may gain more than the employees and/or shareholders of the company. Indeed, it is because the benefits of participation make such a difference to the participants' welfare that they are so easily recruited despite the low payment levels.

Does the absence of an unequal exchange (in the sense of the company gaining more from the transaction than the participants) show that the relationship between the company and the participants in the case study is non-exploitative? One reason why we might reject this conclusion is that the company can be characterised as exploiting the participants not only on its own behalf but on behalf of the future users of its medicinal products. In this case the combined benefits to the company and future users may be much larger than those gained by the company alone, and may exceed those gained by the participants. ([7]) A more fundamental reason is that unequal exchange in this sense is not a necessary feature of exploitation. Wertheimer illustrates this point with the example of a doctor who charges several times the usual fee for a life-saving treatment, knowing that the patient is desperate and has

4. Andrew Levine, *Arguing for Socialism* (London: Verso, 1988): 66-7. Levine is aware that other conditions must also be met for such an exchange to count as exploitative. In Marxist economic theory, from which much discussion of economic exploitation derives, the unequal exchange element of exploitation is characterised in terms of the worker being paid less than the value that his or her labour creates.
5. Alan Wertheimer, *Exploitation* (Princeton University Press, 1996): 13.
6. For analogous reasons *consensual exploitation* is a more interesting category than *non-consensual exploitation*. See Wertheimer, *Exploitation* (Princeton University Press, 1996): 14.
7. For contrasting views of how best to characterise the position of someone who exploits on behalf of a third party see Alan Wertheimer, *Exploitation* (Princeton University Press, 1996): 210-11 and Stephen Wilkinson, *Bodies for Sale: ethics and exploitation in the human body trade* (London: Routledge, 2003): 19-20.

no cheaper alternative available.([8]) Most people will intuitively judge such an action to be exploitative even though the treatment is worth more to the patient than the inflated fee is to the doctor.

This example points to a different kind of asymmetry in the relationship between the company and research participants in the case study. Like the exploitative doctor, the company in the case study enters into what we are assuming to be a mutually beneficial transaction, but on terms that are more favourable to it and less favourable to the other party than the established norm for that kind of transaction. Thus, while the subordinate party may be better off as a result of the transaction than they would be by rejecting it, they may nevertheless *be disadvantaged relative to some other way in which the transaction could have been conducted.* This will only be morally significant, however, if the baseline against which the subordinate party is disadvantaged is itself morally significant.

This idea is captured by Wolff's suggestion that, while exploitation need not make the exploited person "worse off than they would have been without the exploitative arrangement", it does require that they are made worse off in some sense, and that the best account of this is "that the person is made worse off than they ought to be".([9]) The difficulty with this account lies in defining the morally relevant baseline. Taking the established norm as the baseline would make the notion of exploitation excessively relativistic, as the customary level of payment may be inappropriately high or low, so that a departure from it represents a move towards rather than away from a fair exchange.

In the case study we are allowing that the recruits may benefit overall from participation in the trial, and that they may benefit more than the company from their participation. The implication of the view discussed in the last two paragraphs is that they may nevertheless be exploited insofar as they benefit less from the transaction than they ought to. The question then is how much they ought to benefit. How much is the company obliged to improve the benefits that it offers to participants in order to meet the requirements of justice? One way of attempting to answer this question is by focusing not directly on the benefits received by each party but on the conditions under which the parties agree to the package of benefits and burdens.

In both the exploitative doctor case and the case study, the dominant party uses its bargaining power to achieve an arrangement that is more favourable to it and less favourable to the subordinate party than might otherwise have been agreed. In both cases what leads the subordinate party to agree such terms is the lack of preferable alternatives. In the exploitative doctor case the patient has no cheaper way of securing the life-saving treatment that she needs, and in the case study the participants are likely to have few, if any, alternative ways of obtaining money, food, shelter, etc. The participants are not coerced into entering the trial by the company, since the company uses no force and issues no threats (in particular, there is no suggestion that anybody who refuses the company's offer will be worse off than if the offer had not been made). What leads them to accept the offer is the disadvantaged position that they are in prior to the offer being made. The subordinate party may thus be said to be disadvantaged not relative to their situation before entering into the transaction but relative to the position that they would have been in had they negotiated the terms of the transaction from a less disadvantaged starting point.

This analysis of the case study is consistent with the view that exploitation, in the moral sense, consists in taking unfair advantage of someone, and with Wood's more specific suggestion that exploitation (of persons)

8. Alan Wertheimer, "Exploitation in heath care", in *Principles of Health Care Ethics*, Richard E. Ashcroft, Angus Dawson, Heather Draper and John R. McMillan, eds. (Chichester: John Wiley & Sons, 2007): 249.
9. Jonathan Wolff, "Marx and exploitation", *Journal of Ethics* 3, no. 2 (1999): 113.

consists in "using something about the [exploited] person for the exploiter's ends by playing on some weakness or vulnerability in that person".([10]) On this analysis the way in which the company takes unfair advantage of the research participants is by using the imbalance of power between it and the research participants, stemming from the latter's disadvantaged situation and consequent limited range of alternatives, to press its own advantage.

The moral force of exploitation

In order to decide how to respond to the case study we need to consider what is wrong with the kind of exploitation that appears to be present in it.

We have seen that exploitation is not always harmful to the exploited person and does not always involve the exploited person receiving less benefit than he or she provides to the exploiter. We have also seen that exploitation is not necessarily coercive. It might be thought that the validity of exploited people's consent is undermined by the limited range of alternatives available to them. However, this view is problematic given that we accept the possibility of a patient validly consenting to a life-saving operation even when the sole alternative is death.

An alternative explanation of the wrongness of exploitation is that it involves a failure to comply with the principle of respect for persons. Wood, for example, writes that:

> *Proper respect for others is violated when we treat their vulnerabilities as opportunities to advance our own interests or projects. It is degrading to have your weaknesses taken advantage of, and dishonorable to use the weaknesses of others for your ends.*([11])

Interpreting this in Kantian terms([12]) we may note that since exploitation involves *using or taking advantage of* others, it necessarily involves treating them as means. According to Kant's categorical imperative it is permissible to treat people as means provided we simultaneously treat them with the respect that they are due as agents or ends in themselves. Arguably, however, by taking advantage of another person's vulnerability to get a better deal for himself, an exploiter places too much weight on the exploited person's value as a means to his own ends and too little on their intrinsic value as an end in themselves.

Although a Kantian notion of respect for persons is often associated with absolute moral constraints, it does not follow from the account given here that exploitation is always wrong or that people should always be prevented from entering into exploitative relationships. One reason for this is that respect for persons is often taken to involve respecting their autonomy, and this suggests that people should be allowed to enter into exploitative relationships if they do so on the basis of valid consent. It might also be the case that prohibiting a disadvantaged person from engaging in an exploitative but non-harmful relationship would leave them more vulnerable to other, more serious forms of exploitation.([13]) For example, the participants

10. Allen Wood, "Exploitation", *Social Philosophy and Policy* 12, no. 2 (1995): 147. This sort of account can also provide the additional element necessary in 'unequal exchange' accounts of exploitation to distinguish exploitation from gifts and other morally unobjectionable unequal exchanges. Thus, for example, Levine supplements his unequal exchange definition quoted above with the claim that "the exchange must result from relations of unequal power".
11. Allen Wood, "Exploitation", *Social Philosophy and Policy* 12, no. 2 (1995): 150-1.
12. Wood's claim that it is dishonourable to use the weaknesses of others for your own ends also suggests a concern for the character of the exploiter, which would enable virtue ethics to engage with this account of exploitation.
13. See the discussion of agent neutral objections to exploitation in Martin Wilkinson and Andrew Moore, "Inducement in research", *Bioethics* 11, no. 5 (1997): 384-5.

in the case study, if prevented from enrolling in the trials, might turn instead to drug-trafficking, prostitution or illegal sweatshop employment in order to raise money. A concern to avoid people being treated in disrespectful, degrading or harmful ways might then lead us to permit the less serious cases of exploitation in order to avoid the worse cases.

Turning to Question 4, there are two kinds of change that the company could make, or that an ethics committee could insist on, to avoid the research being exploitative. Firstly, the company could choose not to recruit from vulnerable sectors of the population. This would avoid the company exploiting them but could leave them open to greater exploitation from other sources as it would reduce the range of options open to them. It is also arguable that it would fail to uphold the principle of respect for persons if it meant preventing vulnerable but competent persons from acting on their autonomous choices.

There could also be a consequence-based argument against this course of action, as it would mean diverting resources from more needy to less needy individuals. However, if the involvement of vulnerable people, who are tempted to conceal medical factors relevant to the research, undermines the scientific rigour of the trial then consequence-based considerations relating to the wellbeing of future consumers of the investigational products would favour the use of less vulnerable participants.

Secondly, the company could continue to recruit from the vulnerable population but improve the levels of payment and compensation. It would then avoid taking advantage of their vulnerability and would increase rather than reduce the resources available to the disadvantaged group. A disadvantage of this policy is that it would increase the incentive that potential participants have to conceal medical conditions or other factors that might lead to their exclusion from the trial, although it might be possible to counter this by more rigorous screening and verification.

Case Study 6.2
Tuberculosis vaccine research in a developing country

Tuberculosis (TB) is a major cause of morbidity and mortality, with nearly nine million new infections and two million deaths per year worldwide. Incidence of the disease is highest in developing countries, particularly in Africa, but it is also a problem in developed countries, some of which have seen a resurgence of the disease after earlier falls, as a result of antibiotic resistance, reduced immune response due to HIV infection and migration from parts of the world in which the disease is rife. The most commonly used vaccine against TB is Bacile Calmette-Guérin (BCG). However, while this is effective in young children, its effectiveness is more variable in adolescents and young adults, and it is not recommended for patients with impaired immune systems. In addition to problems of antibiotic resistance, drug treatments have had limited impact in developing countries due to cost and poor compliance.

Development of new, more effective vaccines appears to be the most promising strategy for controlling and eventually eradicating TB. Several potential vaccines have been developed as a result of advances in understanding the genome of the infectious agent (Mycobacterium tuberculosis). Some of these have undergone Phase 1 testing in

Europe, and now European researchers working on a Modified Vaccina Ankara (MVA) vaccine wish to carry out further trials in various countries including Mozambique, a country classified by the United Nations as one of the world's least developed and with prevalence rates among the highest in the world for HIV and TB.

The proposed trial in Mozambique is designed to test the effectiveness of the new vaccine when used post-infection and in conjunction with BCG. It will run for five years and will involve the following arms:

1) BCG only in adult males not known to have HIV;
2) BCG plus MVA in adult males not known to have HIV;
3) BCG only in adolescent males not known to have HIV;
4) BCG plus MVA (lower dose) in adolescent males not known to have HIV;
5) BCG only in subjects in the early stages of HIV;
6) BCG plus MVA in subjects in the early stages of HIV.

Participants will be subject to monthly health checks, which will include monitoring of weight, blood tests and sputum tests. They will be given advice on healthy eating and where necessary provided with the resources to maintain a healthy diet (for themselves and their families). Consent will be obtained in the standard way.

Costs will be lower than if the trial was conducted in Europe, and the high prevalence of TB should make recruitment of subjects relatively quick and easy. The researchers argue that it is important to test the vaccine in populations similar to those in which it is intended to be used. However, some members of the research ethics committee question the affordability of the vaccine for a country as impoverished as Mozambique and contend that, while it may be affordable for richer African countries, such as South Africa, the primary use is likely to be in those developed countries that are experiencing an increase in TB infection.

Questions

1. What ethical problems are raised by this case?
2. In what ways might the trial be considered exploitative?
3. How might the researchers respond to accusations of exploitation? Would they be right to reject such accusations?
4. Would it be acceptable to include placebo control arms in the trial if the region in which it is carried out is one in which BCG is not usually available?
5. Should the trial be allowed to go ahead as it stands? If not, are there any modifications that could be undertaken to make it ethically acceptable?

Research in developing countries

Although charges of exploitation in research are made in a variety of contexts, one of the most common is in relation to developing countries. Case Study 6.2 allows us to extend the discussion of exploitation to this context and more generally to consider some of the ethical problems that arise when research is conducted in developing countries.

Question 1 provides an opportunity to consider the range of ethical issues raised by this case. As with all research involving human participants, one of the key issues is the acceptability of the risks and burdens to which the participants are subjected.

In any trial of a medical intervention one of the main risks is likely to be that of adverse effects from the interventions being tested. Given that the experimental vaccine (MVA) is relatively untested, while the BCG vaccine is widely used in many parts of the world, we might expect the former to be the main source of such risks. This would mean that participants in the control groups – who receive BCG only – would be subject to little risk and likely to benefit overall from an intervention that is generally safe, somewhat effective (although less so in the age groups on which it is being tested than in younger patients), and which might not otherwise

be accessible to the participants given relatively low immunisation rates in developing countries like Mozambique. It should be noted, however, that the researchers propose to test BCG – both alone and in combination with MVA – in HIV positive individuals, despite the fact that it is not usually recommended for use in people with compromised immune systems due to increased risk of 'BCG disease' (which is caused by the bovine bacterium in the vaccine). In addition, the risks from both interventions may be higher than they would be if the research was conducted in a developed country, because of factors such as the nutritional status and general health of participants and the less developed medical system and infrastructure.

Although a research ethics committee in the researchers' home country should be able to identify these risk factors, a problem faced by many research ethics committees is that they lack the resources or expertise to undertake an independent assessment of the risks caused by the research they review. In the case of research carried out in a distant location, and particularly one that is very different from the country in which the committee is based, this is likely to be exacerbated by a lack of detailed knowledge of the location where the research is to be carried out. This may make the research ethics committee somewhat dependent on the researchers' assessment of the risks, and in order to ensure that this is as robust as possible they may wish to ensure that this assessment is based on a thorough review of the available evidence and has (with the rest of the proposal) been subjected to peer review. In the case of research to be carried out in a different country the involvement of a local ethics committee may also provide important evidence confirming or supplementing the risk assessment made by the researchers.

In addition to the risks from the experimental and control interventions, participants may also face risks and burdens attached to the monitoring process – for example risks associated with blood tests and burdens associated with the loss of time and possibly of associated income. These are likely to be small but should be considered as part of the overall balance of benefit and risk. The research might also place burdens upon the local infrastructure, for example by taking up the time of health care workers or using facilities and equipment.

On the other hand, research in developing countries can benefit the local health care or research infrastructure. For example the researchers in the case study might pay local health care or research institutions for services or use of facilities, provide training to locally employed staff in research methods or skills related to vaccination programmes, or build facilities and provide equipment that will remain in place after the trial has ended. As with the risks to individual participants, some input from the host community could help a 'home' ethics committee to assess the true extent and significance of these infrastructural benefits and burdens.

A research ethics committee examining this proposal would also need to consider whether the vulnerability of some or all of the research participants creates a need for additional protections or safeguards, and whether it places them at risk of exploitation. The adolescent participants may be vulnerable in terms of their capacity to give valid consent. Some will have the understanding necessary to make an informed decision about whether to participate but others will not, so the researchers need to specify how competence will be assessed and what alternative or additional forms of authorisation will be sought for those unable to give valid consent, taking account of local legislation. There may also be a more general problem with consent due to low literacy levels. Although in principle it should be possible to overcome this by providing information in other forms, it may be difficult for researchers without local knowledge and language skills to ensure that the information is provided and understood unless they have considerable local support, and even with that support literacy and cultural issues may exacerbate the risk of therapeutic misconception.

Other participants may be vulnerable in ways that do not undermine their capacity to consent but do make them liable to harm or exploitation. Participants with HIV may be vulnerable because of their medical needs (which might lead them to participate in the trial in the hope of receiving medical attention for that condition, even though that is not what the trial is about) and the sensitivity of information about HIV status. The latter makes it necessary for the researchers to pay attention to confidentiality and information security, taking account of both moral principles and any relevant

local laws. The level of poverty that requires some participants to be provided with resources to maintain a healthy diet for the duration of the trial is another source of vulnerability, as is the combination of an under-resourced health care system and participants with TB, some of whom may not be able to receive any vaccination or other treatment outside the trial.

Questions 2 and 3 invite us to consider the ways in which the research described in the case study might be exploitative. In the discussion of the previous case study, exploitation was characterised as taking advantage of some vulnerability or weakness in order to further the exploiter's goals. Potentially any of the forms of vulnerability described above could give rise to exploitation. For example lack of understanding by participants (whether due to immaturity or literacy and language difficulties) could be exploited to gain agreement to participate in the trial, and threats to reveal information about HIV status could be used to coerce participants into signing up or continuing their participation. These actions, however, would be clearly unethical, and as in the previous case it is the possibility of consensual exploitation that creates the more challenging ethical problems.

The most likely sources of consensual exploitation in this case are the lack of a well-resourced health care system and the general poverty of at least some of the participants. Given these circumstances, the prospect of receiving medical treatment and/or resources to provide food for one's family might make it rational to choose to participate even though the balance of benefits and risks within the trial is one that a less disadvantaged individual, for example a typical inhabitant of a more developed country with a reasonable income and access to a well-functioning health care system, would be unlikely to accept. Whether or not the trial is exploitative will depend on whether the researchers take advantage of this vulnerability to further their own goals. For example, most people would judge the trial to be exploitative if the sole reason for conducting it in Mozambique was to enable it to be carried out more cheaply than could be done in the researchers' home country.([14]) In the description of the case study, however, it appears that there are reasons other than cost-saving for conducting the trial in Mozambique: in particular, if Mozambique is one of the countries in which it is hoped that the vaccine will be used, there may be good methodological reasons for testing it in that population. The fact that similar trials are planned for a number of countries, following Phase 1 testing in Europe, suggests that the researchers are aiming to test the efficacy and safety of the vaccine in a range of populations representative of its intended end use.

Even if reducing the costs of the trial is not what motivates the researchers to locate it in a developing country, the trial could still be exploitative if the researchers unfairly take advantage of the participants' vulnerability to reduce the costs of the trial. Our judgement about this is likely to depend on whether the participants receive a fair level of benefit in relation to the risks and burdens of participation. However, what counts as a fair level of benefit is likely to be harder to determine in a case like this than in research within a developed country. In the discussion of Case Study 6.1 it was suggested that one way of establishing a fair level of benefit would be to consider what a less disadvantaged participant would be likely to accept. Even in that case it was unclear what level of disadvantage (or lack of it) should be taken as the benchmark, but in international research this is even less clear, since benefits that are relatively cheap to provide to participants in a developing country might nevertheless be much more significant to those participants than the benefits that would be accepted by participants in a wealthier country. Providing very large benefits in relation to local standards of living might also provoke social tensions or other problems. One way of addressing this concern would be to ensure that the balance of benefits and risks for individuals is reasonable in relation to the standards of

14. Angela Ballantyne quotes figures estimating the cost of conducting clinical trials leading to regulatory approval of a new TB drug to be 2.7 times higher in the United States than in Uganda. See "HIV international clinical research: exploitation and risk", *Bioethics* 19, nos. 5-6 (2005): 486.

the country in which they live, but also to consider whether the benefits to the community as a whole are sufficient in the light of the contribution that it makes towards the research. This raises the issue of whether communities, as well as individuals, can be exploited.

Community exploitation

Gbadegesin and Wendler suggest that a community (rather than merely some of its members) should be considered to be involved in research if the research relies on the community's resources, focuses on its customs, traditions or practices, or focuses on a health feature of the community; and that in order not to be exploited the community must receive a fair level of benefits in relation both to its contribution and to the benefits obtained by others. ([15]) One reason for considering the balance of benefits and burdens at a community level, rather than just in relation to individual participants, is that the impact of burdens placed by research on a community's infrastructure may not be confined to research participants, and where this is the case it may not be possible to identify the particular individuals affected.

We have already noted some of the ways in which the community's health care system or research infrastructure might be burdened by, or conversely might benefit from, involvement in the research in the case study. However, a factor that may be much more significant in determining the balance of benefits between the community in which research takes place and others is the end use of the intervention being investigated.

If the research is primarily expected to benefit people outside the community in which it takes place but the decision is made to conduct the trial within the community, because of methodological, practical or financial advantages of doing so, then there is likely to be a concern that the community is being exploited for the benefit of others. In order to address this sort of concern it is sometimes suggested that a necessary ethical requirement for carrying out trials in developing countries is that if the tested interventions prove effective they will be made "reasonably available" to the host communities. For example CIOMS' *International Ethical Guidelines for Biomedical Research Involving Human Subjects* state that:

Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:

- the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
- any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community. ([16])

However, even leaving aside the vagueness of the term "reasonably available", this requirement presents a number of problems.

First, provision of the investigational product is not the only way in which the host community can be benefited. There could be cases in which there are strong practical or methodological reasons for basing research in a particular disadvantaged community, even though the targeted health need is not a priority for that community, and the community is no more likely than others to benefit from the intervention being tested. In such cases it might be possible to avoid exploiting the community by providing benefits other than availability of the tested intervention.

15. Segun Gbadegesin and David Wendler, "Protecting communities in health research from exploitation", *Bioethics* 20, no. 5 (2006): 248-53.
16. Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002), Guideline 10. http://www.cioms.ch/frame_guidelines_nov_2002.htm. See also the alternative to the 'reasonable availability' criterion in Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, "Moral standards for research in developing countries: from 'reasonable availability' to 'fair benefits'", *Hastings Center Report* 34, no. 3 (2004): 17-27, and Angela Ballantyne, "'Fair benefits' accounts of exploitation require a normative principle of fairness", *Bioethics* 22, no. 4 (2008): 239-44.

Second, satisfaction of this requirement does not guarantee that the host community receives fair benefits in relation to the burdens the research places on it. Even if the research is successful, targets a health need that is a priority within the community, and the product is made available to members of the host community, the research may be exploitative if the community is just one of a number to benefit but has borne a disproportionate share of the burdens.

Third, unless the requirement is interpreted in a very narrow way (e.g. as requiring availability of the product for a limited period for research participants only) it will often not be possible for researchers to guarantee that it is satisfied. Enforcing the requirement would therefore mean that valuable research, much of which would benefit the host community, could not be done.

The research in the case study addresses a health problem that is important in Mozambique and other developing countries, and, as we have seen, the researchers can plausibly claim that their reason for conducting trials in such countries is to ensure that the vaccine they are testing will be effective and safe under the conditions prevailing there. As noted in the case study, however, there is a concern that the cost of the vaccine will prevent it from being used in countries as poor as Mozambique, and that, irrespective of the researchers' intentions, it will end up being of benefit mainly to TB sufferers in more developed countries. Questions about future availability depend on political and economic factors that may be inherently unpredictable and which medical researchers and research ethics committees are unlikely to have expertise in. There are, however, things that can be done to minimise the chances of a disadvantaged host community ending up with an unacceptable balance of benefits and burdens.

First, it can be ensured that the host community receives benefits other than future use of the tested intervention, so that even if the latter fails to materialise, the community will still gain sufficient benefit to offset any costs.

Second, there should be consultation with representatives of the host community, so that the assessment of likely benefits takes account of the community's view about such things as the importance to the community of the intervention being researched, the likelihood of resources being available to provide it for members of the community in the event that it proves effective, and the likelihood and significance of any adverse impacts on the community. In the course of such consultations it would be important for the researchers to provide realistic predictions of the likely outcomes of the trial, and of the likely costs of any resulting intervention. It should be noted, however, that agreement to a trial by representatives of the host community does not on its own justify the trial. Firstly, it is necessary to consider whether the autonomy and interests of individuals are adequately protected; secondly there may be questions about whether the representatives truly represent the wishes of the community and whether they have the expertise and experience to judge whether a proposed trial offers a fair balance of benefits and burdens; and thirdly, if the community as a whole is in a weak negotiating position (for example due to a desperate need for the benefits foreign scientific investment can bring) then as with vulnerable individuals it may be rational for its representatives to agree to a mutually beneficial but exploitative arrangement.

Placebo controls in developing countries

We have seen that one important cause of vulnerability among research subjects in developing countries is the absence of treatment options that would be available to patients in countries with more developed health care systems. Question 4 raises a much-debated question about whether this lack of options can make it morally acceptable to conduct placebo-controlled research in developing countries which would be unethical if conducted in a country with better health care provision. We will consider this issue with reference to controversial trials of treatments for the reduction of perinatal transmission of HIV in developing countries.

Trials concluded in the US and France in 1994 established that mother-to-child transmission of HIV could be substantially reduced by treating the mother with the antiviral drug AZT during the last trimester of pregnancy and during delivery, and the newborn child for six weeks following birth. However, the cost of this

treatment was prohibitive for many developing countries, including those in sub-Saharan Africa, the region of the world worst affected by HIV. It was therefore important to establish whether shorter, more affordable courses of AZT would provide worthwhile reductions in HIV transmission. The short course was tested against a placebo control in a number of developing countries where the standard care for HIV-infected pregnancy did not include use of antiviral drugs.

Critics of the trials ([17]) argued that the use of placebo was unethical. One strand of this argument held that the use of placebo violated the principle of equipoise. Whether this is true depends on how the notion of equipoise is interpreted, since the evidence from trials of the longer course of treatment gave some reason to expect that a short course of AZT would provide a worthwhile benefit, but not enough to achieve consensus among the clinical community. However, if equipoise is understood to be violated by evidence short of that which is necessary to achieve community consensus then it is also violated by the 'equivalence trials' advocated by the critics of placebo use. These would compare the short course of AZT to the longer course and measure how much less effective the short course was. In such a trial nobody is denied treatment, but there is reason to expect better results from the established long course than the experimental short course.

A further problem with equivalence trials concerns their methodological validity. The theory is that by measuring how much less effective the short course is than the long course we can establish whether the short course is effective enough to be worth funding. However, as well as being more statistically complex this method assumes that we know the effectiveness of the long course, and although the earlier trials provided information about the effectiveness of the long course in developed countries, it is likely that its effectiveness would differ under developing country conditions. It is therefore arguable that only a placebo-controlled trial could yield the information that is sought. If this is right then equivalence trials could not be an ethical alternative. On its own this would not show that placebo-controlled trials were justified but would show that if they cannot be justified then there is no ethical way of obtaining the desired information about the efficacy of the short course of treatment.

Another strand of the argument asserted that placebo use was unethical as it deprived patients in the control group of a treatment from which they could have benefited. While supporters of placebo use could argue that, since AZT was not available as part of perinatal care in the countries where the trials were conducted, nobody was made worse off by being allocated to a placebo group, opponents held that there should be a single, universal 'standard of care', which research participants are entitled to receive, and that it is unethical to measure the acceptability of placebo against a lower standard in developing countries. This argument was linked to the *Helsinki Declaration*, which (in the version current at the time) stated that participants "should be assured of the best proven diagnostic and therapeutic method". ([18]) It should be noted, however, that defining a universal standard of care is not straightforward, since even in developed countries patients outside trials are not always guaranteed the 'best proven methods'. Moreover, the *Helsinki Declaration*'s view is not universally shared, and other influential guidelines and documents have allowed that the availability

17. For example Marcia Angell, "The ethics of clinical research in the third world", *New England Journal of Medicine* 337, no. 12 (1997): 847-9; Peter Lurie and Sidney M. Wolfe, "Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries", *New England Journal of Medicine* 337, no. 12 (1997): 853-6 (reprinted in *Bioethics: An Anthology*, Helga Kuhse and Peter Singer, eds. (Oxford: Blackwell, 2006): 533-8).
18. The Helsinki view was weakened by the 2002 'Note of Clarification', as discussed in Chapter 5, but the latest (2008) version again appears to prohibit use of placebo under circumstances such as the AZT trials, since a proven treatment exists and those who receive placebo are at risk of serious and irreversible harm.

of treatments in the trial location can in some circumstances be the appropriate standard against which to assess the permissibility of placebo use. ([19])

The ongoing disagreement on this issue reflects the fact that it involves a conflict between two different principles. Supporters of the AZT trials can argue that use of placebo does not violate the principle of non-maleficence if those who are assigned to the placebo group would not have received an effective treatment outside the trial. However, it might be argued that it violates the principle of beneficence by failing to provide the placebo group with a benefit that it is within the researchers' power to provide. ([20]) Supporters of placebo have argued that it is not the responsibility of researchers to rectify existing international injustices or to make up for the failure of governments to provide adequate health care; nevertheless, it could be argued that researchers incur some positive duties towards their subjects in return for their participation or as a result of engaging with them in a partly therapeutic context.

The concept of exploitation might help us to conceptualise this, even if it does not provide a clear resolution to the disagreement. We have seen that exploitation need not be harmful but involves unfairly taking advantage of another person's vulnerability to further one's goals, typically by shifting the balance of benefits and burdens in a way that would not be acceptable to a less vulnerable person. In the case of the AZT trials, it is the participants' inability to access treatments outside the trial that makes it rational for them to enter a trial in which they may be assigned to a placebo arm, so there is a sense in which the researchers do take advantage of their weakness. The question is whether they do so unfairly. Our judgement about this may depend on several factors, mainly relating to the consequences of not doing so. If the decision to employ a placebo control was taken solely for personal gain, or to boost pharmaceutical company profits by avoiding a more costly but nevertheless affordable form of trial, then this may be considered a case of unfair advantage-taking on the grounds that the researchers are treating the vital interests of the participants as less important than the relatively trivial interests of themselves and their organisations. If, however, recruiting vulnerable patients into a placebo-controlled trial is the only reliable way of obtaining knowledge that is required in order to benefit other patients who are at least as badly off as those recruited to the trial, then a charge of unfairness will be harder to sustain and it is arguable that the transaction should not be considered exploitative provided that the participants consent and are not harmed. This then tends to support the view that placebo use in cases of local non-availability of established treatments should be permitted where there is also a compelling methodological case for a placebo-controlled trial, an important research question, valid consent, and where participants are not worse off than they would be outside the trial.

In the case of the TB vaccines trial in Case Study 6.2, assigning participants to a placebo group would deprive them of a treatment that is available elsewhere but not locally, in the same way as the AZT trials (albeit in the TB case a treatment whose effectiveness is questionable in the age groups from which the participants are drawn).

19. For discussions of this point, see Reidar K Lie, "Standard of care owed to participants in clinical trials: different standards in different countries?" in *Principles of Health Care Ethics*, Richard E. Ashcroft, Angus Dawson, Heather Draper and John R. McMillan, eds. (Chichester: John Wiley & Sons, 2007): 730-4; Hans-Jörg Ehni and Urban Wiesing, "International ethical regulations on placebo-use in clinical trials: a comparative analysis", *Bioethics* 22, no. 1 (2008): 64-74. Guidelines permitting placebo use under certain conditions where an established treatment is not available locally include: European Group on Ethics in Science and New Technologies, *Ethical Aspects of Research in Developing Countries* (2003), para. 2.10, http://ec.europa.eu/european_group_ethics/docs/avis17_en.pdf; Council of Europe, *Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research*, DIR/JUR (2004)4 (Strasbourg, 25 January 2005), para. 120, http://www.coe.int/t/dg3/healthbioethic/Activities/01_Oviedo%20Convention/195%20ER%20recherche%20biomedicale%20e45.pdf); Nuffield Council on Bioethics, *The Ethics of Research Related to Healthcare in Developing Countries* (London: Nuffield Council on Bioethics, 2002), http://www.nuffieldbioethics.org/go/ourwork/developingcountries/publication_309.html
20. Cf. Nuffield Council on Bioethics, *The Ethics of Research Related to Healthcare in Developing Countries* (London: Nuffield Council on Bioethics, 2002), para. 7.12. http://www.nuffieldbioethics.org/go/ourwork/developingcountries/publication_309.html

However, it is less clear in the TB case than in the AZT case that there is a strong methodological reason for placebo-controlled trials. BCG is widely (though not uniformly) used in developing countries, and the aim of the trial is not to establish whether MVA plus BCG is better than nothing, but whether the combination is better than BCG alone. It is likely that this can be achieved with an equivalence trial, and while adding a placebo arm might provide some additional information it is not clear that this fulfils any sufficiently important interest to justify not benefiting control group members by providing them with the widely used and inexpensive BCG vaccine.

Case Study 6.3
Nicotine replacement therapy for pregnant smokers

Children of mothers who smoke during pregnancy are at increased risk of miscarriage and stillbirth, pre-term birth and low birth weight, neonatal mortality, sudden infant death syndrome, asthma, attention deficit and learning problems. ([21])
Over a quarter of pregnant women smoke and most of these continue to smoke throughout their pregnancy.

It is known that, in non-pregnant smokers, drug therapies to treat the symptoms of nicotine withdrawal can increase smoking cessation rates beyond what can be achieved by behavioural support alone. However, there has been a reluctance to use drug therapies in pregnant smokers because of the risk of fetal damage. Consequently, little is known about the safety or effectiveness of using medications to treat pregnant smokers.

The proposed research involves the testing of nicotine replacement therapy (NRT) for pregnant smokers. The aims of the trial are to establish the safety and effectiveness of NRT plus behavioural support, compared with behavioural support alone, and to determine which subjects benefit most from NRT during pregnancy. Researchers have chosen to investigate NRT rather than other drug-based anti-smoking interventions as it is considered ethically problematic to introduce untested drugs that would not otherwise be present into pregnant women.

Subjects will be recruited at a prenatal clinic in an English university hospital that serves an ethnically mixed, mainly low-income population. Women who agree to participate will be asked to complete a questionnaire to establish that they meet the eligibility conditions, and those who meet the criteria will be randomly assigned to receive *either* smoking cessation behavioural counselling plus an 8-week course of nicotine patches *or* the same counselling plus a similar course of placebo patches. The outcomes to be measured include self-reported smoking abstinence and cessation rates, biochemical measures of tobacco exposure, birth weight, gestational age at birth, fetal death and neonatal mortality.

21. This case draws on the following reports: US National Institutes of Health, "Nicotine Replacement Treatment for Pregnant Smokers", ClinicalTrials.gov Identifier: NCT00115687 (2008), http://clinicaltrials.gov/show/NCT00115687; Tim Coleman *et al.*, "Protocol for the smoking, nicotine and pregnancy (SNAP) trial: double-blind, placebo-randomised, controlled trial of nicotine replacement therapy in pregnancy", *BMC Health Services Research* 7, no. 2 (2007).

Recruitment will be subject to the following inclusion and exclusion criteria.

Inclusion:

(a) maternal age 16-50 years;
(b) gestational age 12-24 weeks;
(c) patient is able to speak English;
(d) patient intends to carry to term;
(e) patient has a stable residence;
(f) patient currently smokes five or more cigarettes per day and has exhaled carbon monoxide reading of at least 8 parts per million.

Exclusion:

(a) cardiovascular and other medical conditions established as contraindications to the use of NRT;
(b) known sensitivity to nicotine patches;
(c) psychiatric disorder;
(d) drug or alcohol dependence;
(e) inability to give informed consent;
(f) known congenital abnormality in the fetus;
(g) multiple gestation.

Questions

1. What ethical issues are raised by the decision to carry out trials of medications in pregnant women? Can the use of pregnant women as subjects be justified in the case of NRT?
2. What justifications might be given for each of the inclusion and exclusion criteria? Based on the information available are there any groups who appear to be unnecessarily or wrongfully excluded by these criteria?
3. If there are any unnecessary exclusions what ethical issues does this raise? Are there any individuals or groups who could claim to be discriminated against by this proposal?

Access to trials

Like much of the debate about justice in research, the last two case studies have focused on concerns about the exploitation of vulnerable research subjects. One response to such concerns, as well as to concerns about harm, is to exclude those thought to be at particular risk of harm or exploitation from participation in research. But while this can help to avoid unjust imposition of the burdens of research, justice is also about the distribution of benefits and it is increasingly recognised that excluding categories of people from research participation can itself lead to injustice, by depriving excluded individuals and groups of the direct and indirect benefits arising from participation in research.[22] It may also place an undue burden upon those sections of the population not considered in need of special protection (often young males) to furnish the results of research upon which the rest of the population is treated.

Question 1 invites us to consider the ethical issues raised by the participation of pregnant women in medical research. Before considering the nicotine replacement therapy study (Case Study 6.3), it is worth noting that in two of previous studies pregnant women were excluded from participation. Case Study 2.1 (Space Flight Simulation on Healthy Female Volunteers) recruited women, but (because of the researchers' concerns about fetal damage) the women were required to declare that they were not pregnant, to undergo a pregnancy test before the start of the experiment, and to promise to take steps to avoid pregnancy for three years after the end of the trial. The focus of that case was on issues of consent, but it also raises the question of whether such an exclusion is justified. In Case Study 6.2, the treatment groups were defined in such a way as to exclude women (whether pregnant or not) from participating in the trial.

Women, particularly those of child-bearing age, have often been excluded from participation in research out of a well-intentioned concern to avoid causing harm

22. Anna Mastroianni and Jeffrey Kahn, "Swinging on the pendulum", *Hastings Center Report* 31, no. 3 (2001): 21-8.

to unborn fetuses. This can be viewed as a precautionary approach in response to an uncertain risk of harm, but as with other such cases it is necessary to consider the costs of the precautionary measures and to ensure that they are proportionate to the risks that they aim to reduce. In the case of the TB trial the restriction of the trial to male participants could mean that some women in the developing world are deprived of the only opportunity they would have had to receive vaccination against TB. As well as disadvantaging the particular women who could have benefited from participation in the trial, such exclusions result in a lack of data about the safety and effectiveness of the investigational treatment in women.

Similar concerns have been raised about other common exclusions. For example children have often been excluded from drug trials because of concerns about harm and the possibility of exploitation due to their dependence on adults and inability to give consent, but this has led to a lack of data about appropriate dosages for children. Many trials also have upper age limits, which limit the access of elderly populations to the goods associated with research participation.

One way of thinking about what might be wrong with applying blanket exclusion criteria based on factors thought to be correlated with heightened risk of harm or exploitation relates to the concept of consent. While the risks associated with participation in a particular trial may be correlated to some degree with general criteria such as age or sex, the seriousness of those risks for an individual will also depend on that individual's priorities and preferences, as will the importance of benefits such as access to experimental treatments or payments. We might therefore think that exclusion on grounds of risk should be judged on a case-by-case basis, and that in most cases the decision is best made by the participants themselves.

This argument will, of course, not apply to young children and others who cannot give valid consent. There is also a case for not making the participation of pregnant women a matter of individual consent, since the reason for considering exclusion relates not primarily to the welfare of the woman but of the fetus. However, it should be noted that in relation to other influences on fetal welfare, such as smoking and alcohol consumption, we usually provide information and advice, but allow the mother to decide how to respond. Views about the exclusion of pregnant women from trials may relate to the contentious question of the fetus's moral status and the relative weights given to fetal and maternal interests. These issues will be considered further in Chapter 8. However, they are less significant here, as the main concern is not the destruction of fetuses but the possibility of causing damage that will persist after birth and beyond the point where the fetus uncontroversially has full moral status.

A further issue raised in particular by Case Study 6.2 is the breadth of the exclusion criteria. Even in cases where the consent argument does not apply, the variability of risks according to individual factors (both biological factors and preferences) suggests that exclusion criteria need to be carefully drawn in order not to unfairly exclude people whose likelihood of suffering harm is not particularly high. Excluding all women on the grounds of potential risk to a fetus looks like a clear case of an excessively broad exclusion criterion. Although it may be reasonable to take *some* precautionary measures against the possibility of women entering a potentially harmful trial without realising that they are pregnant, excluding all women seems unnecessarily restrictive. Women who are not fertile, or are not heterosexually active, might reasonably consider their exclusion from the benefits of research participation to be unjust and discriminatory. A range of less restrictive precautionary measures is possible, and depending on the nature and risk of the proposed research it might be sufficient to ask potential participants about their menstrual cycle or to require pregnancy tests and undertakings to use contraception.

In addition to concerns about the risks of harm faced by particular participant groups, there might be sound methodological reasons for applying exclusion criteria based on such factors as sex, age or race to trial participation. Ensuring that the participants in a given trial are as alike as possible increases the likelihood that any differences observed between arms are attributable to the different treatment regimes in each arm. Trials that are characterised by a relatively 'uniform' participant population may produce scientifically sound results with

fewer subjects, thus minimising the risk associated with the research. This has to be offset against the limitations that the research will then have when applied to a population outside the world of the trial, which is not uniform in this way. So the consequentialist reasons for limiting participation on the basis of age, sex or race might be neutralised by the goal of producing research findings that are of maximal relevance and use in the clinical context.([23]) Whether consequentialist concerns tell in favour of blanket exclusion criteria in the context of a particular trial might depend upon factors such as the particular risks associated with the treatment being tested, the likelihood of it being used outside the trial to treat the groups that it is proposed to exclude from the trial, and the availability of other treatment options for those groups.

Case Study 6.3 presents a scenario in which women who are known to be pregnant are deliberately recruited as research subjects. In this case there is a clear metholological reason for *including* them – the research concerns the effects of an intervention in pregnant women on the fetus, so cannot be conducted in any other group of subjects. The risk of harm to fetuses is minimised by the choice of intervention to be tested – nicotine replacement therapy, unlike some other smoking cessation treatments, only exposes the fetus to a drug that it would also be exposed to outside the trial. This is supported by inclusion criterion (f), which ensures that only women whose fetuses are already exposed to a significant level of nicotine are recruited. It is also relevant that in this case any risks may be balanced against potential benefits to the fetus itself and not just to the mother.

Questions 2 and 3 call for evaluation of the inclusion and exclusion criteria in the study. Several of these fall under the two broad types of justification for exclusions already discussed: those concerned with the protection of vulnerable individuals, and those concerned with methodology. For example, among the exclusion criteria (a) and (b) are clearly intended to protect those who would be at high risk of harm from the study, while (d) is probably intended to avoid the potentially confounding effects of interactions between addictions to nicotine and other substances. The latter could, however, restrict the generalisability of the results in the way described above, especially if dependence on alcohol and other drugs is common among women who smoke in pregnancy. Exclusion criteria (f) and (g) could also have a methodological rationale, as they might affect measured outcomes such as birth weight, gestational age at birth, fetal death and neonatal mortality.

Some of the inclusion and exclusion criteria might have a more practical effect on the success of the study. Participants with a psychiatric disorder, inability to speak English or lacking a stable residence might be more likely than others to fail to comply with the protocol or to drop out of the trial, threatening its statistical validity.

Among the inclusion criteria, (b), (d) and (f) are necessary for the proposed intervention to be applicable, while (f) could also have the fetal safety rationale suggested above (not introducing nicotine where it is not already present). Inclusion criterion (a) limits the trial to women aged 16-50. Although this will cover most pregnant women it is not clear why those outside this age range are excluded. If it is thought that older or younger women might respond differently to the nicotine patches and thus make the results less clear then it follows that excluding them will limit the applicability of the results to women within the specified age range.

Arguments against exclusion may be similarly categorised: methodological considerations can oppose exclusions where these would skew the results or make them generalisable only to a certain section of the population, and harm-based arguments come into play where individuals are deprived of the benefits of participation or society is deprived of knowledge of how treatments perform in the excluded groups.

23. Vanessa Merton, "Ethical obstacles to the participation of women in biomedical research", in *Feminism and Bioethics*, Susan Wolf, ed., (New York: Oxford University Press, 1996): 224-5.

As well as limiting the generalisability of the results the exclusions could disadvantage individuals (women and their fetuses) who could have benefited from the counselling and supervised use of nicotine patches. Although the purpose of the research is not to benefit individuals but to generate knowledge, exclusion from the benefits of participation becomes problematic where there is no good research-based reason for the exclusion, or where there is a reason but one that could be overcome with additional resources. For example, the inability of non-English speakers to consent, communicate with research staff and participate in the smoking cessation counselling could be overcome by provision of translated materials and an interpreter. The question then arises of whether researchers have an obligation to bear this cost even if this restricts the amount of worthwhile research that can be done.

Question 3 invites identification of exclusion criteria that could be considered discriminatory. Like 'exploitation', 'discrimination' has both a non-moral and a moral use. In its non-moral sense it means distinguishing different things and treating them differently. Discrimination in this sense is an essential part of many research activities – for example discriminating between those sub-types of a disease that are most likely to respond to one treatment and those that are most likely to respond to another, or between population groups that are likely to benefit from participation in a screening programme and those that are not. In its moral sense, 'discrimination' refers to unfair or unjust discrimination. What makes a case of discrimination unfair is that it involves treating some people less favourably than others in the absence of a good reason for doing so. Typically when people talk about discrimination they are referring to one of three types of case: treating a group of people less favourably than others on account of some perceived characteristic that does not in fact exist; treating a group of people less favourably than others on account of a characteristic possessed by only some members of that group; and treating a group of people less favourably than others on account of some difference that does exist but does not justify the difference in treatment.

An example of the first type would be excluding women from pharmaceutical trials on the grounds that they are the 'weaker sex' and more likely to suffer adverse reactions from experimental drugs. This unfairly excludes women, individually and as a group, from the direct and indirect benefits of trial participation on account of a perceived difference for which there is no evidence.

An example of the second type occurs where the reasons for exclusion apply only to some members of the excluded group, and it would be possible to exclude those to whom the reasons apply without excluding the whole group. Thus, those to whom the reasons do not apply are excluded on the basis of characteristics that they do not possess. This relates to the earlier discussion of broad exclusions. For example, it is a form of discrimination of this kind if all women are excluded from a trial that they could benefit from participating in on grounds of fetal safety, when only a small minority are pregnant at any given time and these could easily be excluded without excluding the non-pregnant majority. Similarly, the exclusion of all people with a psychiatric disorder on grounds of vulnerability or inability to comply with the research protocol could be discriminatory if it fails to take account of differences in type and severity of psychiatric disorder.

An example of the third type might be the exclusion from the NRT trial of older or younger women, and those who cannot consent. The women who are excluded by these criteria do indeed have the relevant characteristics, but it is not clear that they provide any methodological or harm-based justification for exclusion.

A distinction is often made between direct and indirect discrimination. A group is directly discriminated against when its members are treated less favourably than others either because of membership of the group itself (as when women are excluded from a trial). A group is indirectly discriminated against when it is treated less favourably on the basis of some criterion which is not necessarily associated with membership of the group but happens to impact more heavily on that group than others. An example from outside research would be a minimum height requirement for certain jobs – this makes women and members of certain racial groups less likely to qualify than others, and will constitute indirect discrimination if there is no

genuine occupational reason for requiring a minimum height. In research, requiring an ability to speak or read a particular language might constitute indirect discrimination against certain ethnic groups, and limiting participation to those who can give valid consent might indirectly discriminate against children (assuming in both cases that there is no sound justification for the exclusion).

Another possible type of discrimination is what we might call *passive* discrimination. This occurs when, rather than actively treating some people less favourably than others, some people are *allowed* to be disadvantaged by *not* treating them differently when some special treatment is called for. So whereas active discrimination involves treating people differently when there is no justification for doing so, passive discrimination involves treating people the same when there is a reason to treat them differently. Outside the field of research, passive discrimination often arises in relation to disability. Legislation in some countries requires businesses and other organisations to make 'reasonable adjustments' to enable people with disabilities to access their services or obtain employment, and a failure to do so would be passive discrimination. Similar considerations can arise within research – for example, a person with a visual impairment might require participant information sheets and other information to be made available in Braille or audio form in order to be able to participate in a trial, and a failure to provide this could be considered discriminatory. In the NRT trial some of the inclusion and exclusion criteria that appear to be justified by the inability of the excluded groups to engage with elements of the trial could be examples of passive discrimination if there are measures that could be taken to enable them to apply. For example, patients with a psychiatric disorder might be able to follow the treatment protocol and engage with the smoking cessation counselling if they were provided with additional support, and non-English speakers might be able to participate if translation services were available. Whether we count the non-provision of such services as unfair and therefore discriminatory may depend on the costs involved, both financially and in terms of risk to the research objectives. In many cases, therefore, whether something counts as a case of passive discrimination will be a matter of judgement. In making this judgement, however, it should be recalled that while inclusion might in some cases jeopardise the viability of the research by making it more costly or methodologically complex, exclusion can undermine the value of its results by limiting their relevance and applicability to real world problems.

Further reading

Exploitation

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Access to trials

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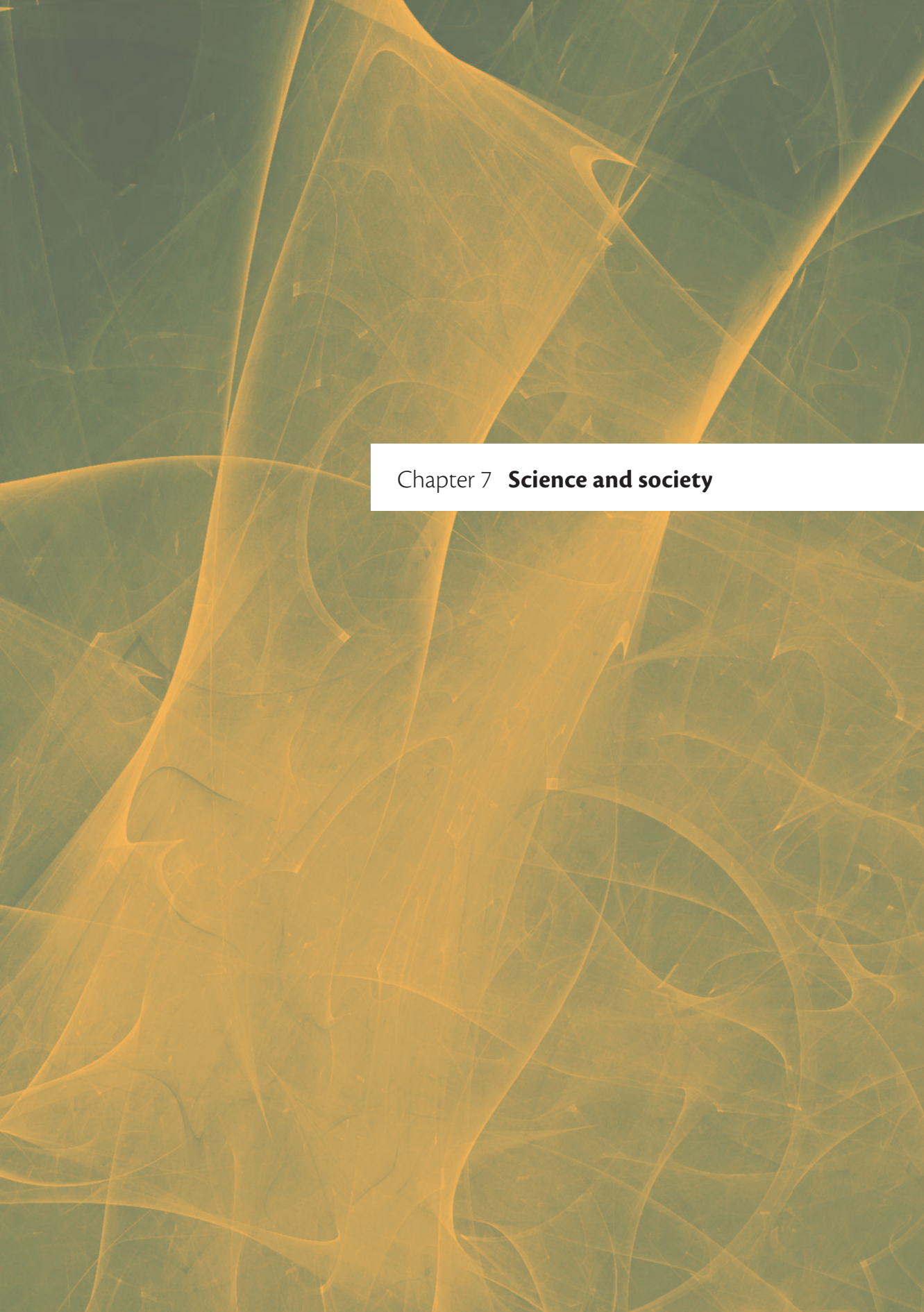


Chapter 7 **Science and society**

Learning outcomes

In this chapter you will develop:

- An understanding of the way in which society and societal considerations may be ethically relevant for the kind of research that is permissible within that society.
- An understanding of the problems that moral difference raises for decisions about the ethics of research both within and across national boundaries.
- An understanding of the distinctive practical and theoretical ethical challenges presented by research that spans cultures or societies.
- An appreciation of the ethical issues involved in assessing and weighing up benefits and risks associated with dual use research.
- An appreciation of the responsibilities of researchers in the conduct of research with particular emphasis on responsibilities for the use of the research, publication, academic integrity and the avoidance of conflicts of interest.
- An understanding of the ethical issues involved in pharmacogenetic research with particular focus on the issues related to the social impact of this research.

Introduction

This chapter examines the ethical issues that arise out of the broader relationship of research and researchers to the society in which they operate.

In the first part of the chapter we examine some key issues in this broader relationship in an attempt to become clearer about the context, and specifically the European context, of science and society. From this examination we derive four themes that will permeate discussion of the case studies in the rest of this chapter and the next.

The issues raised in this first part of the chapter are initially explored through a case study in which the treatment that researchers propose to test is likely to place a significant burden on a country's health care resources. This case begins to consider the extent to which the collective interests of society should determine what research it allows to be conducted. From this starting point readers are asked to consider the broader relations between social concerns and the ethics of research.

The second part of the chapter looks at ethical issues that may arise across societies or cultures. It raises practical questions about research taking place across national and cultural borders and about the role of cultural sensitivity and tolerance in research ethics. Finally this part considers the more theoretical issue of 'relativism' and its significance for the process of ethical review.

The final part of the chapter looks at the obligations and responsibilities of researchers to the society that facilitates their research. This part begins with a case study examining the issues surrounding possible misuse of the knowledge generated by research. It asks readers to consider the ways in which society might deal with the possibility of such misuse and, in particular, researchers' responsibilities for the uses to which the products of their research are put. The final case study in this chapter brings together questions about the proper role of social distinctions in research and questions about the researchers' responsibilities in the conduct of research. It considers the relevance of social concepts such as race and ethnicity to particular kinds of research and the responsibilities of the researcher to uphold academic integrity and avoid conflicts of interests.

The case studies and associated questions are designed to prompt readers to consider these issues by beginning with a specific practical problem and progressing to the more general societal considerations. It should also be noted that there is likely to be significant overlap between the discussions arising from the three cases. So, for example, although Case Study 7.3 introduces issues surrounding the dual use of biotechnology, some of the other cases will raise similar issues.

Science and society

This chapter and the next raise some very important general issues about the relationship between science and society, particularly as they relate to research ethics and the governance of research. It is within this broad context that the specific issues targeted by each of the cases are located.

The first and most basic question to consider here is: should science and scientific research be accountable to society? The most obvious answer to this question is 'yes' but it is worth pausing to examine the reasons for and against, since these may help to determine the appropriate level and form of this accountability. One argument in favour of accountability is a funding or 'resourcing' one: society provides the resources for science and scientific research to take place and so is entitled to have a say in the direction that such research takes. Society has and ought to have an interest in scientific research because it is supported by, and for the good of, society. Additionally, we might think that the products of scientific research, because of their potential to change society and the lives of its members, constitute a force (or more negatively, a threat) that society should control as a protective measure. A second, perhaps related, argument involves society's obligations concerning the welfare and protection from harm of its members. On this view (familiar from Chapter 1) scientific research (and particularly medical research) is justified by its ability to promote the welfare of members of society and protect them against harm.

We might, however, think that both of these arguments are somewhat simplistic. On the one hand, we might query whether it makes sense to think of society as being in a position to decide whether or not to engage with scientific research. It is not as though scientific endeavour is completely isolated from society – the institutions of science are societal institutions and the individuals who participate in the processes of science are members of society. All are products of the histories, traditions and cultures of each society and as such are a part of its fabric.

On the other hand, we might, in the tradition of libertarianism, think that society provides the resources that enable freedom of choice and that some individuals choose to engage in science. So the trends and directions of development in science are best left to the free choices of individuals and/or markets, rather than being subject to the controlling influence of the larger group. On this view, scientific research is the product of the freedoms that exist in society, and it is the duty of society (in the form of its institutions) to intervene as little as possible and only to protect individuals from harms and infringements of their liberties.

Finally, we might think that the welfare and harms argument actual plays out differently. That is, it might turn out that more benefits will accrue to society if science is left to determine its own direction with a minimum of interference.

Without wishing to presume the ways in which a full discussion of these issues might play out, it is reasonable to adopt something like a social contract model of the accountability of scientific research or one centred on the responsibility of society to provide for the welfare and protection of its members. That is, science and scientific research should be accountable to society because it is supported by society for the benefit of society and its members.

Having considered very briefly the question of whether science should be accountable to society, we turn our attention to the ways in which this accountability might be established and maintained.

The relationship between science and society

The products of science – like technology and medicine – are increasingly important in our lives and we are increasingly reliant upon them. However, there is growing suspicion about the direction of much of the scientific research that takes place within our society, about who is in control of it and what their motivations are. The tension between these two competing pressures means that the relationship between science and society is, at least, difficult.

Within this situation a number of trends can be discerned. First, there is increased scope for scientific developments to have a global impact as well as to impact on fundamental aspects of human biological and social life. Second, there is an increased level of commercial involvement in scientific research and in bringing the products of that research to the broader population. Finally, and perhaps as a result of the first two trends, there is increased concern about the nature of the choices being made about the direction of scientific research and the possibility of exercising control over this direction.

Given these trends, it is natural that political and academic interest should focus on the relationship between science and governance – it is, after all, through the mechanisms of science governance, broadly understood, that the forms of accountability can be explored. Biotechnology, particularly in its medical applications, provides a useful focus for consideration of the governance of science for three reasons. First, in this arena there is potential both for significant social benefit and for social harm, or at least controversial social change. Thus the potential effects of research in this area seem to warrant social control or regulation. Second, because of the wide range of potential benefits and harms, the issues here are complex and diffuse, involving a diverse range of players and affecting the full spectrum of society's groups and individual members. Finally, in this arena the relationship between policy makers, experts from a range of disciplines and the public matters a good deal. This relationship and its policy outcomes influence the way in which research is done, how it is applied, as well as the spread and magnitude of the benefits.

Ethics and law

A natural place to look, given this focus on science and governance, is to the legal and ethical regulatory structures in place for oversight and scrutiny of research. The European Commission Expert Group on Science and Governance ([1]) argues that there has been a shift towards the legalisation of ethics in the governance of research, which may undermine the processes of ethics in society. This legalisation has taken place largely through the rise of institutional ethics and can be seen as the product of a number of the trends described above.

The Expert Group suggests that there has been a shift to non-binding governance or 'soft law' – codes of practice, guidance, and reporting measures – which has been dictated in part by the pace of development and the relative inflexibility of 'hard law'. At the same time, increased pressures in the direction of openness and involvement, perhaps arising from increasing public unease with science, have also been important in shaping the forms of institutional ethics currently in place in Europe. The Expert Group suggests that, as a result, research ethics governance in Europe has become dominated by a kind of technological, ethical and legalistic expertise. Elements of this shift have been well-documented elsewhere and lend support to these suggestions. ([2])

> *Ethics has been institutionalised in Europe through the creation of expert committees. Some important questions thus remain unanswered: whether ethical decisions may take place beyond the rule of law; if ethics may appropriately be seen as just a matter of expertise; and how, as is claimed by the EC, such expert committees may convincingly represent "the values of all Europeans".* ([3])

There are a number of points to bear in mind here. Most importantly, the question of expertise and, in particular, ethical expertise is one that is fraught with difficulty. On the one hand some argue that those who study applied moral arguments and moral (philosophical) theory are moral experts in the sense that they have an understanding of the argumentative terrain that comes with this kind of training and experience. ([4]) Others see the theoretical and argumentative training as useful for teaching and encouraging others faced with difficult ethical decisions but not for the purpose of making concrete normative judgements on behalf of those others.

What matters most here is the distinction between, on the one hand, individuals or institutions who take on (or who are given) the position of ethical authority, and, on the other hand, good ethical reasoning and argument. It is plausible to suppose that the proper form of discussion about ethical concerns is one that appropriately involves the society as a whole and is in some sense democratic, but that even so, the authority of the democratic process should be mediated by considerations of sound ethical reasoning and argument.

Individual and collective responsibility

An important set of issues relating to the relationship between science and society is the changing way in which we think of and ascribe responsibility to individuals and collectives. Arguably, the forces that are changing (or at least challenging) the relationship

1. Expert Group on Science and Governance, *Taking European Knowledge Society Seriously: Report of the Expert Group on Science and Governance to the Science, Economy and Society Directorate* (European Commission Directorate-General for Research, Science, Economy and Society, 2007), Chapter 4. http://ec.europa.eu/research/science-society/document_library/pdf_06/european-knowledge-society_en.pdf
2. Mary Dixon-Woods, Emma Angell, Richard E. Ashcroft and Alan Bryman, "Written work: 'The social functions of Research Ethics Committee letters", *Social Science and Medicine* 65 (2007): 792-802. Also see Mary Dixon-Woods and Richard E. Ashcroft, "Regulation and the social licence for medical research", *Medicine, Health Care and Philosophy* 11 (2008): 381-91.
3. Expert Group on Science and Governance, *Taking European Knowledge Society Seriously* (European Commission Directorate-General for Research, Science, Economy and Society, 2007): 52. http://ec.europa.eu/research/science-society/document_library/pdf_06/european-knowledge-society_en.pdf
4. See, for instance, Peter Singer "Moral experts", *Analysis* 32 (1972): 115-7; Cheryl N. Noble, "Ethics and experts", *Hastings Center Report* 12 (1982): 7-9.

between science and society are also changing the ways in which individual responsibility can feature in the consideration of the ethics of research. If it is becoming more difficult to separate out and ascribe individual responsibilities, and if such ascriptions seem to oversimplify the ethical terrain, then this raises a question about the usefulness of contemporary ethical theories that deal primarily with ethics at the individual level. ([5])

It is not clear that these changes are beyond the scope of contemporary ethical theories. It does, however, mean that they must be extended in such a way as to be able to cope not only with the challenges of the changing connection between science and society but also with the challenges posed by the complex set of roles and responsibilities that are features of the evolving society. ([6])

Models of engagement

Arguably the standard model of governance and oversight (in the sense of supervision and/or management) of research is ill-equipped to deal with the ethics of research in the light of the trends described above. Perhaps the most notable difficulty is the ability of this kind of system to take account of different perspectives on the problems being addressed by the research and the forms that potential solutions should take. In addition, such a system of governance will have difficulty coping with the breadth of influence of the new biotechnological developments. It is useful, therefore, to consider various models of engagement that can assist with the broader research governance issues associated with the relationship between science and society.

The report of the Expert Group on Science and Governance describes the development of the relationship between science and society in this context. ([7]) The first step in this development, a reaction to the early recognition of social unease with science, was a move towards the education of the public. In general terms the public's unease was diagnosed as being due to a lack of understanding of scientific research and the benefits that it would bring. This emphasis on public understanding and education presumed:

(i) that if the public understood the science they would then see and accept the benefits that such research promised; and
(ii) that the idea of the public good or societal benefits was something determined by and within the institutions of science and policy making. ([8])

Evidence that this approach was unsuccessful led to a more complex view of dialogue and engagement which is now the dominant approach. Within this approach, however, is contained a variety of models, each of which interpret involvement, participation and engagement in different ways. Each model involves or embeds citizens or interested groups in the processes of research in a different way. These models include:

5. Rene von Schomberg, "From the ethics of technology towards an ethics of knowledge policy and knowledge assessment". (European Commission Directorate-General for Research Science, Economy and Society, 2007). http://ec.europa.eu/research/science-society/pdf/ethicsofknowledgepolicy_en.pdf
6. Larry May and Stacey Hoffman, eds., *Collective Responsibility: Five Decades of Debate in Theoretical and Applied Ethics* (New York: Rowman & Littlefield, 1991).
7. Expert Group on Science and Governance, *Taking European Knowledge Society Seriously* (European Commission Directorate-General for Research, Science, Economy and Society, 2007), Chapter 5. http://ec.europa.eu/research/science-society/document_library/pdf_06/european-knowledge-society_en.pdf
8. Various authors maintain, plausibly, that even though things have moved on from the simple public understanding of science model there is still evidence of the conflation of public understanding with public acceptance. See Sheila Janasoff, *Designs on Nature: Science and Democracy in Europe and the United States* (Princeton NJ: Princeton University Press, 2005).

> *public consultation exercises of different formats, from citizen panels to consensus conferences, to more long-term engagement between research and parts of publics such as patients' associations in medical research.* ([9])

There are a number of complications associated with these public engagement strategies that should be noted. First, the terms employed in referring to those whose 'engagement' is sought have importantly different senses and so different implications for the nature of the engagement. The idea of engaging with 'stakeholders', for example, presumes that a clear account can be given of what is at stake and who has an interest in it. The term 'citizen' does not have this connotation but may presuppose a particular view of the role of the individual in society which is different from that of a private individual. Deciding about an issue as a citizen of a particular society or as a member of a collective is arguably different from deciding as an individual. Second, there are important complexities surrounding the idea of representation or representativeness. Who should represent the public in a particular context? How should individual participants understand their representativeness: as individual (private) members of the public; as concerned, impartial citizens; or as user advocates? In each of these cases the kind of perspective to be adopted is different and so the mode of representation (and public engagement) is also different. ([10])

General themes for consideration

These general considerations about the complex and evolving relationship between science and society give rise to a number of themes that will be referred to throughout the discussion of the case studies in this chapter and the next.

(1) The first of these involves the nature of and extent of the forms of public engagement and stakeholder involvement in research. The kind of questions to bear in mind include: what are relevant forms that engagement and involvement can and should take for this research?; who are the relevant group or groups with which to engage?

(2) Second, these considerations raise important issues about the role and value of consensus in decision-making: how should the consideration of ethical issues incorporate disagreement and when is consensus required?; how is disagreement about the acceptability of a piece of research to be reconciled with inclusiveness?

(3) Third, as we have seen, there are increasingly complex issues surrounding the roles and responsibilities that individuals occupy. In the context of evolving patterns of involvement it is important to ask: how, in particular cases, are we to distinguish the actions of individual agents from those of the collective?; and how does moral responsibility track this distinction in this context?

(4) Finally, each of these themes and their development has more specific ramifications for the way in which research ethics governance is best structured. So with this in mind: how should research ethics governance be structured to ensure proper review, engagement and involvement?; how does such a process avoid becoming overly legalistic or bureaucratic?

As has been mentioned, each of the cases in this chapter and the next deals with its own specific set of ethical issues and also provide important opportunities to further explore these themes.

9. Expert Group on Science and Governance, *Taking European Knowledge Society Seriously* (European Commission Directorate-General for Research, Science, Economy and Society, 2007): 57. http://ec.europa.eu/research/science-society/document_library/pdf_06/european-knowledge-society_en.pdf
10. Mark Sheehan, "Should research ethics committees meet in public?", *Journal of Medical Ethics* 34 (2008): 631-5.

Case Study 7.1
Enzyme replacement therapy for Pompe's disease

A large multinational pharmaceutical company has begun to develop an enzyme replacement treatment for Pompe's disease. The drug is about to enter Phase 3 trials. Pompe's disease is a rare metabolic disorder also known as Glycogen Storage Disease Type II or Acid Maltase Deficiency. In the early onset form of the disease, affected children do not usually live longer than two years. The late onset form of the disease is milder but nevertheless does lead to premature death. There is currently no curative treatment available. However, research done in the Netherlands in the mid-1990s on enzyme replacement therapies was very positive. This research has led to the development of other reasonably successful enzyme replacement therapies for other conditions.

These drugs are likely to be extraordinarily expensive when they reach the market, with costs reportedly running at about EUR 650K per person per year over the course of the patient's life. Despite the small numbers of sufferers, funding this drug after the trial is completed will put a serious burden on the health resources of individual countries. Moreover, there are many more drugs of this kind currently in development that are likely to cost still more and so further burden health resources.

Questions

1. Would the sufferers of Pompe's disease (or their parents or guardians) be able to validly consent to participate in the trial?
2. Should this Phase 3 trial go ahead? Why?
3. Should research involving very expensive treatments be permitted in countries where there are significant budgetary constraints or where the treatment is unlikely to be funded off-trial?
4. What role should broader social concerns (like cost) play in limiting or guiding the kind of research that is conducted?

Discussion

This case draws together two sets of considerations: research-ethics-related questions such as consent and voluntariness as well as questions about the proper role of broader social considerations in determining the kind of research that is funded. In answering the questions it is useful to concentrate on the former issues initially so as to be clear about the point at which the resource question becomes relevant. The case raises questions about consent in cases of 'last resort' – that is, research that involves conditions for which there is no established treatment, leaving the research population with seemingly no other choice but to participate. This links with the discussion of voluntariness in Chapters 2 and 3.

Post-research provision

An initial issue that arises in the discussion of this case is the ethical imperative to continue to fund treatment (if it is shown to be beneficial) once the research has been completed. There is a common presupposition that trial participants should be entitled to continue to receive beneficial treatments that were being tested

on them.([11]) This presupposition may come from a concern to avoid the exploitation or abandonment of research subjects. On the other hand, it might be argued that appropriately informed consent can justify research in situations where for reasons of cost (as in this case) or impracticality the treatment in question cannot be provided post-trial. The thought here is that as long as the participants are fully informed of the fact that once the trial is completed the treatment will no longer be provided (or that there is no guarantee that the treatment will continue to be provided), not providing the treatment is acceptable. A possible intermediate option is not to require ongoing funding or provision of the trial treatment but to require a clearly articulated exit or post-trial treatment plan. Clearly, however, this option is only intermediate if such a plan involves *some* post-trial provision.

Social concerns and research

The case study asks us to consider the relationship between the ethical issues involved in research and broader ethical concerns of society. At its most general, the case is designed to raise questions about the role of society in facilitating, guiding or constraining research. As was discussed above, one of the reasons for thinking that society is entitled to control or limit the types of research that are conducted is that it provides funding and other resources to support it. In the case study we are not told whether the research is publicly funded. If the research is funded by non-state sources, to what extent should these sources or their institutional representatives control or limit research? Should society have less control in the case of non-publicly funded research? One thing to note here is that even if the research in the case study is funded commercially, this is likely to be on the basis that the investment can be recouped in part at least from future sales to publicly funded health care systems.

The specific tension in this case is between the requirements (and autonomy) of research and researchers and ongoing budgetary constraints arising from social decisions about the allocation of resources. Particularly in countries with socialised health care systems, some decisions are required about the kind of ongoing support that can be afforded. The type of treatment described in this case has the potential to place a significant burden on any health system. If the research is not permitted, then demand on resources from future users of these expensive treatments and, in particular, from those coming off the clinical trials, will be avoided. Do these concerns constitute reasonable grounds on which to base decisions about what kinds of research will be permitted?

The relevance of resources questions to research can be seen as a specific example of a broader issue. In these resource questions it is the prior social values, reflected in the resource framework, that are largely responsible for the dilemma. For example, if more resources (whether taken from other areas of health provision, education or defence) were earmarked for funding current and future enzyme replacement therapies, this particular problem would be solved. This means that social values can matter for the kinds of research that can and ought to take place in a given society. Two sets of questions arise from this:

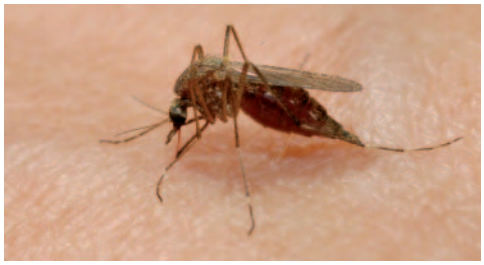
(i) *Other social values:* What other social values, beyond those reflected in the allocation of resources, should play a role in determining, limiting or constraining the kind of research that takes place within a society? Is there research that is unethical because its outcomes have the potential to undermine social values? This question looks forward to Case Study 7.4 and to Chapter 8.

11. For example, see: *World Medical Association, Declaration of Helsinki: ethical principles for research involving human subjects* (2008), para. 33. http://www.wma.net/en/30publications/10policies/b3/index.html. It is interesting to note that the CIOMS guidelines are more qualified on this issue, allowing that the degree of ongoing provision may be influenced by costs and the effects of withdrawal: Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002), Guideline 10. http://www.cioms.ch/frame_guidelines_nov_2002.htm. This guideline and the question of post-trial provision were discussed in Chapter 6 in the context of community exploitation.

(ii) *Including social values:* This question is a more practical one about the process of research ethics review. If there is a role for the values of society informing decisions about research, how can they be included in ethical decision-making processes? How might the review process be conducted to take account of, for example, the public's views on future funding priorities?

Looking beyond the resources issues, this case raises two of the general themes arising from the previous discussion of the relation between science and society. First, the relevance of resource-based considerations suggests that research governance structures should not be independent of broader political debates about funding priorities. If we should broaden the forms of stakeholder involvement, it would seem plausible to include those responsible for ongoing resource allocation in the processes of governance. Second, in connection with the final theme, this case raises the question of how the experience and expertise associated with resource allocation decisions might be best incorporated into the governance process.

Case Study 7.2
International research on the diagnosis and treatment of malaria



For a research project examining the pathological symptoms of fatal cerebral malaria, a group of researchers from a European university wanted to remove the eyes of deceased children.[12] Good indications exist that the degree of damage to the retina caused by malaria will provide a useful clinical marker that could improve diagnosis and optimise treatment. In the African country where the research is to take place, malaria accounts for one-third of all child deaths and hospital admissions.

The participant information sheet that will be given to parents of the deceased children states: "Although the research will involve cutting and then stitching the body, we will replace any parts that we have taken with natural appearing material, and you will not see any marks or changes on the face." No specific information about removing the eyes is included in the information sheet, but such information will be provided if parents ask.

An African bioethics committee has approved the study, considering that the expected benefits justify providing partial information to the parents. In addition, they felt that the information sheet provides sufficient information for parents to make an informed choice, whilst also acknowledging the cultural sensitivities surrounding autopsy. An ethics committee in the researchers' home country, however, did not approve the study, because only partial information was supplied and the consent form was found to be euphemistic and misleading.

Questions

1. Given the account above, is the information given about the nature of the study detailed enough for appropriately informed consent?
2. Do the expected benefits that may be produced by the study justify the amount of information provided to potential participants?
3. Should the study proceed? Why or why not?
4. Who should have the final decision about the research? Why?

12. This case is based upon research described in Joseph M. Mfutso-Bengu and Terrie E. Taylor, "Ethical jurisdictions in biomedical research", *Trends in Parasitology* 18, no. 5 (2002): 231-4.

Discussion

The first three questions raise familiar issues in research ethics, discussed in previous chapters, about the importance of consent and the trade-off between it and the benefits associated with the study. The difference in this case is the international setting of the research, and in this context the first three questions are designed to lead on to the last question and to more theoretical issues associated with governance of international research.

International research tends to emphasise (and perhaps exacerbate) the key ethical tensions in research. This case revisits issues from Chapters 2 and 5 by raising questions about the nature and adequacy of the consent as well as the balance of risks and benefits. The international context also raises similar concerns to those raised in Chapter 6 about the possibility of exploitation, in this case arising primarily from the differing standards for consent.

Relativism, tolerance and cultural sensitivity

An important theoretical issue raised by this case involves cultural sensitivity, tolerance and relativism. The final two questions call for us to consider the standard of consent that should be required as a condition for approval of the research. A range of answers may be given to these questions. One approach would be to insist on a particular standard, either that of the 'home' or the 'foreign' committee. It is important to be clear about whether such an answer is the result of a view about the importance of consent when weighed against the expected benefits of the research or is a product of a view about who should decide. So, for example, we might think that the study should proceed because the standard that should be adopted is that of the culture in which the research is taking place. On the other hand we may think that the study should proceed because the African committee has got the balance correct between expected benefits and appropriate levels of information provision. The former seems to indicate acknowledgment of and respect for moral diversity, whereas the latter is consistent with a more objective view of the ethical judgements concerned.

There are two kinds of consideration that are raised by recognition of the divergence in ethical judgements in cases like this. First, there is a theoretical question about the status of ethical judgements and the possibility of there being a fact of the matter, a 'genuinely' right answer. This is the question of moral relativism. Second, there is a more practical question about the circumstances under which we should tolerate significant difference in ethical assessment and respect cultural differences. A great deal has been written about each of these and we will briefly consider some of the pertinent issues.

Moral difference

A cursory glance at various moral systems and cultures is enough to suggest that there is widespread divergence in moral values and judgements between the peoples of the world, both currently and across time. In spite of this variation some have suggested that there are basic moral principles that are common to all societies because they form the basis on which society can exist. ([13]) However, we need to be careful about how these rules are specified. In particular, if they are specified too broadly then it might look trivial to say that they are shared by all cultures – for example, all cultures might have rules relating to some concept of respect without this implying any substantive agreement.

This all presumes that cultures are fixed, separate entities. The reality of course is that cultures and cultural values are fluid and lack clear boundaries, and so it is not clear what it means for some moral judgement to be 'true in that culture'. However, we might draw an analogy here with languages. Like cultures, languages are difficult to define and yet we have no difficulty

13. James Rachels and Stuart Rachels, *The Elements of Moral Philosophy* (New York: McGraw-Hill, 2009).

understanding the properties of languages and the differences between them.([14]) On this analogy, it makes sense to make judgements about the moral values of a culture or sub-culture as long as we are careful that they are properly qualified and supportable.

Moral relativism

Moral relativists think that we observe something fundamental about the nature of morality when we see these differences in moral judgements and the disagreement they often precipitate. Most commonly, moral relativists think that there really is no universally right answer to moral questions because morality is relative to culture or society. The particular moral values that people hold depend on the culture in which they live or were raised. The initial attractiveness of moral relativism can be characterised as questioning the idea of moral authority. When we reflect on the widespread difference in moral values, we may feel uneasy about our moral convictions and question our grounds for judging those with whom we differ – 'their moral values are as good as ours'.

Tolerance

Our obligation to be tolerant of those whose views, ways and customs are not like ours is often taken to be an important feature of moral relativism. If our moral judgements cannot be privileged over others – our judgements and values are no more right than others – we have no grounds on which to judge those whose moral views are different from ours. Given this, it is natural to think that we ought always to be tolerant of others. But it appears contradictory for the relativist to assert this. The relativist seems to be making a universal moral claim of precisely the kind that is supposed not to exist. The moral relativist cannot claim both that people should always be tolerant and that there are no universal moral truths.

David Wong argues that relativists need not be committed to such a strong tolerance claim. He argues that tolerance is best thought of as a feature of our own culturally influenced (i.e. western liberal) moral values.([15]) So the requirement to be tolerant is not a universal one that applies to all, but rather – as a key part of our own cultural viewpoint – is one that applies specifically to us. Though tolerance is required of us, we cannot impose it on others.

We might also suggest that although tolerance is an important value (within our culture), it is not absolute. For example when confronted with cases of genocide or slavery we are likely to think that being tolerant is less important than acting to prevent the violations of individual freedoms and rights that these acts involve. Importantly, the relativist is neither precluded from asserting the value of tolerance nor committed to an extreme degree of tolerance. In relation to the case study it remains an open question how the relativist will balance respect for the local standards against the high value that 'we' place on individual autonomy.

Relativism and objectivism

Moral relativism is a view about the relation of morality to culture that most often rejects the idea of moral truth and justification. Objectivists, by contrast, believe that there are moral truths and that these truths give us the appropriate authority or justification for our judgements.

We can develop a moderate relativist position, which maintains the claim that there is no universal morality but makes fewer claims about tolerance and perhaps some claims of correctness.([16]) So while acknowledging that there are many ways in which a culture can regulate conflict between people – arguably a central function of morality – we might also allow that some systems can fail to do this and so be false: a culture that,

14. Neil Levy, *Moral Relativism: a short introduction* (Oxford: Oneworld Publications, 2002).
15. David Wong, *Moral Relativity* (Berkeley, CA: University of California Press, 1984); David Wong, "Relativism", in *A Companion to Ethics*, Peter Singer, ed. (Oxford: Blackwell, 1993): 442-50.
16. David Wong, "Relativism", in *A Companion to Ethics*, Peter Singer, ed. (Oxford: Blackwell, 1993): 446.

for example, has no variant of the idea of respect might fail in important ways to manage conflict between individuals.

Alternatively, we might suggest a similarly moderate objectivist position. This might explain moral difference by pointing out that, even if there are genuinely right answers to disputed moral claims, those answers might be hard to discover particularly when – as in the case study – they relate to what ought to be done in a cultural context that is not our own. On this sort of account the existence of stark cultural disagreements need not undermine our belief that there is a right answer to be found (or at least sought), though it might give us reason to be less confident that our own view is the correct one, and hence to be tolerant of the views of others. As with moderate relativism, though, this does not entail an absolute commitment to tolerance.

A moderate objectivism can acknowledge that there may be situations where the differences between cultures are too great for one side to convince the other or for agreement to be reached.([17]) However, Wiggins suggests that even where such disagreement exists there may be situations where progress can be made through perseverance. The thought is that by uncovering the 'deep' differences of perspective, one or both sides can come to see or understand the other's standpoint. Whether such a strategy works can depend on the individuals concerned and the circumstances of their involvement. In the enterprise of trying to understand one another, egos, temperament, claims of authority and attitudes of superiority can get in the way.([18])

Dealing with variations in ethical judgement

When we consider moral differences and the variability of moral judgement in the context of research ethics, two questions are raised. First and most immediately, in situations of disagreement, to what standard should researchers be held? Is research ethics the kind of arena in which perseverance can be successful in reaching consensus? The second question that arises here concerns whether and to what extent variation between committees, whether international or intra-national, is a bad thing. If some variation and disagreement is to be expected, then some difference in views between committees is also. Moreover, if we adopt either of the moderate positions described above, we are in a position to accept variation as a natural by-product of different ways of making sense of morality. Practically, however, variation can be very difficult to handle – multiple committees applying different standards and coming to different conclusions makes getting approval an onerous task.([19])

Again, the broader themes of the relationship between science and society come into play in this case when considering the practical consequences of variations in ethical judgement. On the one hand, variation may signify an appropriately local consideration of social and moral values. It may signify just the right kind of inclusion and recognition of the range of perspectives and values at the social level. On the other hand, variation may represent the misfiring of processes that are intended to give consistency and fairness in the ethical consideration of research. Thus the line of reasoning developed in the section on science and society has important points of contact with the theoretical issues involved with moral relativism.

17. David Wiggins, "Moral cognitivism, moral relativism and motivating moral beliefs", *Proceedings of the Aristotelian Society* 91 (1990): 75-6.
18. Mark Sheehan, "Moral Relativism", in *Principles of Health Care Ethics*, Richard E. Ashcroft, Angus Dawson, Heather Draper and John R. McMillan, eds. (Chichester: John Wiley & Sons, 2007): 93-8.
19. E.L. Angell, C.J. Jackson, R.E. Ashcroft, A. Bryman, K. Windridge and M. Dixon Woods, "Is 'inconsistency' in research ethics committee decision-making really a problem? An empirical investigation and reflection", *Clinical Ethics* 2 (2007): 92-9.

Case Study 7.3
Research on a 'trust' drug

Oxytocin is a natural hormone produced in the hypothalamus in response to stimuli including social interaction, sex, breast-feeding and childbirth. It has an important role in the formation and maintenance of social bonds including those between sexual partners and between parents and their offspring. The mechanisms by which it functions are not fully understood, but it is known that oxytocin makes people more trusting. In one study, participants who had received oxytocin via a nasal spray were more willing to hand money to a trustee knowing that the trustee could choose not to return it to them, and were less likely to modify this behaviour after having their trust betrayed. ([20])

Research has suggested that deficiency of oxytocin may be associated with a range of neuropsychiatric conditions including autism, social anxiety disorder, and borderline personality disorders resulting from childhood neglect. Studies using nasally administered oxytocin have given strong indications that the hormone may have important therapeutic potential for some of these conditions. ([21])

An obstacle to the development of such therapies is the short half-life of nasally-administered oxytocin. Response to the drug peaks in about 50 minutes and wears off about 2 hours after administration. In order to overcome this limitation a group of researchers wish to trial a slow-release version of the hormone with a significantly longer half-life. They hope that an appropriate form of the hormone can be of widespread assistance to those suffering from autism and other disorders.

Speculation has been rife about alternative uses of this kind of product. Worries have included its (mis)use in the interrogation of terrorists or combatants or for the indoctrination of new recruits to fanatical sects. Finally, it has also been suggested that such a drug would add significantly to currently available drugs to form a new form of date rape cocktail.

Questions

1. What are the risks associated with this research?
2. Do the risks associated with the research and with the misuse of the knowledge generated by this research outweigh the potential benefits of the research?
3. Is there anything that the researchers can or should do to prevent misuse?
4. What are the researchers' responsibilities in relation to the possible misuse of their findings?
5. Who (if not the researchers) should be responsible for preventing misuse?

20. BBC News, "Trust drug may cure social phobia" (21 May 2008). http://news.bbc.co.uk/1/hi/health/7412438.stm
21. Maia Szalavitz, "'Cuddle chemical' could treat mental illness", *New Scientist* 2656 (14 May 2008): 34-7. http://www.newscientist.com/article/mg19826561.900-cuddle-chemical-could-treat-mental-illness.html

Discussion

This case study is about the risks associated with research, but focuses on a different kind of risk from those considered in earlier chapters – the risk of misuse. In answering the first two questions we can separate those risks that are associated with the research itself (for example the risk of harm to research participants) from those that are connected to misuse of its results.

Dual use

The main purpose of the case is to introduce the problem of dual use. Dual use problems arise when the knowledge generated by research has the potential to be put to both good and bad uses. This applies to some degree to most if not all research, but the problem has arisen and received attention in a number of more extreme situations. What makes many dual-use cases noteworthy is the magnitude of the harm that the misuse could cause.

An important function of this case is to raise questions about the assumption, easily made in the context of medical research, that the research will benefit people. In Chapter 1 we considered the benefits as providing a necessary moral argument for conducting research involving human subjects. In the case of medical research this argument was at its most powerful when it involved direct benefit to patients. In the non-medical context the question of the benefits of research (or the justification of research) is not always so readily apparent. In either medical or non-medical cases, the possibility of significant misuse can force us to pay closer attention to the justification of the research. So, a piece of proposed research that investigates an important part of human physiology might need further scrutiny if there are serious dual-use possibilities.

A central question posed by the dual-use problem is: how do we balance the risks associated with the possibility of misuse of the knowledge generated by a piece of research against the potential of the research to benefit society? This raises issues about both the responsibilities of researchers and the governance of research. In general we can divide dual-use cases into three categories:

(i) those in which certain research should not be conducted because the risks are too great;
(ii) those in which research should not be published or be allowed to enter the public domain; and
(iii) those in which various methods of oversight of the research and its application might be appropriate.

Dual-use problems are often associated with research that has a potential military application. However, there are some important distinctions to be made here.[22] First, we should distinguish good/harmful uses of a technology from military/non-military uses, noting that, as in the case study, only some of the potential uses that give rise to dual use concerns are of a military nature. Within the category of military uses we should distinguish offensive and defensive uses. Separating these helps to question the assumption that military uses are harmful or bad ones and also enables us to see how closely connected the harmful and beneficial uses may be. For example, we might think that research on the effects of exposure to a particular pathogen that may be used in chemical weapons may provide ways of reducing the harmful effects of such a weapon. However the same research may answer some practical questions about how to make the weaponised form of the pathogen more effective. Both are military uses: the former is a defensive one and, on the face of it, warranted; the latter is an offensive military use and likely to be unwarranted.

It is also important to distinguish two kinds of purpose: primary and secondary. In the example above, the primary purpose is a defensive military one and the concern lies with the secondary offensive purposes. Similarly, in the case study the primary purpose appears to be a legitimate one and the concern arises about secondary purposes to which the research might be

22. Seumas Miller and Michael J. Selgelid, "Ethical and philosophical consideration of the dual-use dilemma in the biological sciences", *Science and Engineering Ethics* 13 (2007): 523-80.

put. This distinction is important because blame is usually attached to agents on the basis of their intentions and motivations. In dual-use cases the secondary purposes may not feature at all in the intentions or motivations of the researchers, yet we may want to say that the research is unjustified because of its potential misuse. This raises the issue, addressed in Questions 3-5, of where responsibility for preventing misuse lies.

A second tension inherent in dual-use cases is between security on the one hand and academic freedom and scientific progress on the other. The force of the security concerns all involve the estimation and weighing up of the risk of harm associated with the bad uses of the research. Some of these risks can be managed by adjusting the levels and form of security in place – clearly greater security will lessen the risk of harm. In some cases the security measures are 'physical' ones that need not interfere with the research itself: physical and data protection systems to prevent theft as well as various security processes to ensure, for instance, that only those with the relevant clearances can access the research and its objects. In others, the security measures involve restrictions on the research that may be conducted or the ways in which it may be disseminated.

Opposing security measures that limit the research and its dissemination are the claims of academic freedom and scientific progress. Freedom to pursue one's own direction of research might reasonably be linked to broader intellectual freedoms such as the freedom of thought and speech, and is considered an important feature of educational and research institutions such as universities. Curtailing these freedoms undermines an important tenet of society. Part of the justification for academic and intellectual freedom is connected to the idea of progress in science: by being permissive about the scope of research and allowing access and dissemination to all, we allow new research to be built on the full range of knowledge generated by research already completed.

Overall, decisions about whether to limit research or restrict dissemination will involve balancing the risks involved in the particular case (along with the extent to which they can be mitigated) against the value of academic freedom and scientific progress. In both cases there is important room for compromise. Policies may be available which will reduce, if not eliminate, risks of misuse while imposing only limited restrictions on intellectual freedom. In the case at hand, one possibility may be to restrict or prevent the publication of the method used in extending the half-life of oxytocin.

Responsibility and security

The direct link between Case Study 7.3 and the broad science and society themes of this chapter is through the distinction between individual and collective responsibility. It was noted earlier that shifting trends in the relationship between science and society mean that it has become increasingly difficult and complex for responsibility to be straightforwardly attributed to individuals. Dual use dilemmas provide a very good example of precisely this issue. Consideration of societal responsibility and institutional response is a crucial element of these cases. At the same time, though, questions still arise from the perspective of the individual researcher. Thus it is important to attend to the individual researcher's responsibility as well as the responsibilities of social institutions.

What are the researchers' responsibilities?

The question of what can be done by researchers is an important one that will vary with the context. One possibility will always be to refrain from doing the research. Other possibilities include reporting that the research is taking place to a relevant authority, not publishing the research at all or in publicly accessible places, and modifying the research (or its published form) so as to make the possibility of misuse lower.

The issue here centres on the obligations that the researcher has to conduct research in a responsible way and very clearly recalls the justifications of the scientific endeavour discussed in the first section. It might be argued, for example, that since the researcher is conducting research for the benefit of the society and/or funded by the society, researchers should take adequate measures to ensure that the research findings are not misused. Given publication, there may not always be much that the researcher can do, but such things as

alerting the relevant authority to the research and its potential misuse may be appropriate. This view makes the obligation to take steps to prevent misuse part of the researcher's responsibility. It might also be suggested that the researcher is both researcher and citizen at the same time. As researcher the obligation is to conduct research that is effective in generating new knowledge. However, as citizen the obligation is to act so as not to endanger society. This means that the obligations of the researcher and the researcher-citizen can conflict and require balancing, perhaps on a case-by-case basis. A final view is that the researcher's responsibilities are only concerned with conducting optimal scientific research; if there are responsibilities concerning the use or misuses of the research, these are not the business of the researcher but of the broader social institutions involved in the oversight of the application of the research.

Who (if not solely the researcher) should be responsible for preventing misuse?

From the perspective of the relevant governance institutions, the questions are the extent to which research should be overseen, the nature of this oversight and the form that any restriction should take. It is useful to isolate in each particular context – national, European or international – the relevant organisations and institutions. These may include (but are not limited to) research ethics committees, research funding bodies, professional associations, governments and international Non Governmental Organisations.

The ideas discussed in the opening section of this chapter about the need for collective responsibility suggest that society as a whole should consider the appropriate policy and institutional responses to these cases. Miller and Selgelid provide an excellent list of the broad range of policy alternatives available. First they give six techniques for controlling the various elements of the dual-use situation. These are:

- distinguishing permissible and impermissible research;
- mandatory physical safety and security regulation;
- licensing of dual-use technologies;
- mandatory education and training;
- mandatory personnel security regulation;
- censorship or constraints on dissemination of research methods or findings.

Clearly there are various ways of enforcing these techniques as well as different levels of control over the scientists involved. Miller and Selgelid categorise them in the following way:

- complete autonomy of the individual scientist;
- institutional control;
- a dual system of institutional and governmental control;
- control by an independent authority;
- governmental control.

The ways in which these forms can and should be utilised will vary from situation to situation. However in the policy context, whether at the national, European or international level, it is important to consider the ways in which these forms of response can be brought together in an overall system of response and oversight covering all cases.

Case Study 7.4
Pharmacogenetics research

Two researchers are collaborating with an international drug company to develop drugs that are targeted at particular genetically related sub-groups within the European community. Their first project involves Europeans of African descent. The idea is to produce versions of heart disease drugs that counteract genetic variants that are known to be

present in this population and may reduce the effectiveness of anti-inflammatory drugs.

The research program will draw on established work on the genetic variation between various groups of different origin. It will then link this genetic variation to drug response. As with other pharmacogenetic research of this kind, it has the potential to make drugs safer and more effective for the relevant population. It is hoped that this research will lead to progress on personal, tailor-made drugs based on an individual's entire genetic profile.

However, questions have been raised about racial and ethnic discrimination which might follow from such research.

For commercial reasons, the drug company has insisted that the research can only be published if it is successful and after the drugs in question have passed all of the relevant approval stages.

Questions

1. What are the benefits of this research?
2. How might discrimination follow from this kind of research?
3. Should concepts like race feature in this kind of research? Is there any (medical) research for which these concepts are relevant?
4. What are the ethical issues associated with personal, genetically-based medicine?
5. Is the company's stipulation ethically acceptable?
6. Do the researchers have an obligation to publish their research?

Discussion

Pharmacogenetics research brings together our understanding of genetics with the study of our responses to drugs. As such, it raises important questions about the ability of science to change the way in which medicine proceeds in ways that may have profound social consequences. Of particular note here is the way in which social categories like race and ethnicity, already ostensibly connected to genetic heritage, can be linked in a systematic manner to particular drug response differences, which may in turn reinforce the social categories.

There are a number of links to be made between this case and issues discussed in previous chapters. The introduction of personalised medicines may raise questions about access to confidential (genetic) information – specific genetic-related issues will be considered in Chapter 8. There are also justice-related concerns about access to the new drugs and to the genetic testing required in order to take advantage of them. Finally, this case relates to issues surrounding discrimination that were considered in Chapter 6.

Pharmacogenetics and ethics

Pharmacogenetics is the study of how genetic variation affects our response to drugs. More specifically, pharmacogenetics

> *takes the patient's genetic information of drug transporters, drug metabolizing enzymes and drug receptors into account to allow for an individualized drug therapy leading to optimal choice and dose of the drugs in question.* ([23])

This kind of research brings with it the possibility of a number of significant benefits. Most obviously, groups of patients and, in the future, individual patients will be prescribed drugs that will be more effective for them

23. Magnus Ingelman-Sundberg, "Pharmacogenetics: an opportunity for a safer and more efficient pharmacotherapy", *Journal of Internal Medicine* 250 (2001): 186.

or will have a lower risk of side-effects. It has also been suggested that developments in pharmacogenetics will enable clinical trials to become much safer for participants by using the knowledge of drug response to exclude those at greatest risk. ([24])

Many of the concerns about the development of pharmacogenetics are justice-related. By tailoring drugs to particular groups it has the potential to create new health inequalities or to reinforce existing ones. One such concern involves the way in which access to drugs will vary between those for whom pharmacogenetic knowledge makes tailor-made drugs possible and those who are not so fortunate. One possibility is that pharmacogenetics creates a new class of 'orphan groups' – groups for whom it is uneconomical to develop tailored drugs and who are consequently forced to rely on lesser 'one-size-fits-all' medicines. ([25])

This could also lead to the exacerbation of existing socio-economic inequalities. If there are significant pharmacogenetic variations that overlap with socio-economic status then it is possible that poorer sections of society will be the ones passed over in the development of targeted drugs, or alternatively that by being so targeted they become the victims of stigmatisation. This of course may not come to pass, but as we shall see below it is important to be careful about the ways in which the scientific distinctions that we make between groups of people match up with social distinctions.

Social categories in research

A key issue raised by Case Study 7.4 concerns concepts of race and their relationship to genetics. The scientific characteristics of interest that influence the body's response to particular medicines are genetic characteristics. However the social categories that we tend to use to classify people are most often related to appearance, behaviour, traditions and lineage.

The main problem that is raised here is the relationship between the genetic characteristics that are the basis of the pharmacogenetic research and the socially based categories of race and ethnicity. The pharmacogenetic interactions operate exclusively at the genetic level and the groupings associated with them may not match the social groupings. So, not all members of a particular social group, in this case Europeans of African descent, will possess the genetic variants for which the drug has been developed. This is the familiar issue of needing to be careful that the group on which the drug is tested is the group that will use that drug.

Further, social groupings like race and ethnicity are often subject to stereotyped views about the behaviours, traits and characteristics of their members, views that are more often than not influenced by historical prejudice and generalisation. If the identification of genetic differences is associated with racial and ethnic groupings, there is a risk that this will reinforce prejudice and stereotyping. It is therefore important to be clear about the distinction between these two kinds of groupings – the genetic and the social.

On the other hand and in spite of this, early pharmacogenetics has used racial or ethnic distinctions as a broad marker for particular kinds of predispositions. In some cases there does seem to be an important correlation between the phenotypic features associated with particular races and ethnicities and, for example, predispositions to certain conditions or reactions to treatments. These correlations are at work in the case under discussion.

The issue in the background here involves the genetic underpinnings of race. One side of this debate insists that because race is an ethically loaded social construction it has no place in science. This side points out that there is a vast amount of genetic variation within those who consider themselves to be of a particular race or

24. Emilio Mordini, "Ethical considerations on pharmacogenetics", *Pharmacological Research* 49 (2004): 375-9.
25. Andrew Smart, Paul Martin and Michael Parker, "Tailored medicine: whom will it fit? The ethics of patient and disease stratification", *Bioethics* 18 (2004): 322-43.

ethnicity.([26]) The other side relies on the relationship between historical origins and genetics, and the increasingly understood connections between genetics and dispositions to behaviour. According to this side, genetics and behavioural research is relevant to how we understand such social categories as race.

In relating this debate to pharmacogenetics, Holm argues that the link between genetics and race is not robust enough to make the pharmacogenetic testing of individuals redundant. That is, there is enough relevant genetic variation within the socially observed categories of race for it to fail as an adequate pharmacogenetic proxy.([27]) Even if this is right, however, the broad correlations that appear to exist between race and drug response may be enough to create social problems: if it is perceived – rightly or wrongly – that some racial or ethnic groups are benefiting more than others from the development of targeted medicines, then this has the potential to create or exacerbate interracial or inter-ethnic tensions and resentments. What this means, effectively, is that the development of targeted drugs creates a new arena for concerns about distributive justice to be played out.

Commercial interests in research

The general issue raised by Question 5 concerns the balance between the commercial involvements required to enable the continued and effective progression of medical science and the dangers associated with involving the profit motive in medical research. The tension arises largely because of a worry about the way in which the (excessive) involvement of a profit motive can skew the practice of medicine and medical research.

In considering these tensions we should recognise the benefits that can result from a market driven medical research industry. For example, a 2003 study argues that of the 2 years of life expectancy gained over the period from 1986 to 2000, 10 months can be attributed to new chemical entities.([28]) An earlier study showed "that people who used newer drugs had better post-treatment health than people using older drugs for the same condition, controlling for pre-treatment health, age, sex, race, marital status, education, income, and insurance coverage: they were more likely to survive, their perceived health status was higher, and they experienced fewer activity, social, and physical limitations".([29]) In a more recent study, it is shown that "the more medical innovation there is related to a medical condition, the greater the improvement in the average health of people with that condition".([30]) These studies are useful reminders of the benefits that can be associated with the pharmaceutical industry. Since the industry functions more effectively as a result of market forces, society as a whole has a vested interest in ensuring that the industry remains competitive. The ability to bring a new product to market faster than one's industry competitors is crucial to a company's ability to maintain competitiveness.

At the same time there are genuine concerns associated with excessive commercial motivation in health care. In the context of research we might worry about the temptation to cut methodological corners or to 'fudge' results. In the worst kind of case we may be concerned that financial incentives might lead to the fabrication of results. The practice of medicine and medical research can survive a good deal of commercialisation, but it is easy to find cases where the profit

26. Troy Duster, "Medicine – race and reification in science", *Science* 307 (2005): 1050-1.
27. Søren Holm, "Pharmacogenetics, race and global injustice", *Developing World Bioethics* 8, no. 2 (2008): 82-8.
28. Frank R. Lichtenberg, "The impact of new drug launches on longevity: Evidence from longitudinal, disease-level data from 52 countries, 1982-2001", in *NBER Working Papers* 9754 (Cambridge, MA: National Bureau of Economic Research, Inc., 2003).
29. Frank R. Lichtenberg and Suchin Virabhak, "Pharmaceutical-embodied technical progress, longevity, and quality of life: Drugs as 'equipment for your health'", in *NBER Working Papers* 9351 (Cambridge, MA: National Bureau of Economic Research, Inc., 2002): 2.
30. Frank R. Lichtenberg, "The impact of new laboratory procedures and other medical innovations on the health of Americans, 1990-2003: Evidence from longitudinal, disease-level data", in *NBER Working Papers* 12120 (Cambridge, MA: National Bureau of Economic Research, Inc., 2006).

motive wrongly intervenes in the processes of medicine – we might think this is true in the case study, where the restrictions on publication, presumably driven by the desire for competitive advantage, prevent the full dissemination of knowledge. The goals (and hence the motivations) associated with medicine and medical research are essentially related to the benefit of patients, whether immediate or future, whereas commercial interests can easily run contrary to these.

There have been a number of steps taken at the international level in recent years to protect against harms associated with commercial interests. These include public registration of clinical trials and the disclosure of results. Of particular note are the recommendations made by the International Committee of Medical Journal Editors ([31]) and the WHO. ([32]) Both of these sets of guidance require that information about medically related trials is publicly available. For example, the WHO suggests that all phases of all clinical trials involving human beings be registered on their International Clinical Trials Registry Platform. An important function of these recommendations is to increase the transparency and accountability of research conducted by the pharmaceutical companies. The disclosures required by the International Clinical Trials Registry open up the activities of commercial research in an effort to protect society from those with an over-eager commercial interest. ([33])

Publication ethics, conflicts of interest and academic integrity

In ethical terms it is quite clear that researchers should conduct their research with integrity – they should not falsify their data, cut corners in research design or plagiarise the work of others. The falsification of data and of findings, like each of the elements of research integrity, is a violation not only of the general moral norm of truthfulness but also of the project of research itself. This links the issue of research integrity back to the discussion earlier in the chapter about the relationship between science and society.

Methodological shortcuts and falsification of results will undermine the benefits that science can bring to society. The extent to which scientific research generally is justified by the benefits it will produce for society is therefore closely tied to the obligation on researchers to conduct their research with integrity. This also has consequences for the publication and dissemination of results, since the benefits of scientific research are more likely to be realised if work is published and read as widely as is relevant. The obligations of researchers to publish and accurately present findings follow on from the public benefit arguments for the justification of research. An interesting part of this involves the publication of 'negative research' – for example, research which is unsuccessful in showing that a particular drug benefits the relevant patient group. It is easy to be excited by the successes of research and to fail to recognise the knowledge gained by learning about what does not work. Systematic reviews and meta-analyses are important parts of scientific research and can be more thoroughly conducted with all of the evidence.

The ICMJE document, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication", is a useful resource in this regard. ([34]) It includes statements about the publication of negative results and about the accuracy of the presentation of research but it also requires

31. International Committee of Medical Journal Editors, "Clinical trial registration: looking back and moving ahead" (June 2007). http://www.icmje.org/clin_trial07.pdf
32. World Health Organization, *International Clinical Trials Registry Platform* (ICTRP). http://www.who.int/ictrp/en/
33. S. Matthew Liao, Mark Sheehan and Steve Clarke, "The duty to disclose adverse clinical trial results", *American Journal of Bioethics* 9, no. 8 (2009): 24-32.
34. International Committee of Medical Journal Editors, "Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication" (October 2008). http://www.icmje.org/index.html

potential conflicts of interests to be declared. Clearly the commercial conflict of interest worries raised above involve researchers (and indeed governance arrangements) being motivated by financially related self-interest rather than a concern to develop medical products that benefit patients. There are, however, other very powerful motivations that similarly can draw the researcher away from the central goals of medical research. These include the academic pressures to publish, to attract funding and to receive the attention of the academic community or the public. These too can lead to similar kinds of misconduct mentioned in the context of commercial interests, such as cutting corners and the fabrication of results. Although there is very good reason for having processes in place for disclosure of such conflicts of interests, it is important to recognise that researchers can act with integrity despite these pressures and that the appearance of a conflict of interest is not necessarily an indicator of wrong-doing.

In all of this the questions concerning science and society are very much present. Commercial interests are crucial to the functioning of European society and more specifically to health care in Europe. At the same time (and like all other sectors of society) the motives and orientation of commercial organisations are not always the same as those of society as a whole or elements of it such as health care, and should therefore be handled with care. When thinking about the form and structure of research ethics governance across Europe these considerations needed to be carefully balanced.

Further reading

Society and research

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Chapter 8 **Ethical issues in the new biotechnologies**

Learning outcomes

In this chapter you will develop:

- An understanding of the research-specific ethical issues involved in reproductive and reproductive-related technology, disability, nanotechnology and genetics.
- An understanding of the more general ethical issues involved in reproductive and reproductive-related technology, disability, nanotechnology and genetics.
- An appreciation of the challenges to the processes of ethical review posed by research on reproductive and reproductive-related technology, disability, nanotechnology and genetics.

Introduction

This chapter examines a range of issues that arise in the context of new biotechnological developments. Broadly it looks at issues in reproductive and reproductive-related technology, disability, nanotechnology and genetics. Each of these technologies is introduced through a case study which raises a specific set of ethical considerations that connect with and apply the discussions of earlier chapters. The most significant connection, however, is to Chapter 7. There, the focus of the introductory section was on the relationship between science and society. Four themes were introduced and discussed throughout the chapter:

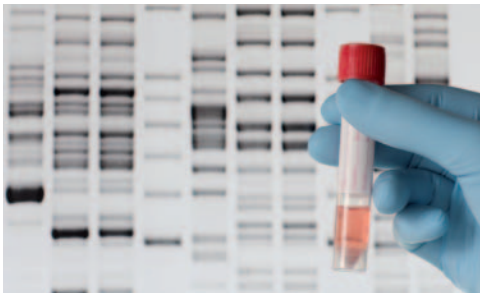
(i) the forms of public engagement and stakeholder involvement;
(ii) the role of consensus in decision-making;
(iii) the distinction between individual and collective responsibility; and
(iv) the form and structure of research ethics governance. The case studies in this chapter extend and develop these themes.

The case studies below raise two kinds of ethical issue. First, they present specific challenges for the process of ethical review – difficulties, for example, associated with obtaining consent, protecting confidentiality and assessing risks and benefits. As such, they invite the reader to look forward and to consider the ways in which the system of ethics review and the contemporary approach to research ethics will be able to cope with the biotechnological developments of the future. This first kind of issue draws on the discussions of the earlier chapters in order to consider future problems confronting those involved in research and research ethics review.

The second kind of issue raised by these cases is more closely connected to the nature and permissibility of the technology itself (as distinct from issues arising specifically from the research process). The four broad topics considered in the cases each encapsulate new challenges to our understanding of ethics generally and quite apart from the research context. As such they represent challenges to the way we think about ethics and society. The first case looks at the ethical challenges raised by new reproductive technologies, including the moral status of embryos and the acceptability and limits of interventions in the reproductive process. The second case examines the status of disability and the proper responses to it in the light of new possibilities for biotechnological interventions. The third case raises questions about decisions under conditions of uncertainty and the adequacy of the precautionary principle in dealing with nanotechnology. The final case study looks more closely at the use of genetics, and in particular at the global use of human genetic data in the context of genetic biobanks.

In discussing each of the cases it is useful to separate these two kinds of considerations initially and then to consider the ways in which the latter, more general ethical issues might affect the former, more specific, research related questions.

Case Study 8.1
Germ-line gene therapy



A clinical geneticist, Corinne, working with colleagues in an IVF facility, has developed a technique for manipulating the genetic structure of implantable embryos. If successful this will have the advantage over embryo selection of allowing couples to have a child free from an inherited defect in cases where all of their available embryos are affected (for example in cases where one of the couple is unable to produce further gametes following illness).

One couple attending the IVF facility, Anna and Boris, has a history of serious, genetically related

renal failure. Several of their closely related family members have suffered very significantly from kidney problems over the course of their lives. Although both Anna and Boris possess the relevant genes, they have not been expressed in either of them to a serious extent. The particular condition itself is too complex to address using this method of gene manipulation. It may however be possible to use Corinne's technique to address one of the key symptoms of the condition.

Individuals who suffer from this kind of renal problem are very often anaemic – lacking sufficient red blood cells to carry oxygen through the body. Corinne's procedure would induce a genetic polymorphism in the embryo that would increase the resultant child's sensitivity to erythropoietin (EPO). Erythropoietin is a protein that stimulates bone marrow to make more red blood cells. It is thought that increasing the sensitivity to erythropoietin will compensate for the reduced levels of the protein (and hence the anaemia) caused by the renal problems. Artificially produced erythropoietin is sometimes given (off-label) to those with severe kidney disorders for precisely this reason and has also, more controversially, been used by athletes to enhance their performance by increasing the amount of oxygen carried by the blood. Moreover, in the 1970s, Finnish cross-country skier and dual Olympic gold-medal winner, Eero Mäntyranta was found to have this genetic polymorphism naturally. It enabled him to produce between 25 % and 50 % more red-blood cells than normal people and greatly improved his endurance capabilities.

Another couple at the clinic, Dana and Eddie, are very committed to an active, athletic lifestyle. Eddie competes at a high level in a number of endurance sports but has always suspected that there is a connection between his inability to 'make it' at the highest level and his genetic inheritance. Dana and Eddie would very much like to avoid this being the case for their children. Together with Corinne they have enthusiastically discussed the possibility of using her gene therapy technique to increase the endurance capabilities of their child. Thus, if it turns out that the child is interested in competitive sport, there will be no concerns about endurance.

Both couples understand very clearly:

(i) that this technique has not been tested in humans and that the success seen in animals may not translate to humans;
(ii) that if the resulting child (in Anna and Boris' case) has kidney problems, this therapy will not solve all of them – it is only intended to address the problems related to anaemia;
(iii) that if the resulting child does not have kidney problems, this therapy will mean that the child will have enhanced levels of erythropoietin (this is true for both couples);
(iv) that if the resulting child has no kidney problems and enhanced levels of erythropoietin, there may be a slightly increased chance of stroke; and
(v) that because these alterations are taking place at the embryonic level it is likely that they will be carried on in future generations.

Questions

1. Is the use of Corinne's technique on Anna and Boris's embryos treatment or research?
2. What are the ethical considerations raised by the use of this technique (whether it is research or treatment)?
3. Is this kind of treatment of embryos permissible? If so why? If not, why not?
4. In the case of each couple, is the use of Corinne's technique on the embryos therapy or enhancement? How does this affect the ethics of the prospective interventions?
5. Do the couples have the right to decide whether or not to go ahead with this procedure? If we assume that the resultant child will benefit from the intervention, do the couples have an obligation to go ahead with this procedure? How much depends on the assumption of benefit to the prospective child?
6. Should there be special regulation or oversight of this kind of activity?

7. Are there any special ethical issues raised by the fact that these interventions may, if successful, affect future generations?

Discussion

This case introduces ethical issues surrounding new reproductive technologies as well as issues specific to the research process. It is useful to consider the research-specific issues both before and after the discussion of the more controversial 'enhancement' and reproductive technology-related considerations. By separating ethical issues raised by the specific nature of the techniques to be investigated from more general research ethics issues, readers will be better placed to assess the particular research ethics problems raised by controversial technologies.

An initial survey of the research-specific issues yields some important connections with the discussions of previous chapters. In particular, the case raises issues of consent and harm relating to the severity of the potential effects on the resulting offspring, the ability of individuals to understand and consent to risks when there is very little evidence to go on, and the right of parents to consent to risks that will be borne by their future children. These issues connect with Chapters 2, 3 and 5.

The distinction between research and treatment

Before considering the research ethics issues associated with this case, we need to establish whether the proposed intervention counts as research. As was discussed in Chapter 1, this is not always an easy question to answer.

On the one hand this has the appearance of research: it is clearly experimental since the clinician is not working on the basis of sufficient, previously established evidence of the efficacy of her intervention, and is attempting to expand her understanding and to develop the technique further. On the other hand, the application and testing of the new technique appear to be on a small scale (rather than in large trials), involving individuals with suitable circumstances who are willing (and perhaps desperate) to participate in order to find a solution to a particular problem. This means that the kind of data that this experimentation can yield will be very specific and any conclusions will be a long way from being generally established.

If the intervention is classified as research its justification may be questionable given that, even if it is successful, there may be relatively little (if any) generalisable knowledge produced. Alternatively it might be argued that this case and others in clinical genetics provide an interesting challenge to our understanding of the nature of research and its relationship to clinical practice.([1]) It is quite often the case in clinical genetics that specific mutations require investigation and exploration. In such cases, one-off responses to the needs of a patient help to build up the geneticist's 'library' of mutations and conditions, and so contribute to experiential or clinical knowledge rather than more general, 'publishable' research.

If this is the way in which knowledge progresses in clinical genetics, requiring large-scale trials of the kind that can generate secure, generalisable knowledge in other fields might simply be inappropriate for these sorts of technologies. This still leaves the question of how the intervention is to be justified. One way would be to show that this sort of piecemeal approach can bring real benefits in terms of the growth of knowledge and the prospects for future treatments; another would be to argue that if the intervention is understood as 'tailor-made' treatment its justification need not be research focused at all but can be based on the benefits to and consent of the patients.

On the other hand it may be thought that however this case and others like it are classified, they still require

1. Michael Parker, Richard Ashcroft, Andrew O.M. Wilkie and Alastair Kent, "Ethical review of research into rare genetic disorders", *British Medical Journal* 329 (2004): 288-9.

scrutiny of the kind that research ethics committees provide. Even if this kind of experimentation is classified as treatment, because of the risks involved and the fact that the clinician may have other aims in addition to the welfare of the patients, there may be some need for regulation and oversight beyond that which is required for more conventional forms of clinical practice.

Research-specific issues

Putting these questions aside for the moment and assuming that the case does count as research, it raises a number of ethical issues. ([2])

The first set of issues is connected to the harm-benefit ratio presented by this research. Given the experimental nature of the proposed intervention, the potential for harm may be quite significant and the justification of the research may therefore be restricted to the prevention of severe conditions rather than production of the benefits associated with enhancements. If the embryo would, without intervention, be likely to develop into a normal child, then the risks associated with this intervention seem likely to outweigh its benefits. Moreover, if we are judging this case according to the standards commonly applied to research, there may be some hesitation in exposing vulnerable subjects (embryos) to significant risks in the absence of clear benefits. These arguments involve two contestable assumptions. First, that the embryo can be counted as a research subject. This relates to wider debates about the moral status of the embryo which will be considered below. Second, it is assumed that there is a morally significant difference between therapy (in the case of Anna and Boris) and enhancement (in the case of Dana and Eddie). This also will be considered below.

For germ-line modifications like this one, we might want research to provide us with evidence not only of the effect in the immediate generation of children born using this technique but also its effects on future generations. This means that studies like this one would be significantly more complex and take considerably longer to achieve the required knowledge. Surviving subjects would need to be followed over the course of their lives in the attempt to map out the consequences of the intervention. The burdens of consent related to these issues would be significant: not only would consent have to be sought from the parents, but also from the direct subjects over the course of their lives and potentially from their children too.

Finally, there are some issues about how treatments such as these might become part of general clinical provision. In particular, given the nature of the interventions and the likely circumstances of their use, how safe and successful would the intervention need to be in order to be made generally clinically available? Does the safety level and the success rate for this kind of intervention need to be the same as is required for other kinds of intervention?

The moral status of the embryo

Clearly the case study raises issues about the proper treatment and moral status of embryos. Four common accounts may be discussed and applied to the research context. According to these, moral status is:

(i) attached to the continuous human organism;
(ii) attached to persons;
(iii) attached to persons and potential people; or
(iv) conferred by agents.

In what follows we will briefly sketch each of these views before continuing to consider the role that they may play in the ethical consideration of research.

First, however, we need to be a little clearer about what is meant by 'moral status'. On one view an entity has moral status, or is 'morally considerable', when it has interests that are morally significant in themselves and not just because they further the interests of some other morally considerable entity. Many people would hold that all sentient creatures are morally considerable in this sense. This does not, however, imply that the

2. Rebecca Dresser, "Designing babies: human research issues", *IRB: Ethics and Human Research* 26, no. 5 (2004): 1-8.

interests of such creatures have any particular weight. On another view, to have moral status is to have interests that warrant a particular, very high level of protection, of the sort that we typically claim for ourselves and recognise for other human beings – for example by attributing rights to them or seeing our treatment of them as being governed by strong deontological constraints. These need not be absolute but are usually seen as being defeasible only under extreme circumstances. To avoid confusion, this is sometimes referred to as having 'full' moral status.

The four common views about the kinds of entity that have full moral status, or something close to it, are as follows.

(i) **Moral status is attached to the continuous human organism.** This view attributes full moral status to the continuous human organism from conception. The thought here is that there are no morally relevant dividing lines apart from the point at which the process begins, namely, conception. One variant of this view is that what matters morally is the point at which the embryo becomes a unique human organism and to thus require that full moral status is attributed only after the possibility of embryo division (resulting in twins, for example) has past (usually taken to be at 14 days).

The main challenge to this view comes from a demand for consistency with common and widely accepted practices. (Of course, rejecting those practices as unethical is an alternative option here.) Clearly, if the human organism has full moral status from conception then abortion at any time in pregnancy is very problematic – this, of course, runs contrary to practice in many countries. Further, it has been argued that if we take this view of the moral status of the embryo, then the most significant human moral tragedy is going largely unnoticed in the form of spontaneous and natural early embryo loss. ([3])

(ii) **Moral status is attached to persons.** Partly perhaps in response to the problems faced by the continuous human organism view, this position distinguishes between 'humans' and 'persons', and attributes full moral status only to the latter. The idea is that 'human being' is a biological category rather than one that captures the morally significant features that makes members of that species morally distinct from other species. The concept of personhood is then applied to those who possess these morally significant characteristics, which are typically said to include sentience, reasons, capacity to communicate, self-awareness and moral agency. ([4])

The main challenge to this view is the implication that those individuals who do not satisfy the relevant conception of a person (often including young children and the mentally incapacitated) lack full moral status and may be treated accordingly.

(iii) **Moral status is attached to persons and potential persons.** This view takes on board the distinction between persons and human beings but attributes moral status to embryos (and children too young to have the defining characteristics of persons) in virtue of their being potential persons. As distinct from the first view, this one allows that embryos may have less than full moral status, as non-persons, but, in virtue of their potentiality, some (non-trivial) moral status which protects them from certain kinds of harms and interferences.

The main challenge to this view is to defend the idea that potentiality is of moral significance. Against this it may be argued that a sperm and an egg also have the potential to become human beings and so consistency would require that they too should be attributed moral status. This view also, fails to attribute moral status to severely mentally incapacitated humans who will never acquire the characteristics associated with personhood.

3. Toby Ord, "The scourge: moral implications of natural embryo loss", *American Journal of Bioethics* 8, no. 7 (2008): 12-19.
4. Mary Ann Warren, "On the moral and legal status of abortion", *The Monist* 50 (1973): 43-61.

(iv) Moral status is conferred. This view moves away from the idea that moral status is determined by the properties of the bearer of moral status. Instead, it is conferred by agents or their behaviour. On this account, an entity has moral status when it is treated as if it has moral status, for example when particular kinds of behaviour or language expressing 'commitment to value' are used in connection with the bearer. For example, we might say that an embryo has moral status when the pregnant woman decides to have the child or otherwise acts in such a way as to treat the embryo as having moral status.

The main difficulty with this view is that it seems to make the judgement of moral status, and in this case the judgement of the moral status of the embryo, too arbitrary and subjective. On this view moral status seems to depend on the whim of individuals.

These general ethical positions provide a basis for consideration of the nature and extent of the limits of permissible research on embryos. How, in particular, should the moral status of the embryo be balanced against the value of important research? The answer to this question will depend on the particular view of the embryo's moral status. If the embryo is understood to have full moral status from conception then it is difficult to see how even very valuable and pressing research will be permitted when it involves the destruction of embryos. A more moderate position might allow research on embryos but will depend on a different view of the moral status of the embryo.

The divergence of views on the moral status of the embryo raises the question (first addressed in Chapter 1) of how regulators and those involved in ethical review should respond to moral differences, especially where – as is often the case in relation to the status of embryos – they are associated with different religious perspectives. The extent to which individuals with diverging views are prepared to compromise to reach a workable decision or policy is likely to heavily influence the functionality of regulatory bodies. In the context of an ethics or policy committee, having a clearly defined remit helps to concentrate attention on issues which those with differing views can agree upon. However, this raises the further question of how the remit of such committees should be defined.

Treatments and enhancements

The different motivations of the two couples in Case Study 8.1 enable us to compare the moral significance of using a technology to treat a symptom of a condition and using it for enhancement. The questions raised by this comparison are whether there is a morally relevant distinction between treatment (or therapy) and enhancement, and under what conditions, if any, research into human enhancement might be justified. In what follows we will consider various issues associated with these questions.

We first consider the distinction between treatment and enhancement. Both couples want access to the same intervention but for different reasons. It is noteworthy that if Anna and Boris's child does not have the kidney condition (if the genes are not 'expressed') then the child will have increased sensitivity to EPO and so will also have increased endurance capabilities. Thus, despite the difference in the couples' intentions, the outcomes may be the same.

A common way to draw the distinction between treatment and enhancement is via the idea of species-typical or normal human functioning.([5]) A *treatment* is an intervention that is designed to improve or restore health to the level of normal human functioning. An *enhancement* is an intervention that is designed to improve on an element of normal human functioning. This distinction is often taken to be a morally relevant one with interventions classed as treatments being permissible (or obligatory) and those classed as enhancements being impermissible.

5. Patrick Lin and Fritz Allhoff, "Untangling the debate: the ethics of human enhancement", *Nanoethics* 2 (2008): 251-64.

A number of objections can be made against this account. Some of these objections deal with the distinction itself but most involve the moral significance attached to it. We permit (and perhaps encourage) mothers to eat special diets and maintain a healthy lifestyle during pregnancy. We allow parents to spend large sums of money to get their children the best education or to push their children, often in very extreme ways, to excel in intellectual, artistic or sporting endeavours. In such cases, the parents' decisions are usually made with a view to enhancing the child's prospects beyond what is 'normal' or 'typical'. An argument from consistency suggests that these values are precisely the ones in operation for Dana and Eddie, and calls on opponents of biotechnological enhancement to give an account of the morally relevant difference between the types of enhancement that they reject and these more widely accepted practices.

One response to this is to be careful about the moral work that the distinction between treatment and enhancement can be expected to do. Instead of expecting it to yield a firm moral boundary, we might suggest that classifying an intervention as an enhancement gives us a 'moral warning flag' – alerting us, for example, to the possibility that, as discussed above, the benefits of enhancement may be less likely than the benefits of treatment to outweigh the risks of an experimental procedure. ([6]) It is worth noting, however, that the distinction between treatment and enhancement is not a reliable indicator of risk/benefit ratio: major enhancements might, for the same level of risk, produce more benefit than the treatment of minor conditions.

Procreative liberty and the harm principle

This case study also raises important questions about the obligations and rights of prospective parents to decide about the kinds of children that they have. This issue has been widely discussed in the bioethics literature. Here we consider the general shape of the debate and the way in which it might apply to the case study. The general ethical issue here is whether there is something wrong with allowing parents to choose the kind of child they will have. ([7])

Perhaps the most common argument in favour of allowing couples to choose the kind of child they have involves the right to reproductive autonomy and the harm principle. These two principles provide a framework for dealing with the reasons that people have for procreating and the kinds of interventions by third parties that are justified.

The right to reproductive autonomy can be thought of as related to the general right to privacy and family life. ([8]) In terms of broad moral principles it is connected to the principle of respect for autonomy. The central idea here is that individuals are understood to have the right to determine when, where and with whom to reproduce. There are a number of ways of understanding this principle and it is important to be careful about what reproductive decisions we take this right to include. ([9])

The harm principle, introduced in Chapter 1, constrains this right. In this context the question becomes whether particular reproductive choices will result in harm to others. If parents' reasons for having a child affect the way in which the child's life goes then we want parents to have good reasons rather than bad ones.

6. Norman Daniels, "Normal functioning and the treatment-enhancement distinction", *Cambridge Quarterly of Healthcare Ethics* 9 (2000): 309-22.
7. For example, is there something wrong with parents choosing to have a child of a particular sex? See *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (Oviedo, 4.IV.1997), Article 14. http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm
8. For example: European Union, *The Charter of Fundamental Rights of the European Union* (2000/C 364/01), Article 7. http://www.europarl.europa.eu/charter/default_en.htm
9. Onora O'Neill, *Autonomy and Trust in Bioethics* (Cambridge: Cambridge University Press, 2002), Chapter 3.

The first observation to make here is that prospective parents usually have a large number of variously important reasons for having a child. This makes it difficult to connect any particular procreative reason with child welfare.

Second, we might worry that a child created to fulfil certain parental ambitions is being treated as a mere means, exploited or 'commodified'. On the face of it, Dana and Eddie's reason for employing the gene therapy technique reason is one which 'instrumentalises' the resulting child, but it is unclear that this amounts to viewing the child as a mere means or that there is anything wrong with this degree of instrumentalisation. Because parents' reasons for having children and ways of valuing them are complex and varied, we cannot conclude from Dana and Eddie's desire to enhance their child's prospects of sporting success that the child is less likely to be valued for its own sake.

There are similar difficulties associated with concerns about psychological harms to the child that might follow from using technologies like this one. For example we might worry that the child will feel inadequate if it fails to 'live up to its genetics'. Again, the primary difficulty lies in demonstrating that genetic enhancement techniques are more likely to lead to such feelings than other manifestations of parental ambition that we do not attempt to prohibit.

While the harm principle focuses on harms to particular individuals as a reason to limit people's choices, some have argued that the potential impact of enhancement technologies on social institutions and values requires parental choices to be carefully regulated. It might be argued, for example, that society may in the long term be damaged by a loss of genetic diversity, or alternatively that the emergence of enhanced elites may undermine commitment to values such as equality and solidarity. Sometimes such claims are linked with the idea (discussed below) of enhancement as an interference with nature. ([10])

Procreative beneficence

A related set of approaches to reproductive choice concentrates more on the benefits associated with parental action. A consequentialist argument along these lines is that if people are allowed to choose for themselves what kind of children to have, this will make the world a better place because they will generally choose to avoid ill-health and in favour of characteristics such as intelligence and a disposition to happiness. There are both connections and important differences between this and the arguments proposed by the eugenics movement of the twentieth century. ([11])

We might further claim that it is the responsibility of parents to give their children the best chance at the best life. This has been called the principle of procreative beneficence:

> *Couples (or single reproducers) should select the child, of the possible children they could have, who is expected to have the best life, or at least as good a life as others, based on the relevant available information.* ([12])

The initial plausibility of this principle can be seen using a simple example. A couple wish to have a child but because there is currently a serious viral epidemic there is a high chance that the resultant child would be seriously adversely affected. If, however, the couple wait until the epidemic has passed (say, several months) then the risk associated with this viral infection will be negligible. Here the timing of the conception of the child will clearly affect the welfare of the child that will be born and it seems morally unproblematic to claim that the couple should wait. That is, the couple should have the later of the two possible children because that later child has a better chance of a better life.

From this example, we can see the force of the principle. Such a principle would tend to support research of the type described in the case study, as it offers the

10. Francis Fukuyama, *Our Posthuman Future: consequences of the biotechnology revolution* (London: Profile Books, 2002), especially Part 2.
11. John McMillan, "The return of the inseminator: eutelegenesis in recent and contemporary reproductive ethics", *Studies in History and Philosophy of Biological and Biomedical Sciences* 38 (2007): 393-410.
12. Julian Savulescu, "Procreative beneficence: why we should select the best children", *Bioethics* 15, no. 5/6 (2001): 413-26.

prospect of enabling parents to have children with better life chances in the future.

On the other hand, what makes this principle a controversial one is that a requirement to have the best possible children is potentially very demanding and may conflict with other moral considerations such as the welfare of the parents or other family members. Procreative beneficence may therefore best be thought of as a *prima facie* duty capable of being overridden by other considerations, or, alternatively, not as an obligation to have the child with the best possible life chances but to have a child whose life chances are good enough. ([13]) This might suggest that there is strong reason to pursue experimental treatments in cases like that of Anna and Boris, where it has the potential to prevent children from being born with conditions that significantly undermine their prospects of living a happy life, but less reason in cases like that of Dana and Eddie. ([14])

Interfering with nature

One common response to technological developments affecting the more fundamental aspects of life is to claim that such developments are 'unnatural', constitute an 'interference with nature', or involve human beings 'playing God'. Claims like these are made by Sandel, Kass, Habermas and others in response to the challenges posed by arguments in favour of enhancement. ([15]) The intuition that lies behind these claims is extremely common and often quite strong. Michael Sandel has observed, "When science moves faster than moral understanding, as it does today, men and women struggle to articulate their unease." ([16])

'Interfering with nature' claims should be distinguished from claims about 'playing God'. Claims about playing God are focused more on the character of the agents involved, whether it is a particular clinician or a legislature enacting policy, and therefore have an affinity with virtue ethics. The 'playing God' claim suggests that the agents in question are assuming a role or making decisions that are beyond their proper authority or 'above their station'. There are some cases where we might think the 'playing God' claim applies but 'unnaturalness' does not (or not as readily). For example, it makes sense to say that a clinician who decides against putting a patient on a life-support machine is playing God but not that he is interfering with nature. In spite of this, for the most part the contexts of application of playing God and interfering with nature are quite close. ([17])

A first step in understanding interfering with nature claims is to examine what we mean by 'nature'. The problem here is that if we understand nature as that which is not human or of human origin, then all human action would seem to be unnatural. If humanity and human action is understood to be a part of nature then everything we do counts as natural. ([18]) It is difficult, either way, to distinguish 'natural' from 'unnatural' in a way that matches our intuitions about good and bad actions. Moreover, even if we can distinguish the natural from the unnatural in a coherent way, we will still confront the problem of why what is natural is good and what is unnatural is bad. ([19])

In spite of these difficulties we might think that there remains a possibility of understanding 'nature' in a way that gives it some moral force. ([20]) Whether or not this

13. Julian Savulescu and Guy Kahane, "The Moral obligation to create children with the best chance of the best possible life", *Bioethics* 23, no. 5 (2009): 274-90.
14. See also Robert Sparrow, "Procreative beneficence, obligation, and eugenics genomics", *Society and Policy* 3, no. 3 (2007): 43-59.
15. Michael Sandel, "The case against perfection", *The Atlantic Monthly* 293, no. 3 (2004): 51-62; Leon Kass, "The wisdom of repugnance", *The New Republic* 216, no. 22 (1997): 17-26; Jurgen Habermas, *The Future of Human Nature* (Cambridge: Polity, 2003).
16. Michael Sandel, "The case against perfection", *The Atlantic Monthly* 293, no. 3 (2004): 51.
17. C.A.J. Coady, "Playing God", in *Human Enhancement*, Julian Savulescu and Nick Bostrom, eds. (Oxford: Oxford University Press, 2009).
18. Richard Norman, "Interfering with nature", *Journal of Applied Philosophy* 13, no. 1 (1996): 2.
19. Giuseppe Testa and John Harris, "Ethics and synthetic gametes," *Bioethics* 19, no. 2 (2005): 161-2.
20. Mark Sheehan, "Making sense of the immorality of unnaturalness", *Cambridge Quarterly of Healthcare Ethics* 18, no. 2 (2009): 177-88.

is so, attempts to make sense of the intuitions that give rise to claims about unnaturalness and playing God may be important in understanding and responding to public reactions to biological enhancements and related forms of biotechnology.

Germ-line and somatic gene therapy

The final question asks us to consider the moral significance of interventions that are likely to directly affect members of generations beyond the one at which they are aimed. This introduces the distinction between germ line and somatic gene therapy. Germ-line interventions affect the cells that will eventually produce viable eggs or spermatozoa, whereas somatic gene therapies do not.

Issues that may arise in this context include the lack of consent on the part of the 'future generations' and the degree of risk and level of uncertainty involved. From the perspective of consent, the central concern is that these interventions will necessarily be made without consulting those who will be affected by them. On the face of it this worry looks misguided. There are many things that may affect the lives of future generations but which do not seem problematic because those affected cannot be consulted. This worry is better thought of as arising because of the overall level of risk and uncertainty. This links with the discussion of the precautionary principle in relation to Case Study 8.3. The general concern here is that because, in the case of germ-line interventions, the alterations may be passed on from generation to generation we need to be significantly more careful about the changes we instigate.([21])

Gene therapy is controversial because it manipulates the 'building blocks' of life. As a result it very much becomes the focus of the worries about interfering with nature discussed above. The social and regulatory reaction to gene therapy technologies has been cautious, particularly after Jesse Gelsinger, an 18-year-old man with ornithine transcarbamylase deficiency, died 4 days after taking part in a gene therapy trial in 1999.([22]) Since then, countries around the world have put in place regulatory processes to approve gene therapy research. A good deal of variation exists between countries in their approaches to gene therapy, with some countries (e.g. The Netherlands) actively seeking to facilitate gene therapy research by streamlining the different national review processes.([23])

Science and society

The questions raised by this case and discussed above have important connections to the broader issues about governance and the relationship between science and society discussed in Chapter 7. Indeed, the controversies associated with these new reproductive technologies can be taken to represent a paradigm case of the tensions within the science/society relationship. These issues illustrate the power of science that underlies much of our current (medical) reliance on the achievements of research. At the same time, the direction that some of this research is taking has given rise to serious unease among a significant portion of the population outside of (and in some cases within) the scientific community.

21. The Oviedo Convention quite explicitly distinguishes somatic from germ line gene therapy *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (Oviedo, 4.IV.1997), Article 13. http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm
22. Nicholas Wade, "Patient dies during a trial of therapy using genes", *New York Times* (29 September 1999), section A page 24 of the New York edition. http://query.nytimes.com/gst/fullpage.html?res=9E06EED8173EF93AA1575AC0A96F958260. Paul Gelsinger and Adil E. Shamoo "Eight years after Jesse's death, are human research subjects any safer?", *Hastings Center Report* 38 (2008): 25-7.
23. Michael L. Edelstein, Mohammad R. Abedi, Jo Wixon, "Gene therapy clinical trials worldwide to 2007 – an update", *Journal of Gene Medicine* 9 (2007): 833-42; D.A. Bleijs, I.T.W.C. Haenen and J.E.N. Bergmans, "Gene therapy legislation in The Netherlands", *Journal of Gene Medicine* 9 (2007): 904-9.

As a result, these issues exhibit each of the four themes from Chapter 7. In order to address public unease, there may be a case for broadening the forms of public engagement and rethinking the way in which the public's concerns are examined and addressed in making decisions about the directions in which research should proceed. Because these issues are deeply contested, consideration should be given to the role of consensus in decision-making about the development of this kind of research. The tensions between the rights of prospective parents, their duties to the children they create and society's interest in protecting both its members and its values and institutions raise questions about where responsibility for procreative choices should lie. These value differences and questions of responsibility also put pressure on the systems and institutions of science governance to encompass the range of relevant interests and views.

Research involving stem cells, admixed human embryos and cloning

Human embryonic stem cells are stem cells that are derived from the developing human embryo. They are most useful in research because of their ability to change into any type of cell, tissue or organ in the human body – that is, their pluripotency. As such they can be used in the treatment of a very large number of conditions. The main ethical issues arise from their source – donated embryos, most often left over from the IVF process. ([24])

Non-embryonic stem cells are stem cells that are not derived from an embryo. Two examples of these are cord-blood stem cells and induced pluripotent stem cells. Because they are not derived from embryos there is substantially less moral controversy about the use of these stems cells in research. However, there are limits to the use of non-embryonic stem cells. First, for all but induced pluripotent stem cells, other stem cells are not as versatile as the embryonic version and so they cannot give rise to the same range of human cells; and second, they do not help with research that is aimed at understanding the developmental mechanisms involved in these processes. ([25])

Admixed human embryos are a range of 'combined' human-animal embryonic cells. The most commonly used in research are 'cybrids'. Cybrids are made by inserting the nucleus of a human cell into an animal egg from which the nucleus has been removed. They are useful in research because they are an easy way to create embryos so that the understanding and control of human embryos and development can be understood. Chimeras are usually formed by merging human and animal embryos whilst hybrids have human and animal chromosomes. The most common objection to these techniques involves claims about interfering with nature – by creating 'half-human, half-animals'. A further objection points to the lack of dignity associated with the creation of these embryos. Such an objection relies on a particular conception of the moral status of the embryo. ([26])

Therapeutic cloning is cloning that is aimed at producing stem cells, tissue or organs for the therapeutic use of the individual from whom they are cloned. The advantage of therapeutic cloning is that the stem cells or other tissue created will have matched DNA to the recipient and so there will be little risk of tissue rejection. The main ethical issue associated with therapeutic cloning is that it requires the creation and destruction of an embryo, which on some views on the moral status of embryos is wrong. ([27])

24. International Society for Stem Cell Research, *Guidelines for the Conduct of Human Embryonic Stem Cell Research* (2006). http://www.isscr.org/guidelines/index.htm. The Hinxton Group, *Consensus Statement: Science, Ethics and Policy Challenges of Pluripotent Stem Cell-Derived Gametes* (2008). http://www.hinxtongroup.org/Consensus_HG08_FINAL.pdf
25. David Cyranoski, "5 things to know before jumping on the iPS bandwagon", *Nature* 452 (2008): 406-8.
26. International Society for Science and Religion, *Cybrids and Chimeras: a statement from the International Society for Science and Religion* (2008). http://www.issr.org.uk/cybrids-chimeras.asp
27. Robert Sparrow, "Therapeutic cloning and reproductive liberty", *Journal of Medicine and Philosophy* 33 (2009): 1-17.

Reproductive cloning is cloning that is aimed at reproduction. As such, it is another form of assisted reproduction for individuals or couples who are unable to have a genetically related child either naturally or using other artificial techniques. This reproductive technique is very widely condemned, perhaps in part due to the perceived possible motivations behind its use.([28]) Our view of those who would clone themselves tends involve selfishness and egocentrism. However, given the impact of environmental factors and consequent variability of gene expression, the extent to which the cloned individual will end up being like the parent is likely to be on a par with normal parent-child similarities.([29])

Case Study 8.2
Research into cochlear implants

A consortium of researchers including developmental psychologists and cochlear implant surgeons has proposed research that will attempt to assess the developmental differences between children with new, improved cochlear implants and those without.([30]) Part of their general research interest includes claims made by the Deaf community that deaf children are better off deaf when they are a part of the Deaf community.

The proposed research involves a small scale cohort study looking at the differences in development between four groups of children:

(i) deaf children without cochlear implants and living in the Deaf community;
(ii) children with cochlear implants who are a part of the Deaf community;
(iii) children with cochlear implants who are not a part of the Deaf community; and
(iv) children who are not deaf and are not a part of the Deaf community.

Ideally they would have liked to include a fifth category – children who are congenitally deaf, without cochlear implants and not a part of the Deaf community – however due to the widespread uptake of cochlear implants in the region, the team has not been able to identify a significant number of potential participants.

The research will involve a series of detailed semi-structured interviews with the parents (beginning before the child is born) as well as simple testing and observation of the child over the course of its early years of development. At this stage they hope to gather some initial data about the range of developmental concerns, with a view to developing an instrument that can be usefully applied in a much larger international study.

Through various academic contacts, they have approached a number of couples in the Deaf community to assess their attitudes to the use of cochlear implants to enable their child to hear. They have found a number of couples within the Deaf community who are prepared to have their children undergo the implant surgery as well as a number who are not. They have also identified a number of couples with a history of congenital

28. *Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research* (Strasbourg, 25.I.2005), Article 1. http://www.coe.int/t/dg3/healthbioethic/Activities/02_Biomedical_research_en/195%20Protocole%20recherche%20biomedicale%20e.pdf
29. Michael Boylan and Kevin E. Brown, *Genetic Engineering: science and ethics on the new frontier* (Upper Saddle River, NJ: Prentice Hall, 2001).
30. We would like to thank Dominic Wilkinson for his helpful suggestions about this case.

deafness in the family who would choose to undergo the implant surgery should their child turn out to be deaf. These couples are happy to participate in the study even if their child is not deaf.

A member of your committee is disabled (though not deaf) and, at the meeting, strongly objects to this research on two grounds: (1) that the tools and measures that will be used by the researchers are biased in favour of the hearing; and (2), that the researchers are clearly pursuing a 'paternalistic', anti-disability agenda. In the former case the committee member explains that the usual developmental milestones are keyed to expressive and responsive measures related to linguistic capability. In the latter case, it is clear any future research of this kind is likely to receive a similar appraisal from this committee member, particularly if it involves any of the members of this consortium.

Questions

1. Putting aside the committee member's objections, what ethical issues arise in this piece of research?
2. How should the committee respond to the first of the individual member's objections, about the research methodology?
3. How should the committee respond to the second of the individual member's objections, about the researchers' political agenda?
4. In the light of the individual committee member's objections should this research go ahead in any form? If so what changes are required?
5. In terms of the general conduct of research ethics committee business, how should this kind of objection be handled? What can be required of individual committee members in this regard?

Discussion

This case raises issues about the nature of disability, discrimination and the use of technological developments with respect to disability. The important tension that arises from the views of the disabled committee member is between the conception of the Deaf community as a culture and the conception of deaf individuals as disabled because they are without full or normal human functioning. This in turn raises ethical issues about diversity and representation within the ethics review process.

The main connections with topics from previous chapters are the involvement of children (Chapter 3) and the issue of discrimination (Chapter 6). From the former perspective the proposed research might look rather straightforward: parental consent can be obtained, with some input, where relevant, from the child as this becomes appropriate. However, we will see that issues arising from the case study raise difficult questions about the limits of standard justifications for parental decision-making on behalf of children.

Questions 2, 3 and 4 lead the discussion towards these questions through the analysis of the disabled committee member's objections. Question 2 focuses on the more methodological aspects of the tension. The issue is whether the tools and methods used by the researchers to measure 'normal' development presuppose the second view of what it is to be deaf. It might be that in order to make this judgement more information would be needed about the criteria used by the researchers, but even with this information the committee might need to consider issues about the nature of deafness, and more generally disability, in order to assess the significance of this for the value of the research. Question 3 focuses more on the overtly political aspect of the disabled committee member's objections. To what extent, for instance, is it appropriate to think of the researchers' project as something approaching 'cultural paternalism' or 'imperialism'? These political issues tie closely to the social model of disability. In relation to both questions it may be claimed that the values underpinning the researchers' criteria for 'success' in child development are not shared by the Deaf community and so the criteria

are not ones against which members of that community should be compared.

The final question calls for consideration of how this issue should be resolved in the specific committee context, as well as having a more general relevance. Perhaps the most significant point to consider in answering this question concerns the way in which ethics committees should handle strongly held, perhaps dogmatic, minority views. Disability thus provides a challenge to the institutions of governance and ethics governance in particular. Theme 2 from Chapter 7 raises the question of consensus in a way that is directly relevant here. In the context of disability and given the views of the committee member in the case, how can the institutions and processes of society strike the right balance between the acceptance of difference and the recognition that decisions must be made.

The nature of disability

The objections to the research raised by the disabled committee member give us reason to consider the main alternative accounts of the nature of disability.([31])

One view of what might count as a disability is that it is a significant deviation from 'normal species functioning'. So we might develop an account of the characteristics that normally functioning human beings have and suppose that someone lacking in one or more has a disability in that respect.([32]) Clearly this kind of approach is problematic. When thinking about disability we do not look at all human characteristics and count as disabled anyone who falls outside the normal range for any one. Rather, we consider a narrower range of characteristics, and the characteristics that make it onto the list will depend on the kind of people we regard as normal – so if this included deaf people and excluded redheads, having red hair would be a disability and being deaf would not.

A more productive route might be to consider the ways in which some people are disadvantaged by not possessing particular 'normal' human characteristics. This is a way of identifying those characteristics in respect of which a departure from normality amounts to a disability: lacking a certain characteristic counts as having a disability when this lack causes disadvantages. (So having red hair, for the most part, does not lead to disadvantage.) There are undoubtedly significant respects in which being deaf can result in very significant disadvantages. The issue between those who hold the 'social model' and the 'medical model' of disability is best understood as concerning the nature of this disadvantage.

On the social model of disability, the disadvantages faced by deaf and other 'disabled' individuals have social or institutional causes. Moreover, these causes could be eradicated if the social situation were changed. So if everyone switched to text messaging from telephones, deaf people would not be excluded from these modes of remote communication.([33]) These claims made by proponents of the social model are nicely illustrated by the example of Martha's Vineyard, an island on which hereditary deafness was so common that the use of sign language became almost universal, with the result that deaf people were fully integrated into the community.([34])

The medical model claims that there are natural or environmental disadvantages that exist independently of any social causes, and which underpin the concept of disability and show it not to be a wholly social construction. These involve the importance of auditory cues alerting people of danger – deaf people are disadvantaged because they cannot respond to these cues. Using sound has an advantage over vision, for example, because it does not rely on the individual looking in the right direction.

31. Neil Levy, "Reconsidering cochlear implants: the lessons of Martha's Vineyard," *Bioethics* 16 (2002): 134-53.
32. Although this idea is connected to Daniels, his own view seems to be more subtle than that sketched here. Norman Daniels, "Normal functioning and the treatment enhancement distinction", *Cambridge Quarterly of Healthcare Ethics* 9, no. 3 (2000): 309-22.
33. Robert Sparrow, "Defending deaf culture: the case of cochlear implants", *The Journal of Political Philosophy* 13, no. 2 (2005): 135-52.
34. Nora Ellen Groce, *Everyone Here Spoke Sign Language: Hereditary Deafness on Martha's Vineyard* (Cambridge, Mass: Harvard University Press, 1985).

Levy suggests a position that combines elements of both. He suggests that in order for a disability to count as socially caused:

> *(i) it must be the case that social arrangements could be altered so as to remove the disadvantage and; (ii) there must be no compelling reason why social arrangements could not be so altered.* ([35])

So, according to Levy, wheelchair users count as socially disabled by the lack of ramps (we could have more ramps and there is no compelling reason why we should use stairs), but they are not socially disabled by their inability to participate in activities like hiking (here although we could all give up these activities and so remove the social disadvantage, their intrinsic value gives us reason not to do so). This second example highlights a difficulty with this approach: it is hard to be clear about what is to count as a compelling reason. Someone who thinks that the disadvantages of being in a wheelchair are socially caused is likely to dispute the idea that the intrinsic value of hiking provides a compelling reason and in general to set a much higher standard for what counts as a compelling reason not to alter social arrangements than someone who does not.

Deaf culture, parents and the state

One of the key issues raised in the context of research on children is the relative responsibility of the parents and the state with respect to the child. The claims of the Deaf community can be taken to challenge the limits of parental control in various ways.

A central point to consider here is the basis of parents' freedom to determine the course of their child's life. One obvious basis for parental freedom lies in the liberal idea that people should be free to live according to their own conception of the good life. The value of this individual freedom to determine how one's life goes extends to one's children and the family is generally seen to be the locus of individual 'experiments in living'. This connects with the idea of the family as an arena of privacy, as discussed in Chapter 4. Consequently, we think it is appropriate that parents shape their children through their choices. This extends to schooling, values, religion, diet and discipline, although increasingly there is recognition that society may limit this parental choice where there is broad consensus and evidence of harmful effects on children.

In medical contexts, the situation is slightly different. This may be a result partly of the immediacy and magnitude of the potential harms arising from medical decisions, compared with those arising from more general social decisions, and partly of the fact that health care professionals are explicitly tasked with looking after the child and have specialist expertise in the area. Although parents retain a good deal of authority to decide for their child in medical contexts, there are perhaps more defined limits. Thus, how we understand disability – as social or medical – can make a difference to how we view the extent of parental authority.

This takes us to the question of culture and the plurality of conceptions of the good. If being a member of the Deaf community constitutes being a member of a distinct culture then arguably we should view the parent's decision about cochlear implants in the same way as we view other culturally based or intra-familial value decisions and authority should rest with the parents.

On the face of it, there is a good reason for thinking that the Deaf community does constitute a distinct culture. Deaf individuals have consistently written about their experiences of Deaf culture and of the benefits of their way of life. There is some evidence of strong attachment to their condition and a sizeable proportion who would not wish to hear even if it were possible.

35. Neil Levy, "Reconsidering cochlear implants: the lessons of Martha's Vineyard", *Bioethics* 16 (2002): 139.

Levy suggests that, amongst other things, cultures should "hold values that differentiate them from the members of other cultures", these values should be "expressed in some material form" and the "members of the culture must engage in activities which are partly constitutive of that culture". The Deaf community qualifies on each of these counts: the existence and almost exclusive use of sign language ensures that the deaf community engages in activities together as well as having a means for developing and expressing its values. Finally, the existence of Deaf literature as well as sign poetry and theatre demonstrate ample modes of material expression of Deaf culture.

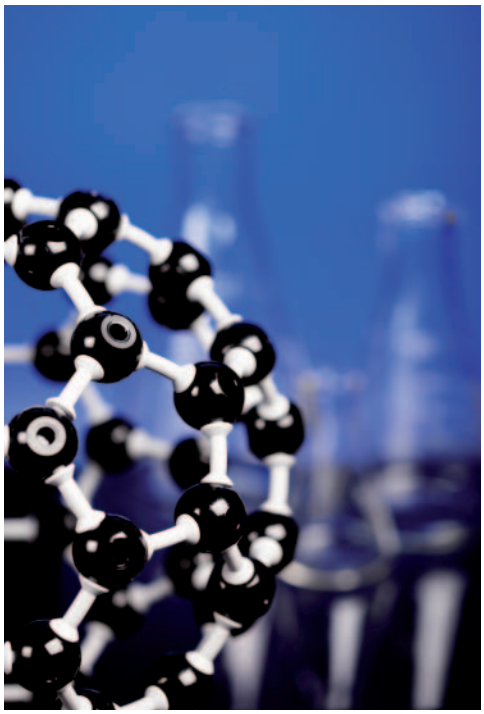
Settling the ethical issues in the case study requires balancing the liberties (and benefits) associated with allowing 'experiments in living' against the potential disadvantages associated with the condition. A consequence of recognising the Deaf community as a culture is the acknowledgement of a set of values and conceptions of the good internal to that culture, the significance of which it may be hard for outsiders to appreciate. This makes it less likely that health care professionals or other people in positions of authority or influence will be able to justify overriding parental decisions on the grounds that they know better than the parents what is in the best interests of their children.

While we might think that it is therefore up to the parents to decide whether or not their child should receive the cochlear implant, the argument for this has been based on an assumption that these parents will be part of the Deaf community and so will see the value of membership of that community for their children. However, one complication is that approximately ninety percent of deaf children are born to hearing parents. ([36]) This makes a difference because hearing parents will have little reason to risk their child being disadvantaged for the sake of a culture about which they know little. This may explain the researchers' inability to find potential research subjects in their fifth category. More generally, it is likely that allowing parental choice in this context (that is, a context in which most deaf children have hearing parents and biotechnology increasingly provides opportunities to restore those children's hearing) will result in the end of Deaf culture. The question of state interference is thus turned on its head, and the question arises of whether the state should intervene to enable Deaf culture to continue to exist, requiring particular children to forego cochlear implants against their parents' wishes in order to allow this to happen.

Another complication is that current-edition cochlear implants are not very effective in establishing full hearing. As a result there is a significant danger that children who undergo the implant procedure will both fail to learn sign language early enough to avoid developmental delays and will not be able to hear well enough to learn spoken language. There is, therefore, a risk that greater developmental harm will occur than if the child does not receive the implant. Hearing parents who choose the implant for their children may be both overestimating the effectiveness of the implant and underestimating the benefits of inclusion in Deaf culture, and may therefore not be well placed to judge the best interests of their children. This may be less applicable to the research in the case study, since this is testing an improved implant. However, given that the research is being conducted precisely to assess the effects on child development of the improved implants, it cannot be known in advance how much more effective they will be.

36. This and the further complication below are discussed by Harlan Lane and Michael Grodin, "Ethical issues in cochlear implant surgery: an exploration into disease, disability, and the best interests of the child", *Kennedy Institute of Ethics Journal* 7 (1997): 231-51.

Case Study 8.3
Research using gold nanoparticles



A team of researchers at a leading cancer research institute has recently become interested in the use of nanotechnology. The team has put together a programme of research that involves two different uses of gold nanoparticles in the treatment of cancer.

The first process used is called 'nanophotothermolysis' – using nanotechnology to generate enough heat to break down a substance to its constituent components. Directed laser energy is used to heat up the nanoparticles until they explode, in the aftermath of which localised cancer cells get destroyed without damaging healthy cells nearby. Several after-effects contribute to the destruction of cancer cells using nanoparticles. These include acoustic shock waves from the explosion, optical plasma and particle fragmentation. In the second process, the gold nanoparticles carry an anti-cancer drug and can seek out the tumour within the body. Once the nanoparticles have surrounded the target cells, infrared light is used to heat the nanoparticles so that they release the drug.

In order for the therapy to work, the nanoparticles must target only cancerous cells and avoid healthy cells. The property that identifies a cell as being cancerous is a protein known as epidermal growth factor receptor (EGFR). This protein surrounds the cancerous cell, but is not found in such abundant quantities in the healthy cells. The nanoparticles attach themselves to the antibody for the EGFR and then destroy the cancer cell without damaging healthy tissue. Both processes have been successfully used in animal models but there is some concern about the scale-related differences – that is, how the different volume of nanoparticles may influence the effects both on the individual and on the external environment.

In both cases the use of these particles promises to be a very effective way of targeting particular cancer cells but very little is known about the consequences of the accumulation of nanoparticles in the body or the environment. Because of their size, nanoparticles are able to move through normal barriers easily and possibly interact with other parts of the body. There is some concern that the remaining particles may translocate to other organs causing toxicity (for example, neuronal uptake in the brain). Another possibility is that these particles will interact together in the outside environment in ways that could be harmful, particularly if there is significant use of this technology. Some researchers at the institute (not working on this project) are uncomfortable about the current volume of nanoparticles in use. They are concerned that enough of these particles might become 'nuisance dusts' and produce serious adverse health affects to those in the vicinity. Some even worry that because so little is known about nanoparticles, they may turn out to be the asbestos of the 21st century.

Questions

1. What immediate ethical problems will the researchers face as they try to build a series of research proposals designed to test their treatments?
2. Given the level of uncertainty associated with the use of nanotechnology and the potential dangers involved, what level of precaution administered either by the REC, regulation or alternate oversight ought to be in place?
3. What level of precaution should be adopted to guard against the possible harmful consequences of the overuse of nanotechnology?

Discussion

The main focus of this case study is on issues related to risk, particularly in cases where there is significant uncertainty about the nature and magnitude of the risk. Like Case Study 8.1, this case raises questions about the risk of harm and the possibility of subjects consenting to research when very little is known about the risks they will face. More general questions about dealing with risks that are unknown or difficult to quantify lead directly to consideration of the precautionary principle. It is also worth pausing to consider various methodological and research design questions that arise about the best way to proceed in gathering knowledge about the potential of these technologies.

Nanotechnology and ethics

Nanosciences and nanotechnologies research is defined by the European Commission as encompassing "all research activities dealing with matter at the nanometric scale (1 to 100 nm)".([37]) At this scale ordinary materials can behave in very unusual ways and exhibit properties that can be harnessed for particular purposes. The case study provides us with one example of the use of this kind of technology.

There is some dispute about whether nanotechnologies raise any new ethical issues, and so whether 'nanoethics' is a distinct discipline. Søren Holm suggests that a new technology might require "its own ethics" when it "either raises ethical issues that are not raised by other kinds of technologies, or … raises ethical issues of a different (i.e., larger) magnitude than other technologies".([38]) Thinking along these lines we might say that some of the potential uses of nanotechnology, for example to produce super-small surveillance devices, raise familiar privacy concerns, and that the use of super-strong carbon nanotubes that will not decay may cause environmental waste problems in much the same way as Styrofoam or nuclear waste.([39]) It is unclear, however, whether we should think of these and other problems associated with nanotechnology as sufficiently different in magnitude from those raised by other technologies to require a distinct nanoethics.

Either way, nanotechnological developments provide a very good vehicle for consideration of the ethical issues raised by new biotechnologies. The kinds of ethical issue that arise in relation to nanotechnology research include environmental health and safety impacts, privacy, human enhancement, and dual use, as well as justice and equality issues.([40]) We will focus on the first of these issues in relation to the precautionary principle, but the others relate to issues that have been considered elsewhere in this textbook.

37. European Commission, *Recommendation on a Code of Conduct for Responsible Nanosciences and Nanotechnologies Research* (2008): 5-6. http://ec.europa.eu/nanotechnology/pdf/nanocode-rec_pe0894c_en.pdf
38. Søren Holm, "Does nanotechnology require a new 'nanoethics'?" (Cardiff Centre for Ethics, Law & Society, August 2005). http://www.ccels.cardiff.ac.uk/archives/issues/2005/holm2.pdf
39. Fritz Allhoff and Patrick Lin, "What's so special about nanotechnology and nanoethics?", *International Journal of Applied Philosophy* 20, no. 2 (2006): 179-90.
40. See also: The European Group on Ethics in Science and New Technologies to the European Commission, *Opinion on the Ethical Aspects of Nanomedicine: Opinion No 21* (Brussels: European Commission, 2007). http://ec.europa.eu/european_group_ethics/publications/docs/final_publication_%20op21_en.pdf

Nanosciences and nanotechnologies research raises important questions about the relationship between science and society. Again some of these questions are closely linked to the precautionary principle and decision-making under conditions of uncertainty. Recent research on public views about nanotechnology used a convergence seminar technique to "gather advice and recommendations from the public that may be useful for future decisions on nanobiotechnology". ([41]) In terms of ethical issues, they found that participants were concerned about the focusing of research priorities (largely on medicine and the problems of developing countries), access to and distribution of the benefits of the research, managing the involvement of commercial interests, and privacy and freedom of choice (in choosing to engage with the technology or not). This research and its piloted methodology may be a step in the right direction in terms of public involvement and engagement in the difficult policy decisions associated with nanotechnology research and other new biotechnological developments. ([42])

The precautionary principle

The introduction to the precautionary principle in Chapter 5 highlighted its origins in environmental protection, its incorporation into European law and the range of areas to which it is now applied. The inclusion of the principle in European (and international) law may be taken as evidence of an emerging consensus reflecting underlying social values that can be applied more generally in situations of risk and uncertainty. However, it should be noted that the precautionary principle remains controversial and in part this results from disagreements about how it should be interpreted and applied.

The broad thrust of the principle is the assertion that where an activity introduces a risk of serious harm, appropriate steps should be taken to prevent or limit that harm even though the scientific data does not permit a precise assessment of the level of risk. As Allhoff puts it, the motivation for the precautionary principle is:

> *to recognize the potential for dramatic and irreversible damage in complex systems and to appreciate the limited epistemic situations in which we are likely to find ourselves in regards to those systems.* ([43])

Among the more prominent internationally recognised formulations of the precautionary principle are the following.

1. Principle 15 of the 1992 *Rio Declaration on Environment and Development:*

   > *In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.* ([44])

2. The Wingspread Statement of 1998:

   > *Where an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically.* ([45])

41. Marion Godman and Sven Ove Hansson, "European public advice on nanobiotechnology – four convergence seminars", *Nanoethics* 3 (2009): 43-59.
42. For a different view of the value of engaging the public on future-oriented aspects of biotechnologies such as nanotechnology see Alfred Nordmann, "If and then: a critique of speculative nanoethics", *Nanoethics* 1, no. 1 (2007): 31-46. Nordmann opposes "ethical discourse that constructs and validates an incredible future which it only then proceeds to endorse or critique" on the grounds that it "squanders the scarce and valuable resource of ethical concern, and misleads by casting remote possibilities or philosophical thought experiments as foresight about likely technical developments" (p. 31).
43. Fritz Allhoff, "Risk, precaution, and emerging technologies", *Studies in Ethics, Law, and Technology* 3, no. 2 (2009), Article 2: 13-14.
44. United Nations, *Rio Declaration on Environment and Development* (1992), Principle 15. http://www.un.org/documents/ga/conf151/aconf15126-1annex1.htm
45. Wingspread Statement on the Precautionary Principle (1998). www.gdrc.org/u-gov/precaution-3.html

3. The European Commission's *Communication on the Precautionary Principle* (2000):

> *The precautionary principle applies where scientific evidence is insufficient, inconclusive or uncertain and preliminary scientific evaluation indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen by the EU.* ([46])

Hughes suggests that what many formulations of the precautionary principle have in common is several structural components. First, there is a set of trigger conditions which determine the kind of circumstances under which the principle is operational. These conditions include a specified level of evidence (E) that is required that a particular harm will be caused and a measure of the severity of that harm (S). The second component spells out the type of action to be taken (A). These are combined as follows:

> *If there is evidence stronger than E that an activity will cause harm more serious than S, then take action of type A.* ([47])

How strong or weak, conservative or liberal, a particular formulation of the principle is will depend on the values of each of the three variables – low evidence requirements and/or less serious harm correspond to an easier set of trigger conditions which make the principle conservative along one axis. Harsh regulatory action in response to the trigger conditions would make the principle more conservative along a second axis.

The strength of the formulation matters because, as critics point out, excessively strong versions will stifle innovation. For some formulations this may give rise to what has been called the "paradox of precaution" – the idea that by restricting the development or application of new technologies the principle actually causes more harm that it avoids. ([48]) Another problem with very strong interpretations of the precautionary principle is that they might prevent us from doing the research that is necessary for a properly informed view of the benefits and risks of the technology in question. On the other hand weaker forms may look trivial, since if the evidential threshold is set too high, the practical upshot of the principle may be indistinguishable from standard assessment tools such as cost-benefit analysis, and it will fail in its intended function of providing a basis for action in cases where our knowledge of the likelihood of harm is too slight to allow a proper application of such tools. The difficulty is to specify the precautionary principle in a way that avoids both extremes.

This may be impossible to do in a precise but generic way, and we might have to see the principle as providing general framework for decisions that have to be made on a case-by-case basis. However, in order to avoid arbitrary or discriminatory decisions it is important that the principle is applied in a consistent way, and in order to minimise the negative effects of the principle, described above, it is important that the trigger conditions are based on genuine evidence of the potential for significant harm (rather than mere speculation) and that the precautionary action taken is proportionate to the potential harm that it is intended to avert. It is important to note that precautionary action need not mean prohibiting a technology but can involve more limited restrictions or safeguards which may reduce the risks while enabling research to continue. This is implied, for example, in the *Rio Declaration*'s reference to "cost effective" measures, while the European Commission's *Statement on the Precautionary Principle* states that "In some cases a total

46. A European perspective on the Precautionary Principle is to be found in: Commission of the European Communities, *Communication from the Commission on the Precautionary Principle,* COM(2000)1 final. http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexplus!prod!DocNumber&lg=en&type_doc=COMfinal&an_doc=2000&nu_doc=1
47. Jonathan Hughes, "How not to criticize the precautionary principle", *Journal of Medicine and Philosophy* 31 (2006): 452.
48. For example, see John Harris and Søren Holm, "Extending human lifespan and the precautionary paradox", *Journal of Medicine and Philosophy* 27, no. 3 (2002): 355-68.

ban may not be a proportional response to a potential risk", and that "Risk reduction measures should include less restrictive alternatives … such as appropriate treatment, reduction of exposure, tightening of controls, adoption of provisional limits, recommendations for populations at risk, etc."

It is also important to be clear about the role of the precautionary principle in the overall process of assessing and managing risk. The principle does not call on scientists to adjust their normal standards of evidence when reaching conclusions about the risks produced by a new technology. It might call for the commissioning of additional research in order to provide a better evidence base for future decisions, but essentially the precautionary principle is concerned with the actions that should be taken on the basis of whatever evidence is available, that is, with risk management.([49]) As such, it is a moral and political principle whose interpretation and application will depend on value judgements about our willingness as a society to accept certain costs (e.g., but not exclusively, economic) in order to avoid certain types of risk. This suggests that the principle should not be seen as fixed but may evolve as social values change, and that some engagement with the public may be appropriate in considering how to apply it in particular cases.

Case Study 8.4
Genetic information and biobanks

Kurt is a teacher in a city in north-eastern Europe. He has been asked to join a large research project that is looking at the genetics of cardiovascular disease. This will involve giving a DNA sample, answering a questionnaire and allowing details of his treatment to be given to the researchers. This study will directly help clinicians decide which drug to give to those patients who are enrolled in the study. Researchers at the local hospital where Kurt is being treated, in collaboration with a team of researchers from a southern European university and a medical sciences institute in China, are conducting the study.

Kurt has been asked to give a broad consent that will allow the researchers to keep the DNA sample and information for use in suitably approved future research projects. This will save them the expense of coming back for consent for each new research project. He can choose whether researchers are allowed to come back to him to ask further questions. The DNA will be processed in China and then sent to southern Europe for analysis. All of the direct identifiers (such as his name and address) will be removed before the samples are sent to

49. See the *Communication from the Commission on the Precautionary Principle*, Summary, section 4: "The precautionary principle should be considered within a structured approach to the analysis of risk which comprises three elements: risk assessment, risk management, risk communication. The precautionary principle is particularly relevant to the management of risk."

China. The samples will, however, be given a code which will remain in a secure location at Kurt's hospital.

The samples and information collected from Kurt will then be put in a biobank that can be accessed by many other researchers for many years into the future. It is anticipated that when the technology is cheaper, whole genome scans will be carried out on some of the samples and these will be put on the web for other researchers to use.

Questions

1. Is it acceptable to obtain consent to the use of the samples and information for many different research projects into the future (broad consent)?
2. Does the coding of samples and information mean that it is not necessary to ask for Kurt's consent for future research projects?
3. Is it necessary to tell Kurt that the DNA samples will be processed in China and will leave the European Union?
4. The researchers discover that people with Kurt's genetic predisposition are more likely to die if they are treated with a drug that is commonly used for heart conditions in that part of north-eastern Europe. Should they tell Kurt?
5. Do the researchers need to go back to Kurt to get permission for his whole genome scan to be put on the web?

Discussion

This case study raises general issues about consent and its role in the developing context of global research and global access to data. It also points to questions that are more specific to genetics and our relationship to and control of genetic information. In turn, these lead to further consideration of questions, raised initially in Chapter 7, about the form and context of research governance and the relationship between science and society. The issues raised by this case study draw upon the discussions of earlier chapters, in particular Chapters 2, 3 and 4.

The increasingly international and collaborative nature of medical research and, in particular, of population and epidemiological research, means greater access to data by a range of researchers doing varying kinds of research will be needed to continue the development of these areas of research. This, when combined with the advances in the processing and analysis of large-scale genetic information, will have profound effects on the way in which research is conducted as well as the progress that can be made in understanding medical illness and treatment. The benefits of large-scale international collections of tissue and data are likely to be significant. Being able to facilitate such research arguably requires a significant shift in the way in which we think of patient and public involvement in research.

Biobanks are repositories for various kinds of collections of human biological material. They can contain a broad range of such material, including DNA, tissue, tumour samples and blood. They are also likely to include linked clinical and/or phenotypic data on the donors of the samples so that the potential for useful, patient-related research is maximised. Though their specific purposes can vary widely, the general purpose of biobanks is to house and facilitate ongoing research on samples that have already been collected. Important policy issues for biobanks include how much access non-depositors have to the collections, the relationship that the biobank has (or might have) to industry and commercial interests, and the nature of any connections with other national or international biobanks.

Broad consent

On the usual model of consent (discussed in Chapter 2), consent is very specifically related to a particular piece of research. It typically involves being given detailed information about the nature of the research and of the participant's involvement in it, who will be conducting it and what the anticipated outputs are. Applying this model to biobanks would require a fresh consent to be sought from donors every time their samples were used by a different group of researchers or for a different purpose. Given the number of donors who might

be involved, this would be costly and impractical and so would seriously limit the usefulness of the biobanks as a resource for researchers. The broad consent model used in biobanking attempts to facilitate as much research as possible, consistent with the principles governing the establishment of the biobank. Each of the questions accompanying the case raises a different kind of consideration about broad consent, its limits and closely related ethical concerns.

Broad consent, like the more specific forms of consent used in other areas of research, involves the participant authorising or giving the researcher permission to do something, based on information and deliberation. However, because the samples contained in a biobank are designed to support multiple research projects, some of them conducted long after the samples have been collected, the nature of the information provided is of a different sort. Broad consent is usually distinguished from 'open' or 'blanket' consent. ([50]) The latter is understood as consent to the unrestricted use of a sample, while broad consent is consent to a wide, but specified range of uses. Thus, broad consent involves the research participant agreeing for their sample or data to be used in a variety of different research projects, sometimes by different researchers and sometimes in very different contexts. This means that unlike open consent, broad consent is based on information about the kinds of research that will be conducted, based on the policies in place for the biobank.

This model of consent is typically justified by reference to the potential benefits brought by the research it will facilitate, the low level of risk involved (provided adequate measures are in place to protect privacy and confidentiality), and by respect for autonomy. On the one hand it might be argued that respect for autonomy requires that competent people should be allowed to consent to whatever arrangements they please, provided they do not harm others, and that this includes broad, or even open consent to the use of samples. On the other hand it might be suggested that the lack of specific information about particular uses of the samples means that such consent cannot be fully autonomous. Broad consent might have an advantage over open consent here, in that the range of uses is limited, so informed decisions will not rely so much on the donor's ability to imagine the range of possible future uses. However, it might still be thought that broad consent lacks the moral authority of more specific consents based on fuller information. If so, then just as when dealing with non-competent subjects in more conventional research situations, more responsibility may fall on the researchers to protect the subjects from harm.

A number of ethical objections have been raised against the reliance of biobanks on broad consent. ([51]) First, in regular consent to research there is the important possibility of withdrawing from the research, but in broad consent for biobanks this can be difficult. The samples and data may have been used in various different research projects and be scattered in various labs and research reports. In response, it should be noted that in the usual case of consent to participate in a particular research project, withdrawal cannot undo the research that has already been done. It is not always possible retrospectively to remove a participant or to undo an experimental procedure. The same is true for biobanks; however, samples and data can, as long as they are adequately tracked, be withdrawn from inclusion in future research if the donor so wishes.

Second, there may be concerns about the protection of privacy and confidentiality. One worry here concerns straightforward breaches of security. It is important on grounds of privacy and welfare that adequate security measures are in place, and important to the validity of the broad consent given by donors that the security measures described at the time of consenting are maintained.

50. Mats G Hansson *et al.*, "Should donors be allowed to give broad consent to future biobank research?", *Lancet Oncology* 7 (2006): 266-9.
51. Björn Hofmann, "Broadening consent – and diluting ethics?", *Journal of Medical Ethics* 35 (2009): 125-9.

Further concerns arise from the reliance on anonymisation as a means of protecting privacy and confidentiality and preventing harm. Question 2 suggests that the anonymisation of the samples and data might contribute to the justification of broad consent. The thought here is that by severing the connection between the sample or data and the individual donor, the risk of harm is reduced so that it is no longer necessary for the donor to protect his or her own interests by controlling the particular uses to which the sample or data is put. However, as noted in Chapter 4, there may be situations in which even anonymous data can be linked back to the individual in such a way as to breach privacy or confidentiality. A possible example of this in the case study is the publication of Kurt's complete genome scan, which could enable people with knowledge of Kurt or his family to identify its source. It is also possible that such identification will become easier in the future as more genetic information about individuals is available to more people. For these reasons it might be thought that this step requires a specific consent at the time of publication rather than relying on broad consent given at an earlier date.

Finally, as indicated by Question 4, there are issues relating to feedback of, in particular, incidental findings. Some kinds of research, and particularly genetic research, can inadvertently reveal clinical predispositions or other information with important implications for the donor. There should, therefore, be some policy conveyed on the consent form about how such findings will be handled. If the samples were fully anonymised (i.e. with no coding to enable them to be linked to their source) this would block the possibility of providing feedback to the donor and hence avoid the moral dilemma at the level of the individual finding. However, clinically oriented researchers often feel uncomfortable with not being able to feed back important information, particularly where it concerns a serious but treatable condition. This might provide a reason (in addition to others mentioned in Chapter 4) not to fully anonymise the samples but to code them as described in the case study. It then becomes important to include in the broad consent an account of the circumstances in which the code will be used to allow feedback of findings. As mentioned in Chapter 4, a common kind of incidental finding mentioned in the context of genetics is non-paternity, and although there are varying accounts of how common such findings are, it does highlight the deep practical dilemmas that this kind of research can involve.

Research governance

Perhaps the best way to understand broad consent, at least as it applies in cases like this one, is as consent to a particular kind of governance arrangement. ([52]) That is, when an individual gives 'broad consent' to the use of their sample or data in future research they are giving permission for someone else, usually in the form of the governing body of the biobank, to decide how to use that sample or data. Given this, the question of governance becomes important again, as does the disclosure of the governance arrangements to the participant.

There is a range of policies and arrangements that can be clearly articulated independently of the specific kind of research that will be conducted. These can form both the organisational principles of the biobank and the terms of the consent. Such terms should include:

- Governance arrangements and structures. ([53]) The consent should be clear about the role, remit and make-up of the biobank's managing and governing bodies. Ideally the governing body should be independent of those with a research stake in the biobank, its operations and decisions should be transparent and accountable to all stakeholders and it should include significant patient and public representation and involvement. ([54])

52. Matti Häyry, Ruth Chadwick, Vilhjálmur Árnason and Gardar Árnason, *The Ethics and Governance of Human Genetic Databases: European Perspectives* (Cambridge: Cambridge University Press, 2007).
53. Council of Europe, *Recommendation Rec(2006)4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin,* Chapter 5. http://www.coe.int/t/dg3/healthbioethic/Activities/02_Biomedical_research_en/Rec%20biomat%20CM.pdf
54. Mairi Levitt, "UK Biobank: a model for public engagement?", *Genomics, Society and Policy* 1, no. 3 (2005): 78-81.

- Arrangements for the secure safe-keeping and storage of samples and data. Potential donors should be informed of the processes in place to ensure the protection of confidential data and samples.

- General policies on commercial involvement, commercial access and intellectual property rights. It should be clear how the biobank plans to manage relations with external bodies including other national and international biobanks and research consortiums, and commercial interests. Clearly the involvement of, for example, pharmaceutical companies, may be of great use to particular biobanks and enhance the prospects of translating research findings into medical practice, but as we saw in Chapter 7, the profit motive brings particular dangers. ([55])

- Overall principles governing the standards, aims and usefulness of research done using the samples/data from the biobanks. Although there may be limits to what can be said about the precise nature of the future research that will take place using the biobank's resources, a good deal could be laid down about the broad principles that will inform the decisions of the governing body of the biobank about which projects to admit and which to reject.

- Feedback mechanisms and donor involvement. Details should be provided about how donors and the public generally can be involved in the processes of the biobank. In addition, it is important to have procedures through which these groups can be kept informed of the research being undertaken and the progress being made.

- Policies for handling incidental findings. As mentioned above, it is important for there to be a clear policy about how patient feedback and incidental findings will be handled. The range of possibilities include: allowing the donor to choose from a list of alternatives (stating what they do and do not want to know about), stipulating that feedback will take place through the donor's general practitioner, or stipulating that there will be no feedback.

This case also raises issues about the global governance of research. The involvement of international partners with research spanning national boundaries means that some consideration is needed about the form of oversight in these contexts. One possibility is to establish an international committee to examine such research; another is to require that specific standards and processes are put in place in each of the participating countries.

The issues associated with the governance of biobanks and the increasingly global nature of research resonates with some of the themes from Chapter 7. The global context of research invites questions about how best to ensure that the global community has the appropriate voice in the progress and dissemination of the products of science and technological research. And again, it raises questions about governance and control of science by society. In particular, how do the governance arrangements in place for biobanks take into account the interests, concerns and values of the public and society as well as the researchers and donors?

Genetic exceptionalism

Question 5 of the case study considers the acceptability of broad consent in the context of broadening access to an individual's genetic information. However, it is also important to notice the possible involvement of others in this sort of disclosure. Genetic information is (as noted in the discussion of Case Study 4.2, Genetic research into susceptibility to respiratory disease in smoky environments) shared between (extended) family members and so information about one person is also information about a number of others. This leads to numerous confidentiality and privacy issues. To what extent does this mean that genetic information and genetic research should be treated differently from

55. H. Gottweis and K. Zatloukal, "Biobank governance: trends and perspectives", *Pathobiology* 74 (2007): 206-11.

other patient or participant medical information? Are these differences enough to mean that different rules apply in the case of genetics? ([56])

There are two plausible ways in which we might understand genetic information to be relevantly different from other information. First, we might think that genetic information is more intimate, personal or private than other medical information. Part of the reason for this extra significance comes from the idea that this information, in some sense, defines 'who we are'. So, according to this argument, it is partly because genetic information gets at something basic, essential or unchangeable about us that it is worthy of special protection. The main response to this common version of genetic exceptionalism is to examine actual kinds of medical information in comparison with genetic information to see whether it is on the whole more personal, intimate or private.

A second version of genetic exceptionalism might point to the shared nature of information referred to above and argue that, precisely because genetic information is not only information about one individual, it is distinctive and should be treated as such. On this view genetic information is better understood as being jointly owned information requiring different standards of confidentiality and disclosure. ([57]) Putting Kurt's genome on display will also involve disclosing (perhaps sensitive) information about his relatives. Whether it is appropriate for only Kurt to give his consent, whether family members also need to be involved, or whether the complexity of these issues effectively rules out the public display of his genome will in large part depend on the extent to which genetic information is special and the weight that we give to his family's stake in that information.

Conclusion

Chapters 7 and 8 have been noticeably different from the previous chapters. They have set out to achieve two broad aims. First, the chapters set out to introduce a range of different ethical issues that arise in the developing areas of biotechnological research. These ethical issues sit alongside the direct, research ethics issues as unfolding issues in the progress of research in the 21st century. Second, the cases and discussions have included elements of the complex and difficult contemporary relationship between science and society. We saw at the outset of Chapter 7, from a theoretical perspective, how ethics is (unsurprisingly) embroiled in questions about the governance of science and its interactions with society generally. We outlined and then began to explore four general themes within this relationship through the case studies.

These aims, delivered across these last two chapters, bring together various elements of each of the other chapters and enable the reader to utilise what has been covered in the context of the developing issues surrounding new biotechnologies.

56. For guidance on genetic research more generally, see *Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research* (Strasbourg, 25.I.2005), Articles 11 and 12. http://www.coe.int/t/dg3/healthbioethic/Activities/02_Biomedical_research_en/195%20Protocole%20recherche%20biomedicale%20e.pdf
57. Michael Parker and Anneke M. Lucassen, "Genetic information: a joint account?", *British Medical Journal* 329 (2004): 165; S. Matthew Liao, "Is there a duty to share genetic information?", *Journal of Medical Ethics* 35 (2009): 306-9.

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Glossary

Absolutism. An ethical approach that treats ethical norms as unbreakable rules.

Advance directive or advance statement. A statement made by a person while competent about how they wish to be treated in the future if they become incompetent.

Anonymisation. The modification of information to remove reference to the individuals from whom the information was gathered. Sometimes, the anonymisation process can involve a 'key' so that the link between information and individuals can be restored under certain circumstances.

Autonomy. The capacity of a person to govern him or herself, on the basis of reasoned decisions and free from controlling influences by others. Autonomy is widely held to involve the capacity for reason and understanding, a degree of self-control, and freedom from coercion and manipulation.

Beneficence. The obligation to bring about benefits or to prevent or remove harms to others.

Biobank. An institution that holds a collection of biological samples with or without related clinical, pathological or epidemiological data. The bank processes, stores, and/or distributes samples for future clinical or research use. In the case of human tissue the bank may hold body parts, organs, tissues, skin, bone and stem cells. Biobanks may also implement conditions of use and impose safeguards to protect the identity of donors.

Biochemical. Relating to chemical compounds and processes occurring within living organisms.

Biotechnology. This has been defined as "The application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services." ([1]) Examples of biotechnologies include: gene therapy, nanotechnologies, assisted reproduction technologies as well as fermentation using yeast and the production of penicillin from certain fungi.

Blind. (1) A randomised controlled trial is blind if the participants do not know which treatment or control arm they are assigned to. It is double blind if neither the participants nor the researcher know which arm the participants are assigned to. (2) In psychological research, questions that will not be analysed but are included in a questionnaire to conceal the true nature of the research from the participants.

Categorical imperative. An action-guiding principle that applies to all agents irrespective of their goals or motivations. In Kant's ethics the categorical imperative is the basis for morality and has various formulations including the principle of ends. (Compare hypothetical imperative.)

Cochlear implant. An electronic microphone and receiver device, part of which is surgically implanted into the skull of a deaf patient (often a child) in order that they can hear.

Coercion. To coerce is to threaten. We coerce someone into doing something when we threaten to make them worse off if they don't do it. Although coercion is (arguably) not always wrong, the absence of coercion is standardly thought to be a part of valid consent. Consent may not be sufficiently voluntary (and hence invalid) if it results from coercion. (See voluntariness.)

Communitarianism. An ethical approach that emphasises people's embeddedness within a community and focuses on the good of the community as a key consideration for ethical decision-making.

1. Organisation for Econonic Co-Operation and Development, "Statistical definition of biotechnology" (2005). http://www.oecd.org/document/42/0,3343,en_2649_34537_1933994_1_1_1_1,00.html. See also http://ec.europa.eu/enterprise/sectors/biotechnology/what-is-biotechnology/definition/index_en.htm

Competence. The ability to validly consent to a decision. Competence is usually taken to involve the ability to understand relevant information, to evaluate that information and make a reasoned decision, and to communicate consent or refusal.

Confidentiality. A concept closely related to that of privacy, confidentiality is that part of privacy that governs the requirement not to reveal information about another person without their permission.

Confounding factor. A variable, other than those being investigated in a study, that can affect its outcomes and result in mistaken or misleading conclusions. A confounding factor may mask an actual association between the variables being investigated or produce the appearance of an association where none exists.

Consent. Some actions are only morally acceptable if the person concerned (e.g., patient, research subject, sexual partner) provides valid consent. To consent is to authorise or give permission. *Valid* consent (as opposed to mere consent) can occur only when three main conditions are met: (1) the consenter must be competent give consent; (2) the consenter must be provided with adequate information in a suitable form and with sufficient opportunities for deliberation and understanding to occur; (3) the consent must be *voluntary*. (See competence, voluntariness.)

Consequentialism. An ethical theory that evaluates actions according to their consequences. A common form of consequentialism is utilitarianism.

Contractual right. A right that is derived from an agreement. (Compare natural right.)

Crossover trial (or crossover study). A research trial in which each group of participants receives each of the treatments being tested (which may include a placebo treatment) in a random order.

Defeasibilism. An ethical approach that treats ethical norms as being able to be over-ruled by other norms.

Deontology. An ethical theory that judges actions according to rules, principles or duties requiring or proscribing certain types of action.

Discourse ethics. An ethical theory that claims that moral norms can only be derived via discourse of the parties affected by the decision.

Distributive justice. The part of justice concerned with the fair distribution of benefits and burdens. Distributive justice is contrasted with rectificatory and restorative justice, which are concerned with compensating or making amends for previous injustices, and procedural justice, which is concerned with the use of fair procedures for decision-making.

Dual use. A dual-use dilemma arises in cases where a piece of research has the potential to be used for both good and bad ends.

Duty-based ethics. See deontology.

Enhancement. See human enhancement.

Eudaimonia. An ancient Greek term, widely used in virtue ethics to refer to the state of wellbeing or human flourishing achieved by a virtuous person. The term is sometimes translated as 'happiness', but should be distinguished from pleasure and other subjective accounts of wellbeing.

Ethical review. The review of a piece of research by a research ethics committee.

Ethics of care. An ethical theory that focuses on the ethical importance of relationships and emotions such as sympathy and solidarity. The ethics of care tends to see moral decisions as highly contextual rather than being based on general rules or principles.

Expected utility. The amount of utility predicted to be produced by an action or policy, based on the utility and probability of each possible outcome.

Extrinsic value. Value that something has only because it leads to other things that are of value. (Compare intrinsic value.)

First-in-human trials (or Phase 0 trials). Preliminary testing of drugs on human subjects in advance of Phase 1 trials. First-in-human trials typically involve low doses and small numbers of subjects.

Flourishing. See eudaimonia.

Focus group. A group of research subjects, brought together to discuss a particular issue. They are often used in qualitative research as a means of gaining information about the views, attitudes and behaviour of particular groups towards a topic.

Four principles approach. An influential form of principlism, based on the principles of respect for autonomy, beneficence, non-maleficence and justice.

Gene therapy. A method of treating illness and disease by inserting genes into a patient's cells in such a way as to change the functioning of the cell. *Germ line* gene therapy achieves this end by targeting cells that are involved in inheritance (such as cells involved in making gametes) thus enabling the changes to be passed on to future generations. *Somatic* gene therapy targets cells that are not involved in inheritance and thus affects only the individual who is treated.

Genetic exceptionalism. The view that genetic information has unique features that require it to be treated differently from other information.

Genetic polymorphism. The existence of two or more clearly different phenotypes within the same population.

Genotype. In the context of genetics, the underlying genetic makeup of an organism. (Compare phenotype.)

Germ line gene therapy. See gene therapy.

Harm. To be harmed is to have one's interests set back or to be made worse off than one would otherwise have been. Harms can relate to any aspect of an individual's welfare, for example physical, psychological or social. Institutions can also be harmed insofar as they can be thought of as having interests distinct from those of their members.

Human enhancement. Any attempt to alter the properties, dispositions, characteristics or abilities of human beings in a way that is thought to be an improvement on their normal or typical state. The term is often contrasted with 'treatment' or 'therapy', which is taken to correct or remedy some deficiency in the target individual or group. The central distinction here is the comparison between 'restoring to the norm' in the case of therapy and 'improving on the norm' in the case of human enhancement.

Human tissue banking. Storage of human tissues for future clinical or research use. See biobank.

Hypothetical imperative. An action-guiding principle that is conditional on a motive or desire. A hypothetical imperative indicates the action required to achieve a particular goal. (Compare categorical imperative.)

Inducement. An inducement is a payment or reward that encourages a particular sort of behaviour; it need not be monetary. Not all inducements are wrong, although *undue inducements* (especially where these are very large and/or in exchange for doing something very dangerous or unpleasant) may render a consent invalid. (See also voluntariness.)

Intrinsic value. Value that something has for its own sake. (Compare extrinsic value.)

Investigator bias. A distorting effect in a study resulting from the presence, actions, expectations or beliefs of the researcher.

Justice. The part of ethics concerned with fairness, especially in the distribution of benefits and burdens. The obligation to treat people fairly.

Liberalism. An ethical and political theory that claims that we ought generally to avoid interference in people's lives unless they are causing harm to others.

Manipulation. You manipulate someone when you (attempt to) get them to do what you want by taking advantage of some aspect of their character or psychological makeup through means other than rational argument. Manipulation often involves deception but need not do so. Although manipulation is (arguably) not always wrong, its absence is standardly thought to be a part of valid consent. Consent may not be sufficiently voluntary (and hence invalid) if it results from manipulation. (See voluntariness.)

Meta-analysis. A statistical technique for combining and analysing the results of a number of different studies on the same topic to enable identification of trends and patterns and more accurate estimation of significant effects.

Methodological rigour. A piece of research is methodologically rigorous if it is well constructed scientifically and able to answer the research question that is posed.

Minimal risk. Minimal risk is often defined either as a risk no greater than that encountered in everyday life or a risk no greater than that encountered in routine medical examination. The concept is typically used to identify a level of risk that may be permissible in research where there is neither a valid consent nor a benefit to the participants.

Moral difference. The existence within a society or between societies of a variety of competing moral views.

Moral objectivism. Moral objectivism is the view that some sense can be made of the idea that there are genuinely true moral judgements. Most forms of moral objectivism present more or less developed views about what the truth of moral judgements could be and how we could come to know them. (Compare moral relativism.)

Moral relativism. Moral relativism is the view that there are no genuinely right or correct answers to moral questions because, for instance, morality is a matter for individuals, culture or society. Moral relativism involves a claim about the nature of morality and moral truth. It claims that morality is best understood in such a way as to make moral judgements not the kinds of things that can be true or false. (Compare moral objectivism.)

Moral status. An entity is said to have moral status when its interests are morally significant in themselves and not just because they further the interests of some other entity. On some views the term 'moral status' (or 'full moral status') is reserved for entities whose interests warrant a very high level of protection comparable to that accorded to persons.

Nanoscience. Research which investigates, manipulates and constructs objects or processes that take place at the nano-scale (1 to 100 nanometres).

Natural right. A right which does not depend on laws, customs or agreements but is possessed by all humans in virtue of their human nature. (Compare contractual right.)

Negative right. A right that establishes obligations on others only to refrain from certain actions. (Compare positive right.)

Non-maleficence. The obligation not to inflict harm on others.

Non-therapeutic research. Research that does not involve testing a treatment on patients who have the condition that is the intended target of the treatment. (Compare therapeutic research.)

Objectivism. See moral objectivism.

Observational research. A method of research which involves no interaction between researcher and research subject, other than the observation of the subject. Observational research can be carried out overtly, with the knowledge and consent of the subject, or covertly, without their knowledge or consent.

Off-label use. The use of a drug for a purpose (i.e. to treat a condition) outside that for which it has been approved.

Participant information sheet. An information leaflet provided to research participants prior to their agreeing to be involved in the research.

Participant. A person on whom research is carried out; a person that researchers study. Also referred to as a subject.

Paternalism. Interference in a person's life, for example by restricting their freedom or interfering with their choices, for that person's own good.

Pharmacogenetics. The study of the way in which genes and genetic variation affect the ways in which patients respond to drugs.

Phase 0 trials. See first-in-human trials.

Phase 1 trials. The testing of drugs on human subjects, usually healthy volunteers, in order to gain information about the drugs' toxicity and pharmacological properties. Phase 1 trials may also be used to determine appropriate therapeutic dose levels.

Phase 2 trials. Drug trials designed to demonstrate a drug's safety and activity in a group of patients who have the condition that the drug is intended to treat. Phase 2 trials may be designed as randomised controlled trials but involve fewer subjects than Phase 3 trials.

Phase 3 trials. Phase 3 drug trials are randomised controlled trials conducted on large groups of patients, usually in multiple locations, and aimed at being the definitive assessment of the drug's effectiveness. Because of their size and duration, Phase 3 trials are the most expensive, time-consuming and difficult trials to design and run.

Phenotype. In the context of genetics, the observable characteristics (such as behaviour, appearance or physiological properties) of an organism. (Compare genotype.)

Placebo effect. A beneficial effect in a patient that is caused by the patient's expectation that the treatment will help rather than by the treatment itself.

Pluralism. The existence of multiple defensible approaches to ethical decision- making.

Positive right. A right that establishes obligations on others to act in fulfilment of the right. (Compare negative right.)

Precautionary principle. A principle employed in ethics and law advocating that steps should be taken to limit or prevent harm even where scientific data does not permit a precise assessment of risk.

Principle of ends. An ethical principle that states that people should always be treated as ends-in-themselves and never merely as means. The principle of ends is associated with Kant's ethics, in which it is presented as a formulation of the categorical imperative.

Principlism. An ethical theory based on a set of principles that must be balanced against each other. The best known example is the four principles.

Privacy. An ethical and legal concept, often considered a right, which safeguards a cluster of related interests. Generally, privacy is the protection of: (i) control over information about oneself, (ii) control over access to oneself, both physical and mental, and (iii) control over one's ability to make important decisions about family and lifestyle in order to be self-expressive and to develop varied relationships.

Procreative beneficence. The principle that prospective parents should choose, from among the possible children that they could have, the one that is expected to have the best life.

Randomised controlled trial (RCT). A research method, widely used in medical research but applicable to other areas, in which participants are randomly allocated between two or more groups. Those in the control group receive an established treatment or placebo while those in the other group(s) receive the treatment(s) under investigation.

Rational agency. A rational agent is a person whose actions are guided by reason. In economics and some philosophical thought this is understood as doing what will satisfy one's preferences to the maximum possible extent. In Kant's philosophy, however, the idea of the categorical imperative implies that reason can require an agent to perform or refrain from performing certain actions irrespective of the agent's preferences.

Relativism. See moral relativism.

Research ethics committee (REC). A committee whose job is to conduct ethical review of research.

Research governance. The regulations, standards and procedures through which research is controlled or managed. Most research governance systems include a requirement for ethical review of research involving human subjects and some constraints on how this should be conducted.

Respect for autonomy. The duty to respect the decisions of autonomous persons, or to support autonomous decision-making.

Right. (1) To have a right is to have a justified claim on others that they should act or refrain from acting in certain ways. Rights typically protect important interests or liberties and are often considered to override other moral considerations. (Compare positive right, negative right.) (2) An action is right if it ought to be performed.

Rigour. See methodological rigour.

Somatic gene therapy. See gene therapy.

Subject. See participant.

Therapeutic misconception. Failure by patients enrolled in clinical research trials to appreciate the differences between therapeutic and research methodologies. The therapeutic misconception can undermine the validity of consent.

Therapeutic research. Research in which an experimental or unproven treatment is tested using as subjects patients who have the condition that the treatment aims to treat. Therapeutic research can therefore offer a possibility of therapeutic benefit to the research subjects.

Tissue banking. See human tissue banking.

Utilitarianism. An ethical theory according to which the right action to perform in any situation is the one that produces the most happiness or utility. Utilitarianism is thus a type of consequentialism, distinguished from other types by the view that the only consequence of an action that matters morally is its propensity to increase or decrease utility.

Utility. A term used within utilitarian and consequentialist moral theory to refer to the welfare or happiness produced by an action or policy.

Virtue ethics. An ethical approach that treats character as the primary focus of ethical evaluation. Virtue ethics typically takes the virtues to be character traits that are elements of human flourishing and evaluates actions according to what they reveal about the virtues of the agent.

Voluntariness. One of the elements of valid consent. In order to be voluntary (and valid) consent must not result from coercion or from manipulation. Undue inducements may also render consent involuntary although arguably only when some kind of coercion or manipulation is involved.

Xenograft. Living cells, tissues or organs transplanted between organisms of different species.

Xenotransplantation. Transplantation of living cells, tissues or organs between organisms of different species.

Zoonosis (or zoonotic infection). An infectious disease transmitted from animals to humans.

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The scope of the textbook is the ethics of scientific research involving human beings. It contains case studies relating to a variety of scientific disciplines, including biomedical and human life sciences, new technologies and the social sciences. These have been chosen to illustrate and facilitate discussion of key ethical issues, and to give a flavour of the range of research settings in which these issues occur.

Readers will be introduced to a range of philosophical perspectives and concepts, but without any particular approach being promoted. Similarly, reference will be made to major religious views where relevant, but without endorsing or rejecting any particular view.

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