

MODULE ONE: INTRODUCTION TO RESEARCH ETHICS

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ABSTRACT

This module will introduce you to the ethical concepts underlying applied ethical decision-making in the area of research involving human participants. We will also learn what the issues are that people involved in research on research ethics are concerned with. Ethics without an understanding of historical and legal context makes arguably little sense. It is for this reason that this module will begin with a brief history of research ethics and ends with a brief overview of the relevant national and international guidelines pertaining to ethical issues in research involving human participants.

I INTRODUCTION

This introductory module will be the most theory-laden of all modules you will encounter during this course. Don't let this put you off. It was written with you in mind. Information about ethical theories has been kept to the minimum possible. You might want to compare what you will encounter here with a quick *crash-course on ethical decision-making*. If you find that one or more of the concepts introduced here have inspired you to read further, here are some suggested readings: Baron,¹ Kuhse,² Singer,³ Frey.⁴ However, this *further reading is not essential for the purposes of this course*. You will also come across *on-line links in the text*, usually referring

¹ M.W. Baron, P. Pettit & M. Slote. 1997. *Three Methods of Ethics*. Oxford. Blackwell.

² H. Kuhse & P. Singer, eds. 1998. *A Companion to Bioethics*. Oxford. Blackwell.

³ P. Singer, ed. 1991. *A Companion to Ethics*. Oxford. Blackwell.

⁴ R.G. Frey & C. Heath Wellman, eds. 2003. *A Companion to Applied Ethics*. Oxford. Blackwell.

to on-line based guidelines. *You should use these links more as a reference library. You do not have to read all these documents, but whenever you are in doubt about how you should act with regard to a particular issue, it will pay off doing some on-line searches in order to find out what these guidelines suggest you should be doing.*

II HISTORY OF RESEARCH ETHICS

Research ethics largely came about because of revelations regarding the gruesome medical experiments conducted by Nazi doctors in German concentration camps during the Third Reich. You will read more about some of those experiments in the module on vulnerable populations. For instance, Nazi doctors in experiments in German concentration camps killed Gypsy twin teenagers in order to determine why some of them had differently coloured eyes. Prisoners of war were forced to drink seawater in order to find out how long a man might survive without fresh water. In other instances, a South African oncologist experimented with women suffering from terminal cancer by subjecting them to dosages of chemotherapeutics that exceeded acceptable levels, without telling the patients or applying for ethical approval from a properly constituted ethics committee. In New Zealand, women were denied standard treatment for cervical cancer. They were never asked to give their properly informed voluntary consent to participate in the experiment. Many of these women died when timely treatment almost certainly could have saved their lives. Prisoners in the USA, in a series of studies, were subjected to malaria, typhoid, and cholera, and it has been asked why anyone would volunteer to accept such a risk. In a recent South African trial designed to evaluate the efficacy of a certain drug regime investigated for its potential to reduce the mother-to-child-transmission of HIV, the investigators provided for a placebo control instead of the (at the time internationally required) best-proven therapeutic method (the so-called *gold standard* of therapy).

Here are some of the questions people professionally involved in research on research ethics are concerned about: what are appropriate clinical endpoints that should trigger the termination of a trial? Are placebo controls defensible in trials with terminally ill patients? Can there be such a thing as true clinical equipoise? Is it acceptable to enrol women of childbearing age in clinical trials? Ought we permit prisoners or people confined to refugee camps to enrol in non-therapeutic clinical research? What is the ethically appropriate answer to the issue of the participation of

incompetent mentally ill patients in research clinical trials? Is it acceptable, in trials undertaken in developing countries, to provide lower standards of care (or different controls) than we would in the developed world?

Perhaps a word on the use of language is in order. For most of the history of research ethics people participating in trials were referred to as *research subjects*. Today it has become fashionable to call them *trial participants*. The underlying rationale is to shift recognition of such people's role from that of a *passive subject* to that of an *active participant*. This is much in line with a form of deontological thinking that is outlined below. It is perhaps worth noting that this has not yet resulted in much support for the idea that trial participants should be paid, as most other people (researchers, trial nurses, trial administrators, etc.) contributing to the success of clinical research. However, in the last decade more papers have been published than in the 50 years preceding this period arguing for payments to be made to trial participants for services rendered. Perhaps this is an indication that modern sentiments as far as the role of trial participation is concerned are beginning to change.⁵

Research ethics is basically about means of ensuring that vulnerable people are protected from exploitation and other forms of harm. Finally, by way of introduction, if you are interested in a readable overview article on current issues in research ethics, you might wish to try Schüklenk.⁶

III ETHICAL CONCEPTS

Ethics aims to achieve two fundamental objectives: to tell us *how we ought to act in a given situation*, and to provide us with *strong reasons* for doing so.

Philosophical ethics, the conceptual heart of research ethics, consists of a variety of competing ethical theories. This has consequences for ethical analyses because the type of ethical theory or religious framework a given ethicist utilises will very significantly influence, if not pre-determine, the outcome of such a

⁵ P. McNeill. Paying People to Participate in Research: Why not? *Bioethics* 1997; 11: 390–396. M. Wilkinson & A. Moore. Inducement in Research. *Bioethics* 1997; 11: 373–389. N. Dickert & C. Grady. What's the Price of a Research Subject? Approaches to Payment for Research Participation. *New England Journal of Medicine* 1999; 341: 198–203.

⁶ U. Schüklenk. Protecting the Vulnerable: Testing Times for Clinical Research Ethics. *Social Science & Medicine* 2000; 51: 969–977. U. Schüklenk & R.E. Ashcroft. International Research Ethics. *Bioethics* 2000; 14: 158–172.

professional's advice. You might think that this suggests that ethics is somewhat arbitrary, and up to a point it probably is. After all, the ethical theory that someone chooses might well influence her to act in particular ways, but there does not seem to be a consensus among professionals in the field as to which of these theories we should choose in the first place. The plurality of ethical theories should not surprise us too greatly, however. It is merely an expression of the deeply held values that people in pluralistic societies hold. As we will see, this does not mean that 'every thing goes' in ethics, quite to the contrary. There is a remarkable overlap on practical issues, as far as the recommendations of even competing concepts are concerned. What is important for you is to *recognise how such conclusions are derived* (i.e. what their *ethical rationale* or reason is), and ideally to *be able to negotiate different ethical views* by virtue of a reasonable understanding of the different ethical backgrounds from which people operate who may disagree with you. You might sometimes even be able to show that their conclusions do not actually follow from their own professed values. If you can achieve this at the end of this module, you have gained a lot by way of building your own ethical reasoning capacity.

IV PRINCIPLE-BASED ETHICS

Principle-based ethics typically refers to an influential approach developed by Beauchamp and Childress.⁷ They essentially propose a system of ethical reasoning comprised of four *prima facie* principles. A *prima facie* principle is a principle that can be overridden by other, weightier competing concerns. In other words, their principles are not *absolute*. These principles are autonomy, beneficence, non-maleficence, and justice. Proponents of these principles argue that everyone should be able to acknowledge them as important, regardless of a person's religious or ethical convictions. These principles primarily concern respect for the choices competent people make, our obligations to help others (provided the costs are not too high), not to harm others, and last but not least, the requirement to act in a fair and equitable manner as far as the distribution of research risks or burdens and benefits are concerned. While all this sounds quite sensible, critics have charged, quite rightly so, that principle-based ethics is unsuitable for practical decision-making because these

⁷ T. Beauchamp & J. Childress. 2000. *Principles of Biomedical Ethics*. Several editions. New York. Oxford University Press.

principles lack an hierarchical order, which renders their ranking in any given situation somewhat arbitrary. Hence, arguably, this form of ethics fails both fundamental objectives of ethics, namely to guide our actions, and to give us reasons for why we ought to act in a particular situation in a certain way.⁸

V DEONTOLOGICAL ETHICS

This type of ethics goes back to the Latin word *deon*, meaning ‘duty’.⁹ This type of ethical thinking has dominated medical ethics for most of the history of medical practice. The idea here, basically, is that *we should be able to derive a set of absolute duties by way of utilising pure reason. The motive for our action matters: it should always be that we want to act ethically and that we act the way we act, because it is our moral duty to do so.* These types of absolute (categorical) imperatives, created by a German enlightenment philosopher by the name of Immanuel Kant, the inventor of this type of ethical thinking, resulted into maxims such as ‘don’t kill’, ‘don’t lie’, and also ‘do not treat other people as mere means to your own ends.’ This is one of the fundamental reasons why we aim to obtain informed consent from competent research participants, because otherwise we would use them as a mere means to our ends. When they agree voluntarily and after having been sufficiently informed to become a part of our project, they arguably make our research objectives their own and thereby are not mere means utilised for our purposes. This might all sound somewhat trivial today, but at the time when this sort of thinking became prominent it was considered revolutionary, because it meant that slavery was actually ethically unacceptable. Deontologists have problems similar to those of the ‘principleists’, because they also have to ensure either that there is no conflict among their duties or at least that there is a ranking among those duties in order to ensure that if I can’t abide by two conflicting duties at the same time, I am able to identify the more important one without fail. The Chicago based oncologist Samuel Hellman has applied this thinking to the arena of clinical research.¹⁰

⁸ C.A. Erin. 2003. Who Needs ‘the Four Principles’? In *Scratching the Surface of Bioethics*. M. Häyry & T. Takala, eds. Amsterdam. Rodopi: 79–89.

⁹ I. Kant. 1960. *The Groundwork of the Metaphysics of Morals*. New York. Harper & Row.

¹⁰ Hellman & D.S. Hellman. Of Mice but Not Men: Problems of the Randomized Clinical Trial. *New England Journal of Medicine* 1991; 324: 1585–1589. S. Hellman. The Patient and the Public Good. *Nature Medicine* 1991; 1: 400–402.

VI UTILITARIAN ETHICS

Utilitarian ethics has developed a different approach to ethical decision-making.¹¹ This mode of ethical reasoning is most suited for problem solving in research ethics. This is so because the guiding principle of this type of ethics is singular and unambiguous, thereby providing a clear procedure for decision-making and decision-justification. The basic utilitarian premise is that *our actions should maximise utility* (normally defined in terms of happiness or preference satisfaction) for the greatest number of people. Its patterns of analysis are congruent with traditional forms of reasoning in public policy.

Research would only be justified if there was a strong likelihood that it would contribute to improvements of the human condition, both with regard to trial participants and future patients (or, when you think about vaccine research, the prevention of people becoming infected or sick in the first place). Utilitarians will always be on the lookout for benefits that are likely to accrue as a consequence of a particular research protocol. If, as members of ethics committees, they are not satisfied that the benefits of a particular trial outweigh its costs (burdens, harms, risks), they are unlikely to approve it.

Critics of this type of ethical thinking doubt that it is always easily possible to quantify risks or burdens and benefits sufficiently clear-cut to determine whether or not a particular project should go ahead or whether it should be denied ethics approval. Critics, certainly swayed by deontological arguments, find it difficult to accept that *only* outcomes matter, and that intentions do not matter at all in the ethical evaluation of actions. Imagine an investigator had failed to get ethics approval for a highly risky trial. With the best of intentions she decides to go ahead anyway. She deceived participants into joining the high-risk trial that the ethical review committee had rejected. Luckily, the research then succeeded in demonstrating that her hypothesis was correct after all. This would allow for the production of quality of life/health improving or possibly life-saving drugs. Utilitarians would retrospectively not condemn the trial or the researcher. Many will find this difficult to accept. Importantly, concepts such as informed consent hold no value in themselves (intrinsic value) to

¹¹ J.S. Mill. 1960. *Utilitarianism, Liberty, Representative Government*. London. Dent. P. Singer. 1993. *Practical Ethics*. Several editions. Cambridge, MA. Cambridge University Press.

utilitarians. They matter only insofar as they impact on the all-overarching utility maximisation objective.

VII ETHICS AND THE LAW

Many people confuse ethics and the law, and a lot has been written about the relationship between the two. We will mention only a few basic, distinguishing features and leave it at that. Just always remember that what you *must* do is laid out in the law and regulations of the jurisdiction under which you work. You *must* familiarise yourself carefully with those requirements. In most modules, we mention, as far as it is feasible, what South African regulations and legislation require. An important distinguishing feature between such enforceable guidelines and mere ethical guidelines is that if you find yourself in breach of the former and you get caught, you will be held legally accountable. This could well amount to civil or criminal *legal* cases being brought against you. Ethical guidelines, on the other hand, inform you about the things that you ought to do for ethical reasons, *regardless* of what local legislation says. Say, you might find that local legislation requires a certain minimum standard of care you *must* provide to participants who might get harmed as a consequence of trial participation. Ethical guidelines may well demand that you *should* provide more by way of compensation and care than what you *must* provide. Ethical documents are, by virtue of the fact that they are not legal documents, unenforceable, legally. It may well be that the community's response or your own conscience will shame you into doing the right thing, but you won't be held accountable in the courts of law, unless you also find yourself in breach of the positive law.

Ideally, ethical and legal documents would have identical requirements, but frequently they have not. You will sometimes also find that ethics documents that have no legal force in their own right, do become *quasi legal* documents, because legally binding documents might mention that you *must* abide by the rules laid down in those non-legally binding documents. A good example of this is the Declaration of Helsinki (about which you will read more under the heading *Rules and Regulations* below). In its own right it is an ethical guideline owned by the World Medical Association, with no legal force in South Africa. However, in the preamble to the Department's *Guidelines on Good Clinical Practice in Research*, the Minister for Health states unequivocally that any clinical research undertaken in the country must abide by the

Declaration of Helsinki. At that moment, of course, the *Declaration* becomes a much more powerful document, because violating its principles would automatically make you violate Department of Health regulations. Incidentally, this is quite problematic, because this particular document is revised on a nearly bi-annual basis, without the Minister having any say in the content of the *Declaration of Helsinki*. If the Minister decrees that South African research must abide by this document, she can only hope that the document does not itself become unacceptable for some reason, or else she would have to change South African regulations in response to this. As you will discover in the module on ‘Other Issues’, some ethical documents have no legal force, yet your adherence to their guidelines is important if you wish to see the fruits of your labour published in a professional journal. Ethical guidelines on authorship, for instance, require that you follow certain procedures. If you do not abide by those procedures, leading journals in your field will refuse to publish your work.

VIII APPLYING ETHICAL CONCEPTS

It has always been a serious challenge, both for those with an in-depth knowledge of ethical concepts and also for those with only rudimentary knowledge of these theories, to *apply* these divergent theories meaningfully to ‘real-world’ problems. In fact, the charge has been laid that this is next to impossible. The reason for this, so sceptics argue, is that ethical theory is simply too abstract to make much sense out of it when confronted with an ethical problem in one’s day-to-day life. Ethicists have countered that if their theories are unsuitable for achieving the primary objectives mentioned in the beginning, namely to guide our actions and to justify them, they would be bad theories to begin with. We found that a several-step model the Australian bioethicist Lyn Gillam developed was quite useful in our own work. It is reproduced below and will be explained in the subsequent paragraphs.

Do-it-yourself guide to ethical decision-making

- Step 1: To what extent is the problem an ethical problem?
- Step 2: What are the ‘facts’ of the case?
- Step 3: What constraints on action are there?
- Step 4: What ethical values are involved?
- Step 5: What sort of ethical problem is it?

- Step 6a: Resolve clashes between principles *or*
- Step 6b: Resolve disputes about one principle
- Step 7: Come to a reasoned conclusion

Some explanations

Step 1: It is not always the case that when you feel uncomfortable or 'guilty' about something you or others have done, an ethical problem has occurred. You have got to ensure that the problem you encounter is one that can be meaningfully addressed by means of reverting to ethical theory!

Step 2: When you look at the deontological and utilitarian concepts, you will notice that different types of information (or facts) matter for the ethical evaluation of a given situation. To a deontologist, any trial during which a participant has been deceived by the investigators would be unethical, whatever the reasons for the deception. Such a theory's rule of thumb would be that we should ask ourselves whether or not we would be prepared to live in a world where deception was an acceptable tool to get our acquiescence. Most people would undoubtedly reject such a notion. Therefore, the deontologist would argue, deception is not an ethically acceptable means to ensure that a particular trial takes place, no matter what the (potential) benefits for humankind might be. Also, of course, a deceived person is a person whose autonomy and dignity has been violated, because she was used as a mere means to our ends. A utilitarian would ask a set of quite different questions, and would be interested in different facts. She would accept that such a deception was a cost factor in the overall scheme of maximising utility. However, she would want to know whether the likely benefits were of such significance that the deception might have been a cost that we should have accepted. Say, if there had been a vaccine candidate that could make all the difference in the fight against HIV/AIDS, and the only way of testing it would be to deceive participants into testing it (possibly unknowingly), utilitarians might well consider deception under such circumstances acceptable. They would stress that it would have been better to get the first person informed consent, because they might be worried about the medium- to long-term consequences of such deception becoming acceptable, but if in a given situation deception would generate the best possible outcomes, they would think, in fact, that such deception is not only ethically acceptable, but that it is ethically required.

Step 3: We live in the real world, and, unfortunately, it isn't a very ethical one at the best of times. Ethical decision-making must

take cognisance of this. It would be of little help most of the time, if you did the ethically correct thing, thereby possibly breaking a lot of local regulations, and finding yourself at the end of the day in jail, or without a job. It is important to be aware of the constraints on our actions, both by way of legislation and also possibly by way of local customs, and by way of resource constraints and other factors. Resource constraints, as an extrinsic factor, might be so severe that they force us into running a particular valuable trial in a way that would make it unacceptable in a non resource-constrained environment. While we have to make sure that we do not use such problems as an excuse for perpetuating lower standards in poorer environments forever after, an ethical case could possibly be made for such lower standards if no alternatives are available.

Step 4: It is important, for your own decision-making, but also for public deliberations (for instance in an ethics committee) to be clear about the ethical values that are underlying your conclusions. It is important to do so, because *transparency* is an important feature of ethics review. Investigators, participants, and the wider public are entitled to know why an ethics committee reached a particular decision during its review process. Spell out for yourself what your ethical reasons and values are for a decision you may have reached. This is not an academic exercise. If you do it seriously, you will already be able to anticipate possible ethical counter arguments others might put forward against a research proposal you plan to submit for review. You can improve your chances of succeeding by way of pre-empting such concerns immediately in your application.

Step 5: You have got to get a handle on the type of ethical problem you encounter. Is it a problem that only occurs if you look at it from a utilitarian perspective or is it a problem that you would encounter in any of the ethical theories we discussed above. It's probably fair to say that *the more ethical concepts your proposed course of action violates, and the less justifiable it is to push ahead with your project anyway, the less likely it is that you would not encounter opposition from other people*. Remember: these theories are reflective of our own deeply held moral convictions. The more of us you put off, the less chance you have to succeed.

Steps 6a and 6b: This really is only of concern for the deontological and principle-based approaches. As we have already indicated above, within both these approaches there is a chance that you would have to decide which principle is more important (hierarchical order) or which principle is applicable in the first

place. It could also be that within an ethics committee members argue over a particular principle. Say, some might dispute that we should accept a proposed principle at all, while others might think this particular principle is more relevant than any other principle discussed. It is probably fair to say that neither of the two concepts is of much help, yet if you wish to utilise them you will have to come to a conclusion that is practical, non-arbitrary, and transparent to others. This is a challenge you should not underestimate. It is always easy in this context to be a sloganeer, shouting ‘autonomy’, ‘exploitation’, ‘dignity’ and so on and so forth, but without an ethical argument underlying and supporting these ‘slogans’ you would be wasting both your and your audience’s time.

Step 7: When you have dealt with these steps and thought about reasons and developed arguments for your conclusions, you will finally be able to present a reasoned argument for a particular practical conclusion that you have reached. This does not mean that others will necessarily agree with you, but if they follow the same process you will be able to engage in a meaningful and productive discussion taking you eventually to a consensus or majority based publicly defensible decision.

IX RULES AND REGULATIONS

The Nuremberg Code is the first, and historically the most important, international research ethical guideline. You will find this and some of the other documents mentioned below in Jonsen.¹² It was the international community’s response to the crimes Nazi scientists committed in German concentration camps. This document was superseded in 1964 by the World Medical Association’s *Declaration of Helsinki*.¹³ You will find reference made to this particular document in many of the modules. In 1991 and 1993 an organisation founded by the WHO and UNESCO, the Council for International Organizations of Medical Sciences (CIOMS),¹⁴ produced its own set of ethical guidelines both for clinical and epidemiological research. This set of documents is of a much more practical nature than the *Declaration of Helsinki*. A number of

¹² A.R. Jonsen, R.M. Veatch & L.R. Walters. 1998. *Source Book in Bioethics: A Documentary History*. Washington, DC. Georgetown University Press.

¹³ World Medical Association. 2000. *Declaration of Helsinki*.

¹⁴ Available at: <http://www.cioms.ch>

national ethics bodies in the Australia, USA, UK, Germany and other countries produced their own sets of guidelines. They are too numerous to discuss them in great detail here. The South African Department of Health¹⁵ issued its own ethical guidelines pertaining to clinical research at the end of 2000. This document, and the requirements for ethical approval, is discussed in greater detail in the module '*Implementation of Ethics Review.*' You will find reference made to this document quite frequently. In this country ethical approval is currently required for all research involving human participants, regardless of the nature of the research. In the sphere of clinical research, in fact, approval is required both from a review committee at the Medicines Control Council (MCC) and a properly constituted local (usually institutional) ethics committee. Should your research also have been sponsored by the country's Medical Research Council (MRC),¹⁶ you might, under some circumstances, also have to get ethical approval from that organisation's ethical review committee. The MRC has issued its own set of ethical guidelines pertaining to research. Quite conceivably, if you received funding from a public or private international agency, say, for instance the US NIH, you might well require ethical approval from that funder's ethics committee, too. It is important that you familiarise yourself with the ethical guidelines and regulations of these various structures way ahead of your actual intended trial starting date, because ethical review takes time, and you have to ensure that your proposal is in line with what those various committees' guidelines require of you. In fact, the writing up of a research proposal for funding should already take cognisance of ethical requirements, otherwise you might end up with the funding but no approval.

Pretty much all ethical documents demand that you get first person voluntary consent from prospective trial participants. An elaborate information giving procedure, usually including a *Participant Information Statement* and a separate *Informed Consent Form* (the prospective participant would have to sign) is a standard operating procedure in most trials. It includes, in accessible language, detailed information for prospective participants, informs them about their rights and obligations should they enrol, and will almost always include a clause informing them that they may withdraw from the study at any point in time without any

¹⁵ Available at: http://www.doh.gov.za/docs/policy/trials/trials_contents.html

¹⁶ Available at: <http://www.mrc.ac.za/ethics/ethicshuman.htm>

negative consequences for themselves. In other words, they are not owned by the investigator once they have signed the consent form. They are free to leave when they see fit to do so.

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