The Human Research Ethics Environment

A talk given at the Illawarra Area Health Service by
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Abstract. In this talk I will give primarily a background and an introduction to the NH&MRC *National Statement on Ethical Conduct in Research Involving Humans*, together with a discussion of some of the current issues in relation to ethics in medical research. It is also intended to give an idea of what issues confront both researchers and Human Research Ethics Committees (HRECs) in their respective submission and consideration of research applications, with reference to local requirements. Please note that the discussion cannot be complete, and for full details of guidelines and procedures under the National Statement, the reader is referred to the Statement itself, available via the NH&MRC website <http://www.health.gov.au/nhmrc/>.

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1. The Declaration of Helsinki, 1964 [HD]. This was made by the World Medical Association. This seems to me to be a fundamental document in the area of medical ethics and research, and it has had an influence on our own National Statement. It is succinct, consisting of 32 articles taking 2-3 pages. It is mainly directed to the responsibilities of the physician/medical researcher. Article 2 says that the duty of the physician is to promote and safeguard the health of the people. In research circumstances, there may be a balance between the "promotion" and the "safeguarding" of health, for the promotion of health may involve research for new treatments etc, and yet this research may have potentially harmful effects on participants in the research. Article 5 says that consideration for the well being of subjects should take precedence over the interests of science and society. Article 10 says researchers are to protect life, health, privacy and dignity of the human subject. Article 8 recognizes the existence of vulnerable populations who may require special care when involving them in research, including those who may be medically and/or economically disadvantaged.

Article 13 says the research should have a clear protocol and conform to scientific principles, and article 15 says research should only be conducted by competent persons. The protocol should always contain a statement of the ethical considerations involved according to article 14—in practice, the statement in protocols is often perfunctory, and the issue is often addressed more thoroughly in the application form of the HREC. Article 13 says the protocol should be a submitted to an independent ethical review committee, and the researcher has an obligation to provide monitoring information to the committee. Thus, the Declaration envisages a system, possibly varying from country to country, of Human Research Ethics Committees, at least for medical research. Participants should be volunteers only and should be informed about the research according to Article 20. The participants should be told what aspects of their treatment are purely clinical and what are research related [Article 31]. In publication, researchers are obliged to preserve accuracy of the results and to report negative as well as positive results. Various articles deal with obtaining consent [Articles 24, 25, 26].

The use of placebos in research, or of no treatment, are not excluded under Article 29, but this seems to have been problematic and, in 2002, clarification of Article 29 occurred in relation to placebo controlled trials, by means of a footnote. Extreme care is to be taken in use of placebo controlled trials—the footnote lists conditions under which placebo controlled trails may be acceptable. It's fair to say that the footnote clarifies the article in a way which is more stringent on placebo use than the original Article 29 appeared to be by itself. This is an indication that the ethics environment does not stand still but, like science, knowledge and expectations change over time.

Where proven treatments have failed on a patient, with the patient's consent Article 32 says the physician is free to use an experimental treatment in the hope of achieving an improvement (the Article seems to envisage this primarily in serious circumstances). When this occurs, the experimental treatment is to be considered as research, so that records are to be kept and also information as to the effect of the treatment.

The Helsinki Declaration has almost nothing to say about the potential commercial aspects of medical research, and seems to regard the researcher as responsible for the research, rather than the sponsor, if there is one—the unstated assumption seems to be that the researcher is fully autonomous even if there is a sponsor for the research. It does not address directly the question of the extent to which sponsors have a research responsibility independent of the local researchers. The Declaration has little to say about the privacy of data and how it should be dealt with.

2. Australia and the National Statement. As far back as 1985, the NH&MRC had said that in order to be eligible for NH&MRC research funds, researchers had to observe standards and procedures set out in the Statement on Human Experimentation and Supplementary notes. In 1992, the NH&MRC bill was enacted. This established the NH&MRC as a statutory entity and sets out its powers etc. It required the NH&MRC to issue guidelines on ethical issues relating to health, specifically including guidelines for the conduct of medical research. It established AHEC, the Australian Health Ethics Committee as a principal committee of the NH&MRC. The *National Statement on*

Ethical Conduct in Research Involving Humans [the NS] results from the obligation on the NH&MRC to issue ethical guidelines for medical research. The NS is some 70 pages, and elaborates considerably on corresponding sections of the Helsinki Declaration, as well as addressing matters not in the Helsinki Declaration. The NS incorporates parts of an earlier statement concerning ethics in general human research (not just medical) of the Australian Research Council (ARC). The NS is endorsed by the ARC, the AVCC and the learned societies—AAS, AAH and the AASS. So the NS should be seen as a set of ethical guidelines not just for medical research, but for research involving humans in general. Even so, I think it remains especially a statement about medical research ethics. But, overall, the NS is more "philosophical" than the Helsinki Declaration and discusses general ethical principles and what constitutes research, as well as practical considerations emphasising medical research.

The NS, understandably, seems to be strongly influenced by the Helsinki declaration. However, whereas the Helsinki declaration said little about the independent ethics committees, the NS specifies an Australian system of such committees, and of how they should operate. Following the Helsinki Declaration, the NS requires that research proposals are to be reviewed by an independent Human Research Ethics Committee (HREC). The NS specifies responsibilities, memberships, procedures etc. The minimum membership for an HREC is 7, and must include a Chair, 2 lay persons, a lawyer, a minister of religion or equivalent, a person with knowledge of the areas of research applications regularly considered, and a medical clinician or approximate equivalent. Some leeway seems to have been allowed for to take account of different circumstances facing the different Committees—HRECs must have members to provide advice over the range of applications which they receive (NS, Section 2.7). HRECs receive no direct government funding, but the receipt of funds for research for an institution from the NH&MRC or the ARC is conditional upon the institution having an HREC (NS page 3). So, if the institution has no HREC it is ineligible for funding and so, in this way, institutions are compelled to have HRECs. This poses a problem as to how positive institutions feel about funding and resourcing HRECs when they receive no explicit

funding for them and when they are forced, in effect, to have them (I regard this as a serious problem at the system level).

3. Ethical principles in the National Statement. The general ethical principles in the NS are *integrity*, *respect for persons*, *beneficence* and *justice* (NS, Section 1). The principles are not totally separate, but interact with each other.

By integrity the NS means intellectual integrity and honesty—including honesty in the reporting of negative as well as positive findings—eg, that a new drug doesn't work, when a sponsor would have hoped that it would work (a potential issue also is the *completeness* with which results are reported and this was, in part, the issue discussed in an article in the New York Times of 21/6/04 by Barry Meier). Integrity in this sense, as implied in the NS, means that research is to be looked at as a *strictly scientific* exercise, not as a commercial or marketing one. This is a serious issue in some circumstances today, especially when commercial issues are involved (eg. recent controversy concerning the company Schering-Plough, and other companies in the US are facing subpoenas).

Respect for persons is taken to mean regard for the welfare, rights, beliefs and perceptions of the different participants, and respect for their customs and cultural heritage. There are various aspects to this principle, but it includes notions of treating people equally, and not basing the manner of treatment of people upon extraneous factors.

Beneficence is taken to mean the general idea of "doing no harm" or at least "minimising risks of harm" to people participating in research. It is also encompasses the intention of the researcher to be one of good will to participants. Following the HD, the NS says that the well being of and respect for participants take precedence over the possibility of contribution to knowledge—this is an obligation both on HRECs in evaluating applications, but also on individual researchers.

Justice is taken to include: not imposing an unfair burden on groups of people who may be subject to "over researching", considering the relationship between the participants in the research and the (ultimate) beneficiaries of the research, and consideration of fair methods of selection of participants which do not artificially exclude certain groups. In particular there should not be discrimination in selecting participants on inappropriate grounds.

The NS takes the view that where a participant is unlikely to benefit from the research, participation is justified only upon grounds of minimal risk (NS, Section 1.6). Thus, risks are to be balanced by the likely benefits to the *individual*, rather than against the overall possible collective benefit—if an individual stands to benefit from the research, it may be justifiable to allow a greater degree of risk than if the benefit of the research can only be realised by others. All of this means that the NS does not simply take the view that if a participant gives consent to participate, even an informed consent, then that participation can be condoned automatically by an HREC, or that the research can be carried out by the researcher. Putting this in another way, we can imagine that a potential participant may in fact give informed consent, even when the risks of participation are not acceptable—in such a case, the fact that informed consent has occurred does not mean an HREC is justified in giving approval to the research. The point is that, again, the concept of informed consent is a question of balance, because the knowledge of the participant must nearly always be incomplete. The implicit view in the NS, it seems to me, is that although informed consent may be given, the balance of knowledge and awareness of the research is not the same between the potential participant and the researcher, so that the consent of the participant by itself is not enough to justify the research going ahead. One of the tasks of an HREC is to make this sort of judgment.

The NS places requirements on researchers, so that researchers are accountable (see later).

4. Procedures of HRECs and their obligations. The primary role of an HREC is to "protect the welfare and rights of participants…" (2.5). As above, this means an HREC may "over-ride" research even when a process of informed consent is envisaged.

HRECs are to reach decisions by agreement, wherever possible, not by vote. Again, this is the scientific and "non-political" approach. No scientist imagines, for example, that taking a vote on whether the earth is flat would be a suitable method for determining the truth of the issue. This can lead to extensive discussion of applications by HRECs. An effect of this requirement also is that an HREC tends to take account of all concerns expressed by all members.

HRECs are to keep written records of decisions at a specified level of detail (NS, 2.30). HRECs must have a mechanism for considering complaints, and have a nominated person for doing this. It must ensure that participants are aware that they can complain and know to whom the complaint can be directed. Annual compliance of an HREC is audited by AHEC.

HRECs have a responsibility to monitor the research they have approved (NS, 2.23—2.38). In practice, few if any HRECs have the resources to do this, and this remains a serious problem for the system as long as this requirement stands under the present level of government support. HRECs often simply ask for an annual report concerning ethical aspects of the project, and question whether changes to the research have altered any ethical aspects.

HRECs must ensure their members have no conflict of interest in considering applications. There is provision for expedited review for "minimal risk" research (NS, 2.27). However, most medical research is not in this category for, "research with potential for physical or psychological harm should generally not be considered for expedited review" (NS, 2.28).

HRECs must take account of the scientific validity and/or value of the research (NS, 2.8). This can lead to some applicants being surprised at the wide potential powers of an HREC—namely, not simply to curtail research on ethical grounds, but on the grounds of validity. It leads to critical scientific assessment (in some cases) of applications by HRECs, and can be controversial (not so much in the case of medical ones however).

An HREC may be obliged to suspend or discontinue research, even when it has given prior approval for it (NS, 2.44). Typically, this would occur when new information became available.

An HREC may seek or receive advice, from other HRECs or experts (the local HREC has done this in relation to use of the drug sibutramine, for example, and has taken independent statistical advice for some applications). It may invite a researcher to a meeting for discussions (NS, 2.18, 2.19) and it may request amendments to research proposals (NS, 2.18).

A common misconception is that an HREC approves the research if it is ethical, and does not approve it if it isn't—and of course, the HREC does this, but also a lot more. For, the task of the HREC is to implement the NS, and this may involve a process of (possibly extended) *negotiation* to try ensure that the provisions of the NS are being observed in the best possible way. An HREC may need to seek clarification of a proposal (not infrequently more than once) before it feels in a position to make a decision. A decision is not always clear cut one way or the other, as it is a question of balancing conflicting risks and benefits, as recognised by the NS. My impression is that most research ends up being approved, but sometimes only after lengthy negotiation and modification to the original application. There is also considerable variety in how different HRECs respond on this issue. A criticism of some HRECs has been that they are not sufficiently involved with research so as to understand and enter into the world of research, and make informed decisions with this knowledge.

5. Obligations upon researchers. Researchers are to inform HRECs of other centres where the research may be conducted and of the state of consideration of such research by other HRECs (NS, 2.31, 3.7).

Research methods and results should be published in ways allowing scrutiny and which contribute to public knowledge. However, in cases with commercial implications (typically involving company sponsors) this requirement can be, and sometime has been, problematic. A related issue is public access to the research results apart from formal publication. As in the case of the HD, it could be argued that the NS tends to treat the researcher as an autonomous unit with full control over the research protocol. It can be argued that this is the way it should be, but the issue poses some problems for HRECs.

In the course of research, if risks are seen to develop, or possibly be developing, the research may need to be stopped or modified, and the HREC should be notified by the researcher(s) of the emerging risks (1.17, 12.10, 12.8). A consequence is that a researcher cannot enter into an agreement with a sponsor which could limit the researcher from publicly identifying unenvisaged risks emerging in the course of the medical research. Thus, in theory, the Olivieri case in Canada (where a researcher drew attention in public to dangers in a clinical trial, having agreed with the sponsor that such public disclosure would not occur) could not occur in Australia!

As a matter of routine, the requirements of the TGA and CPMP/ICH on good clinical practice must be followed (12.12). This has been and continues to be an issue in Australia from time to time. There are special requirements in the case of human tissue samples (15.1, 15.2). These include informing participants about the use to be made of the samples and provision for appropriate storage and privacy surrounding future use of the samples. The main issue here can be how much is known about the future use of the sample, even by the researcher, and how much the participants should be entitled to know before giving consent. This is especially an issue in some genetic and pharmacogenetic research.

6. The local HREC. This is governed by an agreement between the University and the IAHS. The HREC has 13 members. It considers of the order of 400 applications per year. Meetings last 5-6 hours, may consider up to 20 initial applications. About 2/3 of applications are University, 1/3 are IAHS or related to the IAHS as joint research or research using IAHS facilities. The HREC has an application form for researchers. The HREC has an Executive to consider expedited reviews, and to respond to applications after they have been considered by the full Committee.

7. General concerns of the local HREC with medical applications, in particular clinical trials. Concerning clinical trials, the HD applies in full, (NS, 12.3) specifically in relation to protocols, qualified researchers, scientific validity and clarity, placebo use etc. Note that protocols from sponsors do not always have a very full statement of ethical issues. In some cases, it could be said that the observation of Article 14 of the HD is perfunctory. The NS closely follows the HD on the use of placebos or non-treatment (NS, 12.4). The conditions of the CTN and CTX schemes of the TGA must be met. Any association between the researcher and the sponsor must be notified to the HREC. Insurance issues are emphasised.

As mentioned, the NS says in 2.5 " The primary role of an HREC is to protect the welfare and the rights of participants in research and the primary responsibility of each member is to decide, independently, whether, in his or her opinion, the conduct of each research proposal submitted to the HREC will so protect the participants."

In clinical trials, the scientific validity of the trial is rarely an issue, and most of the HRECs consideration of applications is to do with welfare of the participants.

The following are some of the points that are frequently raised in discussions at the HREC concerning approval of medical research. Researchers with proposals coming before the Committee may facilitate and shorten the approval process by specifically addressing these points in their applications, as appropriate. The HREC is considering

changes which will facilitate this procedure for researchers. Note that circumstances surrounding different applications vary considerably, so not all points will necessarily be relevant or equally important for a given application.

- Relationship between the research/trial and normal treatment. During the research, to what extent will normal medication and treatment be suspended, and what are the resulting effects on and risks for participants?
- Receipt of independent advice by participants. Will potential participants in the research be given independent medical advice, for example from their normal doctor or GP, as to whether it is a good idea to participate in the research or trial?
- Monitoring the well-being of participants during a trial. How closely are participants monitored for the necessity of possible clinical intervention during the research/trial? If a participant in the research/trial fails to respond to treatment, or if problems develop for an individual participant in the trial, does the protocol specify recommended action? Is there a set of specific withdrawal criteria in the protocol and are these likely to meet all possible eventualities? Of course the protocols are information before the Committee, but comment from the researcher(s) can he helpful in elucidating requirements in the protocol.
- Possible restrictions on comment concerning the trial by researchers, even when this is in the public interest. Are there any restrictions on the researchers or anyone else, which would have the effect of limiting the attention that could be drawn to any new information that could affect the well being of participants in the trial? A consequence of Clause 1.17 in the National Statement is that there is an obligation on researchers not to enter into agreements with sponsors that could inhibit comment on any perceived adverse effects of a trial. Researchers and their teams should be free to disclose to participants and the wider community any health risks that could be associated with the trial, including any which are identified after the trial has commenced. (This is not an empty issue. In the Olivieri case in Toronto, a researcher was subject to a clause in the contract with the sponsor Apotex which aimed to restrict comment by the researcher if the well being of participants in the trial came

into doubt. The researcher claimed after the trial commenced that the well being of participants was being affected and a controversy erupted.)

- Uses of the research data. To what uses will data from the research be put? In general the HREC would look for an indication or assurance that the data will be used for the immediate purposes of the trial and not for other purposes. Participants are entitled to know all the uses to which the data are to be put. In some cases, such as a genetic sub-study, the HREC would like to see a protocol specifically for the sub-study.
- Approval of the study drug(s). Has the study drug been approved for use in other countries and/or in Australia? The point here is that if it has been approved, more is likely to be known about the drug, so knowledge on this point can affect the assessment of risk factors by the HREC.
- Treatment for participants and accessibility of the drug(s) on completion of the trial. In some cases questions arise as to the treatment of participants after the trial is complete. This may be especially the case if the study drug is not available after completion, or if the study drug is available on completion but is too expensive to be used because it may not be on the PBS.
- Effect on participants if the trial is prematurely stopped. The well being of participants may be affected if the trial ceases, for example, because the drug has been approved in some part of the world, not necessarily Australia. In such a case, similar considerations as in the previous point arise.
- Use of placebos or non-treatment. The NS (12.4) says that use of a placebo or non-treatment is unacceptable if " (a) other available treatment has already been shown to be effective and (b) there is a risk of significant harm in the absence of treatment". But the NS says (12.4) where there is genuine uncertainty about the net clinical benefit of treatment, a placebo or non-treatment arm may be considered. The HD refers to the need for "compelling scientific or methodological reasons" or where "patients who receive placebo will not be subject to any additional risk of serious or irreversible harm". These statements are quite strict, even though open to judgment, and the HREC often finds the placebo issue extremely difficult. In such applications the HREC is more than usually concerned with the monitoring of participants during the research and with withdrawal procedures for them. The use of placebos continues

to be a controversial and unresolved issue in some areas of medical research, with papers discussing the pros and cons of their use.

- Participant Information Sheets (PISs) and consent procedures. The HREC is often concerned that participants are fully informed of any risks, side effects or any disadvantage that participants in the research/trial may suffer, as well as the benefits which tend to be naturally emphasised. Thus, the HREC is looking in a PIS for suitable information for participants on the points above, as appropriate. The HREC looks for clarity and appropriate "completeness" in an information sheet, in a language which can be understood by the potential participant. The HREC has a role to play in making it easier for applicants to know what its concerns are likely to be (see below). Reciprocally, applicants need to give careful thought to preparing a PIS, bearing in mind the preceding remarks.

8. Other specific areas and the concern of the HREC. Guidelines on innovative therapy follow the HD, to be treated as research. The guidelines on dependent patients point out that free and voluntary consent may be problematic because of the condition of the patient, and a possible perception of coercion. As well there is the issue of the burden on such a participant given their condition. Various categories are examined in the NS and these include research in or involving : emergency care, intensive care, neonatal intensive care, terminal care, unconscious persons, persons with impaired communication capacity, persons highly dependent on medical care (NS, 6.1 to 6.9). HRECs are mostly concerned with the information given to patients and relatives, maximising the understanding of it in what could be difficult emotional circumstances, and satisfying itself that the circumstances do not impair the principle of informed consent for the patient and/or relatives or carers (NS, 6.10, 6.11). HRECs are also concerned with those who may be in dependent or unequal relationships with a researcher, as this may affect the ability to give free and voluntary consent to participate in research (NS, 7.1 to 7.3).

9. Issues, present and emerging. These include

- Level of support for HRECs at both the Government and institutional level.
- Increasing workload and reporting requirements. These include, for example, additional reporting requirements connected with legislative changes in NSW.
- The capacity of HRECs to monitor the research which they approve.

- Serious adverse events occurring in clinical trails, and whether the response mechanism is appropriate.
- Problems with multi-centre research and the implementation of the SSAS in NSW.
- At the local level, developing a new application form and improving turn around time. Possibly having two committees.
- At the local level, facilitating the consideration of medical applications by making it clearer in advance to the researcher as to what the HREC is likely to be concerned about in the applications.
- Trying to ensure that potential participants in research have a sufficient grasp of the research to give a genuinely informed consent. This is sometimes a problem owing to the complexity of some medical research, as reflected in the complex protocols for clinical trials. This is related to having participant Information Sheets appropriate to the task.
- Increasing awareness of ethical issues.

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