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Reforming the ethical review system: balancing the rights and interests of research participants with the duty to facilitate good research

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Abstract

Researchers have frequently complained that the NHS ethical review system stifles good research. At last measures are being put in place to address this criticism, but will they undermine the protection of research participants? The Declaration of Helsinki recognizes that medicine will not progress without good quality research, but also demands that the well-being of research participants takes precedence over the interests of science and society. This article examines the implications of the ongoing reform of the NHS research ethics review system for researchers, ethics committees and research participants.

Introduction

The Declaration of Helsinki states in paragraph 5: 'In medical research on human subjects, considerations related to the wellbeing of the human subject should take precedence over the interests of science and society'.¹ But this principle should not be read in isolation. Paragraph 4 acknowledges that 'medical progress is based on research which ultimately must rest in part on experimentation involving human subjects'. In order for science to progress, good research must be facilitated. A narrow interpretation of paragraph 5 would lead to serious restrictions on research, of which uncertainty of outcome is an inherent feature. If protecting the wellbeing of the participant required risk to be eliminated, most research projects would be untenable. John Harris, for example, calls for a wider interpretation based on the benefit patients and research participants gain from living in a society where good research is prioritized.² If this is accepted, and we suggest that it should be, then what the Declaration demands is that the risk to participants is carefully controlled. It must not be undue or excessive. Participants' rights must be respected and exploitation must be avoided. It can ask no more, for to do so would seriously limit medical progress, contrary to the public good. The balancing of the imperatives contained in paragraphs 4 and 5 is the key to ethical research, as is reflected in the Central Office for Research Ethics Committees' (COREC) *Governance Arrangements for Research Ethics Committees (GAfREC)*.³

Research ethics committees (RECs) are responsible for acting primarily in the interests of potential research participants and concerned communities, but they should also take into account the interests, needs and safety of

researchers who are trying to undertake research of good quality. However, the goals of research and researcher, while important, should always be secondary to the dignity, rights and wellbeing of the research participant.³

Recently, a number of reforms have been introduced which aim to facilitate research by bringing together aspects of research governance, and standardize protection of participants. They address Research and Development (R&D) and ethical review, both of which are required before an NHS research project can be initiated. The Clinical Trials Directive aims to foster harmonization and greater efficiency in the process of ethical review of clinical trials throughout Europe.⁴ In the UK, the effects of corresponding domestic legislation and the lobbying of disgruntled researchers have necessitated reform of the NHS ethical review system, which forms the focus of this paper. A new ethical review *service* will be created, but whom will it serve? Is an appropriate balance between facilitation of research and protection of research participants achieved?

Responding to researchers' needs

Prior to 1991, RECs in the UK operated on an informal basis. The model was very much one of professional self regulation. The Declaration of Helsinki and the experience of the volunteers who served on ethics committees formed the basis for ethical decision making. However, changing attitudes to medical paternalism meant that greater openness and accountability were required. NHS RECs were formally recognized in Department of Health guidelines for the first time in 1991,⁵ marking the start of the current trend towards greater governmental oversight and control. In 1997 multicentre research ethics committees were introduced to review research taking place at more than one research site,⁶ but the process remained cumbersome. The Central Office for NHS Research Ethics Committees was set up in 2000 to improve the system, but researchers complained of additional bureaucracy.⁷ The work of RECs became increasingly complex, both as a result of advances in medical science and an increase in the quantity and complexity of legislation which has tended to encroach into ethical matters previously left to the discretion of RECs.⁸ Resentment amongst the research community grew. The time and effort involved in gaining ethical approval was felt to be disproportionate to the ethical significance of the research, especially where the risks to the participant were minimal.⁹ Uncertainty and disagreement over the remit of RECs both in terms of the types of activities that require ethical approval and the extent to which interference with the scientific design is

ethically justified have also been problematical. The Medicines for Human Use (Clinical Trials) Regulations 2004 (Clinical Trials Regulations) was introduced to implement the European Clinical Trials Directive. The remit of ethics committees was diminished. The scientific merit of the protocol is no longer the responsibility of RECs. The UK Ethics Committee Authority (UKECA) was established to oversee the ethical approval of clinical trials and the National Patient Safety Agency (NPSA) took over responsibility for COREC in 2005 to institute further reform following a report from an Ad Hoc Advisory Group in 2005.¹⁰ In the following sections we assess the extent to which the Clinical Trials Regulations and the current reforms of the NHS-REC system¹¹ manage to resolve these issues without jeopardizing the rights and interests of research participants.

Clinical trials

In terms of recognizing the need to strike a fair balance between the rights and interests of research participants and the duty to support good quality medical research the objectives of the EU Clinical Trials Directive are sound. The preamble to the Directive emphasizes the importance of obtaining the consent of research participants whenever possible. The need to protect the wider interests of research participants is also emphasized, particularly in the case of research involving vulnerable groups incapable of expressing their consent.¹² At the same time the Directive recognizes that the application of different procedural and ethical requirements in different Member States has led to unacceptable delays and complications in obtaining approval for important research.¹³

The EU Directive has been implemented in the UK by the Clinical Trials Regulations which, in addition to ensuring the advantages of uniformity throughout Europe, aim to facilitate the process of obtaining ethical approval for clinical trials conducted entirely within the UK. Specific measures to facilitate ethical approval of clinical trials include the requirement for a single favourable opinion regardless of how many sites are involved in the trial.¹⁴ Ethics committees must give their opinion within a specified time limit, which would normally be 60 days,¹⁵ and they are also limited to a single request for further information.¹⁶ So long as the substance and quality of ethical review are maintained these procedural measures will not necessarily weaken the protection of research participants.

There are, however, two potential areas of concern where it is possible that the Clinical Trials Regulations lower the standard of protection afforded to research participants.

The first area of concern is that the ethical standards incorporated by the Clinical Trials Regulations are based on an outdated version of the Declaration of Helsinki in which the protection afforded to research participants is less extensive than under the current version. The Clinical Trials Directive and the subsequent Good Clinical Practice Directive¹⁷ refer only to the 1996 version of the Declaration, which was substantially re-written in 2000 and amended again in 2002 and 2004. In the UK, the Clinical Trials Regulations refer to the 1964 Declaration of Helsinki as amended in 1975, 1983, 1989 and 1996, but the subsequent amendments are ignored.¹⁸

The aim of the revision in 2000 was to enhance the protection of research participants. The most significant changes concern paragraphs 29 and 30, which relate to placebo-controlled trials and post-trial access to treatment. Paragraph 29 demands that new methods are tested 'against those of the best current prophylactic, diagnostic, and therapeutic methods'. Arguably this would compromise the scientific basis of research and even prevent research in developing countries where the cost of the best-proven treatment may be prohibitive. Paragraph 30 requires that: 'At the conclusion of the study every patient entered into the study should be assured of access to the best proven ... methods identified by the study'. But who should foot the bill? Such was the controversy¹⁹ that notes of clarification were added in 2002 and 2004, respectively. Cases where placebo-controlled trials may be viewed as ethically acceptable despite the existence of proven therapy are listed, and the requirement of continued access is left to the adjudication of ethics committees. Paragraph 29 and 30 were set down in the interests of protecting participants. Their subsequent amendments and the emphasis in the European Directive and UK Regulations on the 1996 rather than the 2000 version, emphasize the importance of good science. There is deemed to be adequate protection of research participants in the outdated version of the Helsinki Declaration.

Second, and of potentially greater concern, is that the role of ethics committees under the Clinical Trials Regulations is curtailed and subject to greater political influence. Previously, ethics committees exercised a great deal of discretion in forming a view as to whether a research proposal was consistent with broad ethical principles. Now they are directed 'in particular' to consider the 'relevant matters' set out in Regulation 15. In summary, those relevant matters include a consideration of the relevance of the trial and the design; the balance of benefits

and burdens; the protocol; the suitability of the investigator and the facilities; the information and procedure for obtaining informed consent; financial arrangements, including sources of funding, payments to the subject and investigator; and insurance or indemnity arrangements to cover legal liabilities in the event of death or injury. Rather than being based on an unfettered interpretation of the Declaration of Helsinki, the decision of an ethics committee should now be referable to one or more of these relevant matters.

The Clinical Trials Directive requires statutory authorization of ethics committees reviewing clinical trials. In the UK, rather than create specialist ethics committees to deal only with clinical trials, the decision was made to authorize certain ethics committees within and outside the NHS to review clinical trials in addition to other research. Consequently UKECA – formed in May 2004 – now authorizes a number of ethics committees. Others exist outside its authority and they may continue to review research other than clinical trials. For many committees, however, the era of self-regulation has ended. Whilst UKECA is independent of the medical profession it is not independent of the Government. As a result, some fear that the Government's emphasis on the potential economic benefits of research might lead to the removal of ethical barriers.²⁰

The moral duty to support research of good quality derives from the contribution it makes to the public good.²² As a result, ethics committees not only have a duty to investigators and research participants, but also a wider duty to society. It is appropriate that RECs should be publicly accountable for their conduct and decisions. The Clinical Trials Directive recognizes this and seeks to make ethics committees more accountable by laying down clear and transparent guidelines for their operation.²¹ In the UK these guidelines are incorporated into the Clinical Trials Regulations. Ethics committees are therein made responsible to UKECA to ensure that they perform their duties in accordance with the Regulations. UKECA has wide ranging powers. They include the power to authorize ethics committees to undertake review of clinical trials, monitor their performance and, importantly, to provide advice and assistance.²² Additionally, the chairman and two other members of each committee are appointed by UKECA.²³ Whilst a significant degree of independence, in terms of operation, decision-making and membership is lost, the important question is whether or not the trade-off between independence and accountability is proportionate.

Similar arrangements for political oversight of ethics committees are in place elsewhere in Europe. In Denmark for example, the Minister for Science, Technology and Development appoints the chairman and one other member of the Danish National Committee for Biomedical Research. A further two members are appointed by the Minister for the Interior and Health.²⁴ The Declaration of Helsinki states only that ethics committees should be independent of the investigator and the sponsor, not that they should be independent of the government. Moreover, the Declaration states that ethics committees should be constituted in accordance with the laws and regulations of the state, which itself implies a degree of political control. One of the aims of the Clinical Trials Directive is to ensure the continued public confidence in clinical trials and the ethics review system. Increased political accountability and the end of self-regulation may in fact contribute to this objective by increasing the independence or perceived independence of ethics committees from the medical and research professions.

Concerns have been raised that the newly fettered RECs have been 'hamstrung by Europe'²⁵ and 'may no longer be able to function because of political control'.²⁶ On the other hand, political oversight of ethics committees does not necessarily mean that the interests of research participants will be jeopardized. The Clinical Trials Regulations may usher in a new era of greater accountability and reassure the public of the quality of ethical review and of the independence of ethics committees from the medical and research professions. The important question is whether the more restricted role of ethics committees is justified, bearing in mind the need to balance the interests of science and society in facilitating research with the rights and interests of research participants. Ethics committees exist to protect research participants from harmful and unethical research, but the Declaration of Helsinki also tells us that the interests of participants must be balanced by society's interest in continued medical progress. John Harris goes further.²² He argues that there is a moral duty to conduct medical research of good quality, and calls for a wide interpretation of paragraph 5 of the Declaration of Helsinki and for a new principle to be inserted:

'Biomedical research involving human subjects cannot legitimately be neglected, and is therefore both permissible and mandatory, where the importance of the objective is great and the risks to and the possibility of exploitation of fully informed and consenting subjects is small.'

This suggests that the intensity of ethical review should be no greater than what is minimally required to safeguard against the exposure of consenting research participants to undue risk and exploitation. That is not to say that the moral duties of investigators towards participants should be weakened. The principles expressed in the Declaration of Helsinki are primarily addressed to 'physicians and other participants in medical research involving human subjects'.²⁷ The more restricted remit of ethics committees under the Clinical Trials Regulations ensures that moral and legal responsibility for the safe conduct of research in accordance with principles of good clinical practice lies primarily with the investigator. Whilst this might entail that greater emphasis should be placed on ethics training for investigators, it is surely preferable to an overly intrusive ethics review system.

Protecting the participant

Fears that the measures introduced to facilitate research will lead to poorer protection of participants must be balanced with new measures contained in the Directive and the UK Regulations to ensure their protection. The Regulations reinforce the obligations of the investigator with the introduction of criminal sanctions for, amongst other things, commencing a clinical trial without ethical approval or making false or misleading statements that their research complies with principles of good clinical practice.²⁸ Other measures to ensure the protection of research participants include greater powers of inspection and monitoring of clinical trials – particularly adverse event reporting.²⁹ Informed consent and the protection of confidentiality ensure that the rights and interests of participants are more uniformly protected, and vulnerable participants who cannot consent are rigorously protected in the new legislation, arguably to the detriment of research in those areas.³⁰

We suggest that whilst there is greater danger that the interests of research participants will not always be protected to the extent that they were previously, the Regulations contain sufficient safeguards to ensure that research participants are not exposed to undue risk. The scope of ethical review is appropriately limited bearing in mind the duty not to impede research of good quality. The supposed threat to the independence of ethics committees from political oversight can be overstated. As ethics committees are now charged with performing statutory duties and must act in the public interest, we also suggest that it is appropriate that ethics committees should be accountable to a political authority. The Clinical Trials Regulations are thus a proportionate response to the need

for both independence and accountability in the ethical review system.

Other types of human research

Only 15% of research applications concern clinical trials.³¹ Outside the realm of clinical trials, ethical review of NHS research is subject to the guidelines contained in the *Research Governance Framework* and *GAfREC*.³³ Whilst some of the new facilitative measures contained in the Clinical Trials Directive will apply to all NHS research, the protective measures contained in the Clinical Trials Regulations apply only to clinical trials. Facilitative measures include the imposition of a 60-day time limit on the review procedure and require a single UK-wide opinion for multicentre research. This alteration will benefit single centre and multicentre research, as well as clinical and non-clinical research. *GAfREC* is largely concerned with process, but also lists the requirements for a favourable ethics committee opinion. Informed consent is amongst them,³² but some of the other safeguards built into the Clinical Trials Regulations, such as guidelines relating to participants who cannot give informed consent, are absent or only vaguely expressed in *GAfREC*. Care must be taken to ensure that the new measures to facilitate NHS research do not weaken the protection of research participants.

Some countries (Belgium, Denmark, The Netherlands and France) have extended the scope of the Clinical Trials Directive to all 'biomedical research involving humans'.³⁰ If, as we suggest, the Directive strikes the right balance between facilitating research and protecting research participants, should we not extend the scope of the UK Regulations to all biomedical research on human subjects?

One potential barrier to this approach is that unlike clinical trials, which form a reasonably homogeneous subset of research activities, 'biomedical research on human subjects' encompasses various activities that differ greatly in their methodology and risk profile. Even within the realm of clinical trials there are significant differences between phase I trials and phase IV trials, for instance. Some have argued that the requirements of the Regulations are excessive in relation to non-commercial research where the objective is to investigate the effectiveness of licensed medicines.³³ As a result, the stringent and formal requirements of the Clinical Trials Regulations may be excessive where the burdens and risks imposed on research participants are small.

A second problem that would have to be overcome if the Clinical Trials Directive were applied to all human

research is the difficulty of distinguishing research from other activities. Whilst research is easily defined as an activity aimed at the acquisition of generalizable new knowledge, it is much more difficult – impossible even – to differentiate exclusively between (i) research and treatment, and (ii) research and clinical audit/service evaluation.

As Lewens argues, this is because a single activity may be multifunctional.³⁴ There is, therefore, a grey area that encompasses activities that are both research and treatment (or audit). Whilst such activities may be said to be more or less like research, or more or less like treatment (or audit), the boundaries are blurred and it becomes a matter of judgement as to which set of regulations should be applied. We suggest that within this uncertain area it is inappropriate to lay down rigid legal criteria, particularly where – as in the case of the Clinical Trials Regulations – they may be enforced by criminal sanctions.

With the exception of research involving NHS staff, the remit of the new ethical review service will not differ significantly from the current remit set out in *GAfREC*.³⁵ As Ashcroft *et al.* rightly observe, the forthcoming reforms of the NHS research ethics service do not solve the problem of differentiating research from other activities.³⁶ The Ad Hoc Advisory Group recommended that the remit of NHS RECs should not in future include surveys and other non-research activities if they present no material ethical issues,³⁷ which implies that non-research activities should be reviewed if there are significant risks. A similar approach has been adopted in Australia. There the troublesome distinction between research and audit is avoided by emphasizing risk rather than purpose as the primary criterion for ethical review.³⁸ However, COREC and the NPSA rejected this approach, preferring to maintain the *status quo* whereby audit is excluded from the remit of the research ethics service.³⁹ Alternatively, a triage system is to be introduced, which aims to make the intensity of ethical review more sensitive to the ethical significance of the proposed activity. Under the proposed system, applications will be screened and those with no material ethical issues fast-tracked. Ethics advisers will be at hand to provide guidance. Triage only addresses half of the problem with the remit of ethics committees; approval of research that does not present any significant ethical issues is dealt with more proportionately, but audits that do present material ethical issues will still evade the review process, potentially putting participants at risk. In this respect triage is no worse than the current system and there are efficiency benefits for researchers, but an opportunity to protect participants from unethical audit and avoid the troublesome

definition of research has been missed.

The extent to which the interests of research participants are protected will depend on the quality of review undertaken at screening and by the new ethics advisers and their interpretation of the threshold criteria of 'minimal risk' and 'no material ethical issues'. A discussion of these criteria is outside the scope of this article, but they are not black and white categories and involve a significant degree of ethical judgement. Diversely constituted committees are well suited to the deliberative nature of ethical decision making and something important is lost by relying on individual ethics advisers. Moreover, it is not clear how independent the decisions of ethics advisers will be given, that they will be employed by a *research ethics service*, which – as the tenor of the reforms demonstrate – is sensitive to the interests of the research community.

There are dangers that the degree of protection afforded to the interests of research participants will not be as high as was previously the case, but this must be balanced by the justified concerns of researchers that much good research was impeded by excessive delays and disproportionate review. Elsewhere in Europe it is common to limit the remit of ethics committees by excluding certain types of research.⁴⁰ In Denmark and The Netherlands for example, surveys and questionnaires do not require ethical review. The scope of ethical review is even more restricted elsewhere: in France ethical approval is only required for studies involving medical intervention, medication or physical risk; and in Austria REC approval is only required for clinical trials involving drugs. Whilst the rationale for this approach is that the excluded activities do not usually present any significant ethical issues, the danger is that they may do sometimes. Where this is the case and such studies are not subject to independent ethical scrutiny, participants will be put at greater risk. In the UK such studies would be picked up at screening and are more likely to be reviewed by an ethics committee. The triage system therefore retains the breadth of oversight of research that was a particular strength of the previous ethics committee system, but achieves this in a manner that is more sensitive and proportionate to the ethical significance of the proposed activity.

Conclusion

The Declaration of Helsinki recognizes that a balance needs to be struck between the interests of research participants and the interests of society in continued medical progress. John Harris goes further, arguing that there is a moral duty to facilitate, conduct and even participate in medical research of good quality.² In the past the research community

has complained that the ethical review system weighs the balance too much in favour of research participants.

Following the introduction of the Clinical Trials Directive and the ongoing reform of the UK NHS-REC system, a rigorous and bureaucratic process that gave substantial freedom to ethics committees has given way to a more streamlined process with curtailed freedom to ethics committees. There is now a danger that the balance has swung too far in the other direction and that the interests of research participants are no longer adequately protected.

We have argued that in relation to clinical trials the protection of research participants' interests has been diminished in two ways. First, the Clinical Trials Directive and the UK Regulations endorse an outdated version of the Declaration of Helsinki, which affords research participants a lower standard of protection than the current version. Second, oversight by UKECA and the end of self-regulation means that ethics committees are no longer free from political influence. Nevertheless, it is our view that research ethics committees retain enough freedom to counter these factors.

Measures designed to bring about a level of consistency do not always work against the interests of the participant. Indeed, better training and networking of ethics committee members, better communication and the sharing of case studies can and will lead to greater protection of participants. In addition, the Clinical Trials Regulations contain significant new measures that will serve to protect the consenting participant from exploitation and undue risk.

Research falling outside the remit of the Clinical Trials Regulations poses more of a problem. Though facilitative measures will apply in practice to all NHS research, the protective measures contained in the Regulations will not. The approval of research by individual ethics advisers and the narrower remit of ethics committees will reduce the quality of ethical review and potentially expose participants in non-clinical trials to greater risk. However, reform has been necessary to ensure that research of good quality is not unjustifiably impeded. Whilst the role of ethics committees has been weakened and more emphasis placed on the responsibility of the investigator, this does not necessarily mean that research participants are vulnerable. Ethics committees provide just one of a number of safeguards and the Department of Health and professional bodies will need to review their guidance to researchers and ethics committees to take this into account.

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