Ethical review of multi-centre research: a survey of multi-centre researchers in the South Thames region

ABSTRACT – *Objective:* To generate baseline data about the experiences of researchers applying to five or more local research ethics committees (LRECs) for ethical review. The new multi-centre review system will be compared with these data.

■ *Design:* Ninety-seven researchers, whose status as multi-centre researchers was unclear, were identified from various sources in the South Thames Region. They were each sent a questionnaire asking for their views on the substance of ethical review and their experiences of the process of ethical review.

■ *Results:* Of the completed questionnaires, 24 fitted the multi-centre criteria of applying to five or more LRECs. Responses showed dissatisfaction with LRECs' treatment of the scientific aspects of research, but satisfaction with aspects relating to consent and protection of patients' welfare. Respondents experienced great difficulty in the administration of the process of ethical review.

■ *Conclusion:* The need for a new system of ethical review for multi-centre research is beyond doubt. It remains to be seen whether it will be an improvement.

In April 1997 the NHS Executive issued a guidance note on the ethics of multi-centre research[1] announcing that a system for reviewing multi-centre research was to be established. This involved the creation of new, multi-centre research ethics committees (MRECs) responsible for reviewing the ethics of research proposals involving human subjects that are to take place within the geographical boundaries of five or more local research ethics committees (LRECs).

For the effort expended in its establishment and maintenance to be worthwhile, the new system must be more efficient than the existing one. South Thames Research and Development Directorate, the body responsible for instituting the new system, funded the Centre of Medical Law and Ethics at King's College to generate some baseline data against which the new system can be evaluated. These data were generated a) to discover whether LRECs were working to a high standard (pages 238–41) and b) to uncover the experiences of multi-centre researchers in seeking approval from several different LRECs. This article describes the results of the survey of researchers. There is a number of published articles discussing the experiences of individual researchers applying to many LRECs for the same project[2–5] but none, to our knowledge, has systematically surveyed both the standards of practice of LRECs and the views of a group of multi-centre researchers applying to, amongst others, those same LRECs.

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Method

The researchers whose views we wished to survey were those who, were the South Thames MREC already in existence, would have applied to it. These would be researchers based in the South Thames Region whose research was to take place within five or more LRECs' geographical boundaries. Under the new system, researchers are obliged to seek ethical approval from the MREC in the region where the principal researcher is based.

Discovering who fulfilled these criteria in the previous two years was a difficult process, since the information was hidden in different places. Whilst we could have used LRECs as a source, it would not have been possible to identify a principal researcher who would have applied to the South Thames MREC had it existed, and it would have been difficult to know which multi-centre studies, that had been to several LRECs, were actually the same study. Instead, our three main sources of information were:

1 *The NHS National Research Register at South Thames Regional Office* which was by no means complete. At this time the Culyer initiative was not yet operational and the only registered research was that funded by NHS Research and Development. Since we were only interested in those researchers who were based in the South Thames Region, our choice was quite limited.
2 *Pharmaceutical companies* yielded more fruit. We asked the medical directors to identify those employees who had been involved in the ethical review process for multi-centre research in the previous two years. We stated that preferably, but not essentially, the principal researcher of any such project should be based in South Thames. For our survey, the respondent was frequently the Clinical Research Scientist/Associate from the sponsoring pharmaceutical company.
3 *Medical charities* were mostly unhelpful. Only the Cancer Research Campaign was willing and able to give us details of researchers. One charity had no up-to-date information available; the others were unwilling to release their data.

These sources identified 97 possible respondents, who were each sent a questionnaire*. Of these researchers (who might or might not have been conducting multi-centre research), 27 were unable to complete the questionnaires, most having completed his or her work and moved on. A further 33 researchers neither replied to the survey nor

were contactable by letter or telephone, whilst 37 responded with completed questionnaires. Of the 37 respondents, only 24 fitted the criterion of seeking approval from five or more LRECs. The results in this article are based on the experiences of these 24 respondents. Since the main reason for non-response was that the researchers had moved on, we consider the results to be valid, as they do not reflect only the views of dissatisfied researchers, but come from all the researchers still contactable.

The questionnaire asked researchers to answer questions about one research project only. The questions were divided into *substantive issues* (the nature and quality of ethical review) and *procedural issues* (how many LRECs were applied to, how many had the same application form, etc).

Results

Content of ethical review

The questionnaire sought the researchers' views on what ethical review involved. They were asked whether any or all of the questions listed in Table 1 were relevant to the ethical acceptability of their research. The only two questions all 24 respondents felt were relevant were those concerning seeking consent and the procedures that research subjects would have to undergo. However, 18 of the 24 respondents felt that all six questions were relevant, so there is substantial agreement. In the survey of LRECs (pages 238–41) the same six questions were put, and all LRECs who responded agreed that all six were relevant to ethical review.

Table 1. Researchers' views on the content of ethical review.

Questions relevant to ethical acceptability of research	No. of respondents in agreement (n=24)
• Is the research project asking a reasonable/important question?	18
• Will the research project, as designed, answer the question being asked?	19
• Are the procedures which research subjects will have to undergo acceptable?	24
• Will compensation be made available to research subjects?	21
• Is adequate care being taken over the research subject's confidentiality?	20
• What procedures will be followed to seek consent of the research subjects?	24

Researchers' comments on LRECs' interpretation of their role

Respondents were asked to give examples of LRECs' differing interpretations of their role. Their comments included:

> Several felt my protocol involved no ethical considerations; two felt the research was audit and outside their remit/no ethical issues; many gave clearance as chairman's action ratified subsequently; others confirmed their decision at committee without taking chairman's action or asking for completion of forms, etc; two gave approval subject to restrictions which I appealed against; one gave approval to proceed but asked to approve the proposed questionnaire at the relevant point in research.

> They were broadly very similar, giving great emphasis to the patient information sheet, but sample sizing, visit frequency, complexity of assay procedures and indemnity were covered slightly differently.

> Questioning of the use of minute statistical procedures and manner of presentation of data (eg tables vs graphs) in final report.

> Some wished to have reports of progress of study whereas others did not. Some took chairman's action, others did not.

> Very different. One hundred plus ethics committees. Some – chairman's action; some – refused.

> One committee seemed more interested in the statistical calculations and the protocol analysis than the 'actual trial'. Another committee wanted to totally alter the trial design so that it answered a different question than the one that we wanted. This was because one committee member wanted to know if the drugs used would work in a different disease area. Finally, every trial that we submit for ethical approval will come back with very varied reasons for rejection from each committee. Other committees will approve it straight away.

> Some LRECs seem to be more concerned with the financial aspects of the study. Others with reviewing patient information/questionnaires rather than the proposed study.

Researchers' comments on LREC rejection of proposals

Of 24 research projects, 11 were rejected outright by one or more LREC, all but one giving reasons. The researchers' views of the relevance of the reasons to the ethical acceptability of their project were almost unanimously negative. The comments offered by respondents included:

> All rejections (about 5 out of 60) related to misunderstandings of the protocol. In most cases they simply hadn't read the protocol properly.

> The issues [raised] were not fundamental in that there was no consensus amongst LRECs. It was sometimes reflective of a dominating counter-argument from a sole individual or small group.

> [From a respondent who had stated that the reason for rejection was that the child was not giving its own consent and parents' approval was passive:] Children of this age vary in their maturity to give consent. Parents had opportunity to opt out child. Insistence on these procedures is useless therefore unethical to do it etc etc. These requirements were disproportionate to the type of research methods we were using.

> When proposals are rejected by ethics committees, the reason seems to be that they have not understood the protocol or the justification for undertaking the research. One chairman of an LREC refused approval for one of our

gastrointestinal studies because he felt that GPs should not be prescribing our product in the indication that we were researching. His reason for this was not due to its being dangerous to the patient or ineffective but because he preferred to use a 'competitor's' product rather than ours and felt GPs should do the same. I do not class personal preference as a valid basis for determining if a project is acceptable or not.

The LREC requested delay until two ongoing studies were reported. They were questioning a pharmacological effect which was already established in the CTX application, yet when sent full details were (we believe) unable to understand the complexity of the arguments as their knowledge of the area was limited. At the time 12 LRECs had passed the protocol first time.

Some persistently failed to understand the rationale or reason behind certain procedures being included in a protocol. Others had problems with the safety profile of a compound unjustifiably.

Rejected by one LREC as a study was industry-sponsored.

We were led to believe that the refusal was based on internal political issues as opposed to the ethical acceptability of the proposal.

Researchers' comments on LREC requests for changes to their proposals

Researchers were asked how many LRECs requested changes to their research protocols before approval (Table 2). Only 3 of the 19 respondents who answered this question had received no requests for changes. Of the others, three had changes requested by more than half of the LRECs applied to. The remaining 13 respondents had requests for changes from between 8% and 50% of LRECs applied to.

In contrast to their views on the reasons for outright rejection, more researchers accepted the relevance of the LRECs' requests for changes. Table 2 shows the types of changes requested by LRECs; the vast majority of these centred on the information made available to patients, an area that researchers had unanimously agreed was relevant to ethics (Table 1). Requests for changes to procedures that research subjects would have to undergo, and changes to inclusion and exclusion criteria, both of which would affect the design of the research projects, were far fewer. However, more than 50% of changes requested were not regarded as relevant to ethics. We should point out that the respondents' comments about LRECs wanting to change the design of the research given earlier in this article were not reflected in the answer to this question, which asked for *actual* examples of requested changes.

Table 2. Examples of changes requested by LRECs.

Changes requested	No. of respondents (n=21)
• Changes to information to be given to research subjects	17
• Aspects of compensation available to research subjects	4
• Changes in procedures that the subjects would have to undergo	2
• Changes to exclusion/inclusion criteria	1
• Changes to procedures for ensuring confidentiality	1

Researchers' views of the improvement of the ethics of their research following LREC review

Respondents were asked whether they thought their research was more or less ethical following ethical review. Twelve of 21 respondents thought that their research was either no more ethical, or less ethical following review.

Researchers' comments on the current system of ethical review

Despite the stunning lack of confidence in ethical review indicated by how few respondents thought their research was improved ethically by LRECs, almost all support the idea of ethical review (Table 3). However, most would also like to see changes to the current system, and most of the changes hoped for are to procedures rather than to the substance of ethical review.

Procedural issues

Respondents were asked about the administrative aspects of the process of ethical review; the most pertinent results are described here*.

It took researchers from 11 weeks to eternity (some researchers had still not heard from some LRECs) to obtain ethical approval before they could begin their study. The longest took two years, and the average was just under eight months.

Only two respondents found that some LRECs were willing to accept the views of other LRECs. Only one respondent found that some LRECs had the same application form (those in South and West Region).

Some respondents said they took a whole working day to complete each form, while others took a few hours. The longest time taken to complete the different application forms was 15 days.

Nine of 24 respondents said that some questions differed noticeably from one application form to another, particularly those concerning specific safety requirements, details of former studies, numbers of patients recruited locally *versus* numbers of patients in the study overall, the number of collaborators named on each consent form and the investigator's view about what were the ethical issues in the study.

The shortest time taken by an LREC to give a final answer ranged from 2 or 3 days to 119 days; the average time taken by these 'fast responding LRECs' was 35 days. The

Table 3. Researchers' comments on the pre-MREC system of ethical review.

Comments	No. of respondents (n=24)
• Support the idea of ethical review	20
• Would like to see changes to the current system in the UK	19
• Dissatisfied with the type of issues LRECs address	8
• Dissatisfied with procedural aspects	16

longest time taken by an LREC to give a final answer ranged from 77 days to 357 days; the average time taken by these 'slow responding LRECs' was 175 days.

Discussion

The substance and nature of ethical review

The picture drawn by the respondents of the kinds of issues LRECs were addressing is mixed. Whilst the views given are negative, there is room for discussion by them about what are relevant ethical issues. For example, scientific issues *are* relevant to ethics, as one of us has argued elsewhere[6]. It would not, in our view, be right to conclude from these responses that the standard of ethical review by LRECs was low, although some appear unacceptably idiosyncratic to multi-centre researchers. This is not to excuse the worrying indication that some LRECs do not furnish themselves with the necessary information to make decisions about the scientific validity of the research they scrutinise; nor would we wish to condone the evident lack of communication between LRECs and researchers. There is clearly a need for members of research ethics committees and researchers to join together to learn more about the nature and quality of ethical review.

The process of ethical review

The survey of procedural issues should make all of us sympathetic to pre-MREC multi-centre researchers. They spent hours completing different application forms for the same study, and months, if not years, waiting for final clearance from all LRECs before they could begin their research. The cost in time and money need not be spelt out here. Moreover, even if every LREC had the same application form and was sufficiently well-resourced to be able to turn its business around quickly, researchers would still face the puzzle of receiving different ethical views. This in itself supports the notion of a single MREC to make the overall decision about multi-centre research proposals.

In conclusion, we would argue that whilst the standard of ethical review of research projects may or may not have been satisfactory, the differences between LRECs undoubtedly created administrative problems for researchers. The need for a new, nationally organised system of ethical review cannot be in question.

Data from the new system are now being generated to compare with these data. In particular, it is hoped that the MREC system will speed up the process of ethical review without compromising standards. Insofar as it has been possible to show that the standard of review was high before the new system was introduced, we have tried to do so. Data are being collected from principal researchers, local researchers, sponsors and co-ordinators of research, and LRECs. Results of these surveys will be published in due course.

**The survey questionnaire and a fuller table of results showing multi-centre researchers' views on the administrative aspects of the process are available from the authors.*

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