Current experience of central versus local ethics approval in multicentre studies

The need for ethical review

In order to protect the interests of research subjects, whether patients or healthy volunteers, it has become accepted practice for researchers to submit their studies to prior review by an appointed body of their peers [1]; in the UK this takes the form of a local research ethics committee. Where National Health Service patients or facilities are involved this submission is obligatory and is the responsibility of the district health authority concerned. Such ethical review must cover all aspects of the study including its scientific validity, the safety and availability of subjects, the suitability of the investigator and local facilities, the quality of the information and consent procedures, the provision for indemnity to cover the liability of the investigator in the event of mishap, and the implications of the financial arrangements for both subjects and investigator [2]. Additionally, in the case of therapeutic trials funded by a pharmaceutical manufacturer, an undertaking to follow the Clinical trial compensation guidelines of the Association of the British Pharmaceutical Industry [3] is almost universally required.

Local or central review?

However, since only a few of these matters are subject to local variation, it is widely perceived that in the case of multicentre studies, the necessity to make a full submission to many of the 200-plus local research ethics committees across the country is wasteful of both time and resources. Previous attempts have been made to avoid this through the formation of a central ethics committee which, by reviewing the scientific, moral and financial aspects of the study, can free local committees to consider only local factors which may not be known to the central committee. These attempts have met with limited success only. The establishment of such a committee by the Royal College of General Practitioners in 1981, to consider multicentre studies in the primary care setting, has led to renewed optimism in recent years. We therefore decided to submit to that committee a study involving 35 practices nationwide.

Our recent experience

The study in question was a double-blind, actively-controlled phase III trial of a new member of a well established antibiotic class in 300 patients with acute lower respiratory tract infection. The full protocol, investigator’s brochure, grant schedule, patient information leaflet and consent form were submitted to the clinical research ethics committee of the Royal College of General Practitioners and, after some discussion and minor adjustments, approved. Subsequently a letter was sent to each of the 26 local research ethics committees to inform them of the study’s existence and approval by the College, and offering further information upon request. After various intervals we received either approval without further review (seven cases; 26.9%) or a request for a full submission to the local committee (19 cases; 73.1%). Of the 19 committees requiring full local review, only eight (42.1%) approved the study without asking for further information or changes. The matters raised are presented in Table 1.

Disparate concerns

The issue most frequently raised was the intelligibility of the patient information leaflet. No concern was expressed that the information given was either inaccurate or incomplete, although in two cases additional emphasis on the patients’ rights was requested. Some committees required insertion of their own standard paragraphs, and in four cases there was a request to make the information easier to read and understand.

Three committees questioned the safety of the trial drug; their questioning was overtly linked to the recent withdrawal of another compound of the same general chemical class; their concerns were satisfactorily resolved after reference to the national regulatory authority which had granted the clinical trial exemption. Another committee initially objected on safety grounds but further enquiry revealed that its real concern was over the perceived unsuitability of the local investigator. The committee had been unwilling to state this as a reason and so had settled on the safety issue.

Two committees expressed doubts about the efficacy of the trial drugs, one of the innovative compound and the other of the established comparator. The protocol was accepted after reference to relevant experts and previously published scientific data.

The study required patients to undergo a postero-
were which included or and, anterior chest radiograph before entry into the trial and, in view of the recent guidelines of the Royal College of Radiologists [5], two committees, both of which included a radiologist, questioned the justification for this. After assurances that there were clinical and safety reasons for the radiograph, other than purely scientific, the protocol was approved. Three different committees required assurances regarding either the protection of patient confidentiality, the provision of indemnity against adverse events or the scale of financial support for investigators: these were provided.

Table 1. Responses from local research ethics committees

| Reason for delay/further consideration | n  | %  |
|----------------------------------------|----|----|
| Changes to patient information leaflet | 4  | 21.1|
| Toxicity/safety of trial drug          | 3  | 15.8|
| Efficacy of trial drug/comparator      | 2  | 10.5|
| Need for chest radiograph              | 2  | 10.5|
| Suitability of investigator            | 1  | 5.3 |
| Confidentiality                        | 1  | 5.3 |
| Indemnity                              | 1  | 5.3 |
| Financial                              | 1  | 5.3 |
| None                                   | 8  | 42.1|

*Two committees raised two issues, one committee raised three issues.

A matter of time

A further area of interest was the length of time taken to achieve all this. Figure 1 shows the number of days from initial contact to approval for all committees in the two subgroups. This period only includes time attributable to the due process of review; delays on our part in preparing or submitting information or material once requested, and postal time are excluded from all data. Thus the delays described wholly reflect the time taken by committees to process submissions and replies to their enquiries once they had received them. In many cases these periods mainly reflect the gap between meetings, where a minor query, the answer to which could be supplied by return of post, would need a month’s wait until the next committee meeting. (In our experience, ‘chairman’s action’ in these circumstances is becoming increasingly rare). In one case, however, a committee scheduled to meet monthly did not hold a meeting for six months.

Within the ‘requiring full local review’ group, it is difficult to define the proportion of delay time due to primary review rather than further enquiry. In theory, the eight committees that did not require further information or changes should, if they met monthly, have had a maximum delay time of around 30 days. In fact, no committee in this group took less than 54 days to respond, and the mean time for the eight fastest committees was 63 days, although they were not necessarily the eight that had no queries. These times are highly suggestive of organisational problems. If a committee made an enquiry and the reply was considered at the next meeting after it had been received, this should add a maximum of 30 days to the review time. Calculating a ‘maximum total delay time’ for this group on the basis of 30 days for each of the 15 enquiries generated (generously allowing committees with more than one query to consider each separately at consecutive meetings) plus 30 days for primary

Fig 1. Ethics Committee ‘time to approval’ from initial contact. (For difference between groups p < 0.05—Wilcoxon (Mann Whitney) Two Sample Rank test.)
review, predicts a total delay time of 1,020 days, with which the actual figure of 1,729 days does not compare favourably.

The problem with multicentre studies

The wide variation in performance between local research ethics committees has been widely reported and is quite reasonably attributed to differences in historical background, local administrative practice, financial resource and the ability and enthusiasm of individual chairmen or convenors. The need for change has similarly been thoroughly explored [6–8]. The issue that particularly concerns us in the consideration of multicentre studies is the relationship between local and central research ethics committees.

The guidelines published by the Royal College of Physicians in 1990 [9] and by the Department of Health in 1991 [2], give general advice on the constitution and role of research ethics committees, but have little to say on the specific problems of multicentre studies. The widely hailed guidelines on ‘Good clinical practice for trials on medicinal products’ promulgated by the Committee on Proprietary Medicinal Products of the European Commission endorse the same principles but similarly circumnavigate this particular issue [10]. Indeed, our experience has shown that where local committees are trying to implement the recommendations of the above bodies, despite the financial strictures and mushrooming workload many face, their efforts frequently worsen the situation—particularly with regard to multicentre studies.

Overlap and duplication

The points raised by the local committees were, with the exception of one concerned with a purely local issue, those that had been debated and agreed by the clinical research ethics committee of the Royal College of General Practitioners, and incorporated in the study documentation. This committee is undoubtedly expert in evaluating research projects in general practice and compares favourably in experience and the qualification of its members with all but the very best local committees. In the absence of any overall policy or guidance it is clear that the latter must make their own judgement of how best to discharge their duty to advise their health authority. They may quite properly decide either to accept the decision of a central committee of high repute or to review all aspects of the project for themselves.

Dodging the issue

The one issue that was raised which unquestionably lies with the local committee, was that of the suitability of the local investigator. It is of interest, and of some concern, that the responsible committee felt unable to state this objection openly and opted instead for a less credible alternative. The real problem was only elicited in conversation after it was agreed that the information be treated as confidential and the investigator not be informed. There appeared to be two reasons for this: first, to avoid the risk of suit for defamation, and second, to avoid local controversy and confrontation. Clearly, legal advice should be available to local research ethics committees to reassure them that if a properly managed, non-malicious and limited disclosure of such a judgement is made, and indeed required, in the execution of their duty to their health authority, they are protected from legal repercussions by the principle of ‘qualified privilege’ [11]. The desire not to upset local practitioners who may also be colleagues is understandable but hardly consistent with the duty laid upon committees. However, the current uncertainty of their position with regard to their duties and powers is likely to increase their reluctance to risk such dispute.

Needless effort

Our experience demonstrates the pitfalls awaiting researchers involved in such multicentre projects. The lengthy delays encountered in considering and reporting on submissions were caused by the need to rewrite protocols, patient information leaflets and consent forms, and the reiteration of study details that were already clearly stated in the protocol which the individual committee had clearly not had time to read thoroughly. All these had to be reconciled with the scientific requirements of the study and the wishes of dozens of different committees with differing backgrounds, interests and, inevitably, prejudices. These delays place a significant handicap on researchers trying to perform the studies which are understandably demanded to establish the safety and efficacy of new products, particularly in the primary care setting.

The need for a lead

Unless the ethical review of research is put on a sounder, more professional footing, for which the pharmaceutical industry would surely be prepared to pay on a fee-for-service basis, the present favoured status of the UK as a site for therapeutic research will be undermined. Although this report concerns a therapeutic study, it is clear that academic multicentre studies, particularly epidemiological ones, are similarly impeded with a considerable loss of research time and the waste of already inadequate research funding. The recent efforts of the Association of the British Pharmaceutical Industry, the Royal Colleges of Physicians and General Practitioners, and the Department of Health to bring some order to this muddle are very welcome, but the particular conflict between central and local ethics approval needs urgent consideration and a defi-
nite lead—ideally from the latter. We are all currently singing from different songsheets—and the discord is painful.

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