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ANALYSIS

Problems with ethical approval and how to fix them: lessons from three trials in rheumatoid arthritis

Jonathan Mendel and colleagues call for greater transparency on ethics committee decisions to improve trial design

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Clinical trials are subject to costly and onerous regulation that aims to ensure they are well designed, with risks to participants minimised wherever possible, and any serious outstanding risks communicated clearly to participants. We set out to assess how well current regulatory frameworks meet these aims, and the extent to which the relevant regulatory documentation can be accessed for independent scrutiny, using three recent trials of interventions for rheumatoid arthritis.

A recent study reported that over 10 000 people with rheumatoid arthritis have been randomised to control groups receiving ineffective treatment in trials of biological disease modifying antirheumatic drugs, risking "irreversible deterioration in condition."[1] We investigated the process of ethical approval, and the information given to patients, for two trials of ocrelizumab included in this study (STAGE[2] and FEATURE[3]). We also reviewed documents for a homeopathy trial in rheumatoid arthritis because problems with ethical approval and informed consent in complementary and alternative medicine have been reported.[4] Rheumatoid arthritis is a common disease for which many new therapies have been developed over the past two decades; it is therefore ideal for exploring these issues, which are relevant to clinical trials in all areas of medicine.

Barriers to accessing ethics documents

We experienced extensive delays and challenges obtaining documents and information for all the trials. Genentech/Roche sponsors both the STAGE and FEATURE trials. JM approached the company by email and phone to ask about the justification for using a placebo control group, request copies of documents and correspondence with the ethics committee on this issue, and request copies of documents given to participants (a template consent form and patient information sheet). Roche initially refused, stating that the Association of the British Pharmaceutical Industry code of conduct prohibits commercial promotion of drugs directly to patients. Although JM is not a healthcare professional, the request gave his academic email address and explained the purpose of our study. We were therefore surprised to see this regulation being cited as a reason not to share information. BG (one of three medical doctors on the project) then contacted Roche. However, while Roche did send us parts of the documentation from the ethical approval process, it they declined a request for copies of all correspondence with this ethics committee, explaining "ocrelizumab is undergoing regulatory assessment and this information forms part of the confidential filing dossier." We then requested these documents from the Health Research Authority, under the UK's Freedom of Information Act.

We chose the homeopathy trial at Wrightington, Wigan, and Leigh NHS Foundation Trust because it was highlighted on social media[5] as an example of ethical problems in complementary and alternative medicine research. We made a freedom of information request to the trust for a copy of all documents submitted to the ethics committee in relation to this trial, and all related correspondence to and from this committee. The trust replied promptly, but many relevant documents were missing. It was only after extensive correspondence that we eventually received all the requested information.

We reviewed the trial documentation to assess (where relevant) how the use of a placebo comparator was justified; how well the trial processes met ethical expectations for research on human participants; and whether adequate information on shortcomings or risks with the comparator was given to patients.

Problems with risk mitigation

Ocrelizumab trials

FEATURE and STAGE randomised patients with active rheumatoid arthritis and inadequate responses to methotrexate to treatment with either ocrelizumab or placebo plus

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methotrexate for a prolonged period (up to 48 weeks in STAGE) before reallocation to active therapy or open label treatment with ocrelizumab. As rituximab (which has the same molecular target as ocrelizumab) was an established treatment for active rheumatoid arthritis, this potentially deprived participants of effective treatment for as much as a year. Inadequate treatment can lead to irreversible structural damage, additional pain, and functional impairment.

FEATURE's ethics application acknowledges that "the main ethical concern with this study is the need for the control arm to receive placebo ocrelizumab infusions. However, this group will receive methotrexate throughout the trial, which is considered standard first-line therapy in many institutions and the participants can continue with analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and steroids if receiving these medications at a stable dose prior to the trial."

Methotrexate is used as first line treatment, but trial participants had already had unsuccessful treatment with methotrexate and so were no longer at the first line stage. The applicants quote a single cohort study by Kapral and colleagues[6] as evidence that methotrexate is effective, even in those for whom it has previously been ineffective. However, the findings of this study cannot be readily generalised, and the initial dose of methotrexate (median 10 mg) was much lower than in FEATURE (16.3 mg at baseline). Most patients in Kapral's cohort whose initial dose of methotrexate was similar to that in FEATURE did not respond to "re-employment." Instead of relying on this study, discussion of risk mitigation could have been grounded in a review of the available evidence.

Another ethical problem with the trials' design is that rescue therapy was permitted but not mandated. The presence of real or perceived barriers to escalating treatment through rescue therapy is supported by the fact that only 26% of placebo treated participants in STAGE received rescue drugs, despite active disease at baseline and previous lack of response to methotrexate. Furthermore, only 27.6% of the placebo group achieved a 20% improvement in a composite measure of disease activity (ACR20), equivalent to a minor clinical response, at week 48.

Participants in STAGE who received the active drug had a significant structural benefit compared with controls, confirming that patients taking placebo were disadvantaged despite the availability of rescue therapy. This risk could have been mitigated if other biological drugs with evidence of effectiveness had been used as comparator.

A research ethics committee looking at FEATURE asked for "clarification regarding whether the patients in the placebo arm would be deprived of other treatment options." However, it seems to have accepted reassurance that "patients would be able to take additional medications (NSAIDS and steroids) as needed, and that there were many options for escape therapy." We found no evidence that the committee further discussed this key issue or using another biological drug as an active comparator (despite their widespread use at this stage of disease).

Homeopathy

The exclusions listed on the ethics committee form for the homeopathy trial differ from those in the research protocol (box), but there is no evidence that the committee raised this. Moreover, some of the trial's exclusion criteria seem unjustified since homeopathic remedies beyond the C12 potency (that is, diluted 12 times at a ratio 1:100 resulting in a final dilution of $1:10^{24}$) contain no active molecules to, for example, interact with biological drugs.

Failure to communicate risks of placebo during informed consent

Roche supplied only an excerpt from an application to a UK ethics committee for the FEATURE study. This recognised that "the main ethical concern with this study is the need for the control arm to receive placebo ocrelizumab infusions." However, the committee did not ensure that participants were told this. There is room for professional debate on the extent of specific risks, and it is not necessary to share all information seen by the committee with participants. However, it is important that participants are aware of major concerns with the research so that they can make an informed choice; the fact that the control group's treatment was seen as the main ethical concern suggests that it should have been shared with participants. At the least the committee might be expected to discuss whether this information should be shared.

The consent forms for the two drug trials did not explicitly state the additional risks to members of the placebo control group such as increased pain, impairment, and permanent structural damage. Also, while the risks of corticosteroids are explained, the consent forms do not make explicit the risks of increased doses as rescue therapy.

Failure to communicate methodological shortcomings and results of previous research

The ethics committee approved the homeopathy trialists' outlined procedure for soliciting informed consent. However, the information provided was problematic. The patient information (as revised after ethics review) stated that homeopathic remedies are "usually based on minerals or herbs." This implies that they contain active ingredients, but remedies beyond the C12 potency contain no active molecules. The patient information stated that "there is currently little clinical evidence about the efficacy of homeopathic remedies" but did not state that the totality of the available evidence fails to show that highly dilute homeopathic remedies are effective beyond placebo.[7]

The patient information states that the "research may benefit you or future patients because the findings will inform treatment." The sponsoring NHS trust declared that "an appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality." However, it is hard to see how a small non-randomised trial of homeopathy—which, the ethics committee noted, covers similar ground to previous higher quality trials—will alter current best evidence. While some or all patients may still have made an informed choice to participate, knowing the shortcomings, the ethics committee form does not discuss whether the study is a good use of patients' time or NHS resources.

Towards greater transparency

Our analysis suggests it is naive to accept ethics committee approval alone as evidence that ethical concerns have been appropriately reviewed, with the trial appropriately designed, best evidence considered, and harms minimised. Similarly, statements that informed consent was obtained do not guarantee that participants were given the information that a broader range of clinicians, researchers, and patients would regard as appropriate for informed consent. We recognise that there is room for disagreement on the concerns raised by any individual

Inconsistencies in homeopathy ethics documentation

The homeopathy trial ethics committee form states that patients taking biologically active drugs or who have used homeopathy in the past six months are excluded; however, the only exclusions mentioned on the research protocol are people who are "under 18, have previous experience of homeopathic treatment, are pregnant or breast feeding or have severe co-morbidities that might affect RA treatment." The ethics form does not mention exclusion of people who are breast feeding or under 18.

trial or document, but a better route is transparency: it should be straightforward for anyone to access the details of the ethical review and the actual information given to patients in order to critically appraise them. At present, there are substantial barriers to accessing the relevant documents.

These issues are important throughout medicine. In our experience, similar methodological shortcomings are characteristic of many studies of biological drugs for rheumatoid arthritis,[1] of complementary and alternative medicines,[4] and of other areas of medical research. While a systematic review of a larger sample of trials would be desirable, the difficulties in accessing basic ethics documents means that such scrutiny is unlikely to be feasible.

Poor regulation of research can cause direct harm to patients and undermine its credibility. However, the failings identified could be improved. We suggest the following, which reflect established recommendations for medical research:

Systematically review evidence relating to current and proposed treatments—A robust understanding of the possible utility, risks, and benefits of a proposed trial requires examination of what is already known about the topic. In the examples above, a systematic review could have ensured that a much clearer picture of the evidence was available to the ethics committee and participants. Although a systematic review is not sufficient (for example, investigators might produce a highly biased review), having such a review available for critical scrutiny will be an improvement.

Assess the quality of the proposed research, and tell patients about this—Ideally, ethics committees or other appropriate bodies should critically evaluate the quality of the evidence submitted by investigators and the research proposal. While there will be a large grey area, some trials are sufficiently unlikely to prove informative that committees should be able to reject them. If the ethics process permits poor quality research, the limitations of the research should be made explicit to patients so they can make an informed choice about participation. This might become part of what Iain Chalmers describes as a "patient-led good controlled trials guide."[8]

Ensure that risks are appropriately mitigated—Including risks associated with placebo.

Give patients a summary of existing evidence and of any risks of participation—When patients face risks from participation in a trial, or where previous research casts doubt on a therapy's plausibility, this should be clearly and explicitly explained.

Make all documentation around ethical approval and consent freely available—Blank consent forms should be made publicly available alongside trial registration, accompanied by the participant information sheet. Similarly, correspondence with ethics committees and other bodies with a similar role should routinely be made publicly available. This will allow ethics processes to be independently reviewed, publically discussed, and learnt from.

Larger scale research is needed to investigate the prevalence of the problems we have identified with ethical approval and informed consent. Such studies would allow assessment of differences between committees and facilitate accountability. At minimum, a review of transparency policies for institutional and national ethics review bodies is needed. Ethics processes are important to society, and should be open to public scrutiny. Openness is vital, both to minimise avoidable participant harms and to maintain public trust.

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Contributors and sources: JM is a social researcher who has worked on questions of evidence and policy. BG is a clinical academic working on evidence based medicine and research integrity. EE has carried out extensive work on the critical evaluation of alternative medicine, and SW is an experienced consultant rheumatologist who helped to establish the Australia & New Zealand Musculoskeletal Clinical Trials Network. This article arose from discussions between JM and BG about consent, equipoise, transparency, and ethics committee processes. The information sources were the trial reports, ethics committee materials (where available), related documents, and our correspondence with some of the parties involved. JM and BG conceived the study. JM wrote the first draft. SW led on critiquing the Roche trials, EE on critiquing the homeopathy trial. All authors revised and extended the paper. JM is guarantor.

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