WHAT DO RESEARCH ETHICS COMMITTEES SAY ABOUT APPLICATIONS TO CONDUCT CANCER TRIALS?

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The European Clinical Trials Directive 2001/20/EC aimed to harmonise standards for clinical trials throughout the European Union, and was implemented in UK law by the Medicines for Human Use (Clinical Trials) Regulations 2004. As a result, all trials of investigational medicinal products must comply with the Guidelines for Good Clinical Practice issued by the European Medicines Agency, and conducting a trial now requires a range of approvals from different agencies. These are generally sought in parallel. Clinical Trial Authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) is required, but before applying to the MHRA the approval of the trial sponsor must be obtained, and the trial must be registered with the European Clinical Trials Directive Database. Research governance approval from the NHS organisations in which the trial is to be conducted must be given. An important requirement is a favourable opinion from a Research Ethics Committee (REC). A REC application involves completion of a form and submission of supporting documentation, which is then considered at a REC meeting that applicants will be invited to attend. Details of success rates of applications to RECs specifically to conduct cancer trials are unknown, but figures from the National Research Ethics Service (NRES), which coordinates the REC system, suggest that only 15% of all applications to conduct research receive a favourable opinion at first review by a REC in the UK.¹ The majority (64%) of opinions are "provisional" and require further response and modification before a final decision is rendered, while 8% of all submissions receive an "unfavourable" opinion (the remainder are withdrawn or otherwise deferred).

Recent years have seen much complaint from researchers about the process of gaining REC approval,² primarily focused on the perceived complexity and burdensome nature of the

process, and the apparent capriciousness or unreasonable nature of decisions.³ However, there have been no systematic analyses of what RECs say about proposals to conduct cancer trials. As part of a programme of research on regulation and governance of medical research, we conducted an analysis (using methods described elsewhere⁴) of 80 anonymised REC decision letters on the NRES database concerning cancer trials. These were issued between March 2004 and December 2006, and all conveyed “provisional” and “unfavourable” opinions on applications to RECs to conduct trials involving medicinal products in oncology.

This work suggests that RECs do appear to identify some important troubles in applications to conduct cancer trials that are not given a favourable opinion at first review, and that applicants could improve their chances of success by being aware of these. The ethical issue most frequently raised by RECs (96% of letters) was informed consent. REC letters advised applicants to ensure that any written material given to candidates for trials is accessible, written in lay language, and minimises use of technical terms. In over a third of letters (35%), RECs were anxious that cancer patients could be very ill and desperate, and thus highly vulnerable when faced with the offer of a trial. In almost one in five letters (18%), RECs were concerned about inappropriately raising patient expectations. One letter, for example, complained that an information sheet that said “We hope that participation in <named trial> will help you by providing the best available treatment for your cancer” was inappropriate because it gave too positive a message. RECs were, in 36% of letters, also concerned about consent issues relating to the collection and use of human tissue during cancer trials. Concerns included the type of tissue to be taken, the amount and proposed uses for the tissue, when and how it would be obtained, pain during removal of the material, and what would happen should the patient wish to withdraw. Applicants may wish to give careful attention to these issues when preparing applications.

RECs were very often (95% of letters) concerned about possible risks to participants, including physical safety, side effects of drugs, effectiveness of the study drugs, additional trial procedures, and aspects of the drug schedule. Any indication that the information being provided to patients is misleading may be criticised. One letter, for example, pointed out that the cancer drug side effects were described as “mild” in the patient information sheet, but in the investigator’s brochure it was noted that 16 patients had experienced serious adverse events thought to be related to the drug.

Scientific design is frequently (71% of letters) a focus of concern for RECs. For example, one letter giving an unfavourable ethical opinion suggested that the anticipated number of responses would be too few to permit detailed analysis of associations with multiple baseline factors. Again, applicants may wish to prepare their scientific case as convincingly as possible if they are to reassure the REC about its robustness.

Just under half (48%) of letters raised concerns about how the confidentiality of trial participants would be protected. RECs required explicitness in the arrangements for data protection, including explanations in the information given to patients about whether the data could be transferred outside the country where they were collected.

Finally, applicants need to make sure that their applications are free of mistakes. RECs frequently (76% of letters) complained about errors, including missing information (46% of letters), “slip ups” (such as ticking the wrong box) in 41%, discrepancies in the information provided in 28%, and failure to comply with correct procedures (such as trial registration) in 16%.

This analysis provides important indications of what applicants need to do, and what they need to avoid, to enhance their chances of securing a favourable ethical opinion for a cancer trial. RECs will be looking for evidence that applicants are sensitive to the ethical issues raised by their research, including evidence that they have given explicit attention to how participants' interests will be safeguarded and that full and truthful disclosures have been made. The wording of patient information,⁵ and more mundane issues relating to completeness and accuracy of the required paperwork, are all important.

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