Insights into how to conduct a clinical trial in the UK

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SUMMARY

New researchers may find starting and conducting clinical studies in the UK complicated and time-consuming. In this article, we describe our collective experiences and provide some pointers on how to navigate through the various committees and regulatory bodies. The article is intended to aid junior researchers in understanding the study process and to provide them with some insight on how to get through this complex system successfully.

STARTING A CLINICAL TRIAL

Research is an integral component of any modern health service incorporating evidence-based practice. To a junior researcher starting a clinical study it may seem a daunting task, especially given the recent increase in regulation by research ethics committees, R&D offices and other regulatory bodies which is the result of the introduction of new legislation, both nationally and within the European Union. With a little insight into the process, however, one can take a systematic and timely approach to these approval processes and hopefully the journey will not be too time-consuming and stressful for beginner researchers.

Clinical studies usually start with a hypothesis, typically conjured up by the researcher. Once the hypothesis is in place, a number of key steps need to be taken, including writing a protocol, applying for funding, and obtaining approvals from ethics, R&D and other relevant regulatory bodies (Figure 1). We will now discuss the application processes for the various regulatory bodies.

APPLYING FOR FUNDING

There are a number of governmental, commercial and charity funding bodies in the UK that are set up to finance and encourage research. The *Research and Development for a First Class Service* paper was announced by the Department of Health in March 2000.¹ This introduced new changes to the Department's NHS research funding policy. Since then, NHS R&D funding has been organized in two separate

systems: NHS Support for Science, and NHS Priorities and Needs R&D Funding. An increasing number of clinical trials at all stages are funded by the pharmaceutical industry,^{2,3} probably reflecting the fact that the pharmaceutical industry now spends more on medical research than in the past. Other common funding bodies in the UK are the Medical Research Council (MRC), the Wellcome Trust, the British Heart Foundation (BHF), Diabetes UK, and other medical research charities. Funding can be secured for research fellow salaries, consumables, equipment, NHS support costs and any other cost incurred for the study. Each funding body has different application requirements, details of which are beyond the scope of this article. However, it is important to know—especially if you are currently in full-time work and only starting to think about research—that most funding bodies will take three to six months to make a decision.

RESEARCH ETHICS COMMITTEES

The role of research ethics committees (RECs) is to essentially protect the rights and welfare of any human participants by collectively considering the ethical implications of a research proposal, rather than to conduct a scientific review. Indeed, in the recent Warner report it has been recommended that ethics committees focus on ethical rather than scientific issues.⁴ However, the process of ethical review for multi-centre studies is not without problems,⁵ and in Autumn 1997, the Multi-centre Research Ethics Committee was established in the UK. Multi-centre studies in the UK require approval from the MREC, which process is intended as a rapid standardized approval process to facilitate the execution of clinical trials. Following MREC approval, the application can go to a local REC (LREC): this process was significantly improved by the guidance issued by the Department of Health on how LRECs should handle an MREC-approved application in 1998.⁶

Following the EU Directive on Clinical Trials (May 2004),⁷ researchers in the UK now submit their application to RECs using a nationally standardized online electronic form. The Central Office for Research Ethics Committees (COREC) launched version 5.3 of the NHS REC application form (<https://www.corecform.org.uk/AppForm/>) in January 2007. There have been significant changes to the application form in the last few years, which have made the

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Figure 1 Steps of undertaking clinical research in the UK. ARSAC: Administration of Radioactive Substances Advisory Committee; IRMER: Ionizing Radiation (Medical Exposure) Regulations; MHRA: Medicines and Healthcare Products Regulatory Agency

form substantially easier to complete, understand and manage. The changes in version 5.1 of the form included the introduction of question-specific guidance situated within the form next to each question, inclusion of the checklist within the form itself, and the ability to print Part C separately. Version 5.2 came out in October 2006, the main change being the addition of a distinct form for Research Tissue Banks (this allows the tissue banks to apply for generic ethical approval to conduct research using stored tissue samples and to release anonymized samples to researchers). In the latest version of the form, 5.3, Part C has been merged with the national NHS R&D application form to create an integrated Site-Specific Information Form.

The online form consists of three parts and up to 57 pages (Table 1).

- Part A consists of up to approximately 72 questions, mainly covering the scientific justification for the study, proposed methods, funding details, data monitoring and conflicts of interest;

- Part B consists of up to 28 questions requiring detailed information on the use of medicinal products and devices and the involvement of human biological materials and radiation. In the case of trials which address the therapeutic efficacy of particular drugs, evidence of application to the Medicines and Healthcare Products Regulatory Agency (MHRA) must also be provided;
- Part C is now the Site-Specific Information Form and consists of up to 39 questions assessing the suitability of the local investigator (such as qualifications and research experience) and the adequacy of site facilities.

At first glance the online form looks long and heart-sinking, but some questions do not require a response, and neither do some sections if the initial response to that section is negative. MREC approval must be sought where the researcher plans to involve multiple centres, or where there is a possibility that more than one centre will be involved—for example if not enough patients can be

Table 1 Various forms required by different regulatory bodies to approve clinical trials in the UK

	<i>Ethics and R&D</i>	<i>IRMER</i>	<i>ARSAC</i>	<i>MHRA</i>
Number of pages	50	5	8	28
Number of questions	139	25	40	43
Number of signatures	4	2	4	1
Number of Copies	1	1	1	2*
Cost	Free	Free	Free	£100 to £2700
Supporting data	Required	Required	Required	Required

IRMER (at UHB Trust) Version 1.1 (9th April 2004), R&D Version 1 amended 6-05-2005, ARSAC revised form April 2005, Ethics form version 5.1, May 2005.

*1 hard copy and 1 electronic copy (CD-ROM or floppy disk)

recruited from the initial centre, and additional patients are recruited from other nearby centres. If only a single centre will be involved, the researcher should apply for LREC approval, bearing in mind that the electronic forms are identical and the length of time for them to be processed is almost identical.

It is often necessary in research to expand the area of patient recruitment (i.e. different hospitals). In these circumstances, if you have MREC approval, the researcher will need to fill out a Site Specific Assessment (SSA) online form for the Trust you want to recruit patients from. This is essentially another Part C (Site-Specific Information Form) of the ethics form, but it can be printed out separately and submitted to the appropriate LREC for the hospital. Where a researcher has LREC but not MREC approval, it may still be valid to send an SSA form, providing the hospital is within the domain of the original LREC. This will need to be clarified with the LREC.

RESEARCH AND DEVELOPMENT APPROVAL

To start a research project within an NHS Trust, NHS R&D approval is required for each Trust in which the study will be conducted or from which patients will be recruited.⁸ Most Trusts will require the researcher to have at least an honorary contract with them in order to conduct studies within their Trust. The R&D approval process usually involves the NHS undertaking costings for the use of NHS resources and facilities. The time required to gain final approval from the different Trusts varies from one to two months.

MHRA APPROVAL

The Medicines and Healthcare Products Regulatory Agency (MHRA) is the government agency responsible for ensuring that medicines and medical devices work and are safe. European Union Directive 2001/20/EC was published on 1 May 2001⁹ and was fully implemented on 1 May 2004. The

Directive introduced new procedures for the authorization of clinical trials involving medicinal products in the European Community. These procedures include obtaining a EudraCT number (<https://eudract.emea.europa.eu/eudract/index.do>), and submitting an application form (EudraCT Version 3.0.1) and supporting documents. There is also a fee, which ranges from £100 to £2982, if applicable. The MHRA administers Directive 2001/20/EC in the UK—for further details please visit www.mhra.co.uk. Recently, new requirements and specifications have been introduced for the labelling and packaging of active and placebo drugs in clinical trials.¹⁰ This stipulates that only qualified persons working for either governmental or commercial pharmaceutical companies will be able to undertake the labelling or packaging of drugs for clinical trials, which may cause some delay in initiating studies as the number of qualified, eligible persons in the UK is rather limited.¹¹ While this may not be a problem for large pharmaceutical company-sponsored studies, it could generate difficulties for smaller research studies. Furthermore, the additional costs incurred for packaging and labelling of research medicines from private companies can be as much as £2000, which should be remembered when drawing up costings and applying for funding.

A tip worth remembering is that in studies where medicine is used to assess a physiological response (e.g. the use of insulin to reduce glucose levels or the use of accipimox to lower plasma fatty acid levels), MHRA approval is not required. To be absolutely certain that your study does not require MHRA approval then it is best to email your questions and an attached proposed protocol to the MHRA (clintrialhelpline@mhra.gsi.gov.uk). Another useful tip to remember is that if your study involves the same product and has the same sponsor as a trial previously approved by the MHRA in your unit, then it is possible to submit an 'Additional Protocol' (up to a maximum of two per unit) to the MHRA for an extra cost of only £100 rather than the full fee of £2485 for patient clinical

trials (Phase I, Phase II or Phase III with a known product trial).

THE ADMINISTRATION OF RADIOACTIVE SUBSTANCES ADVISORY COMMITTEE APPROVAL

In order to undertake a clinical trial involving administration of radioactive substances, ARSAC approval must be obtained. This includes applying for an ARSAC certificate by submitting an application form with supporting data. The form consists of three parts, with four signature required (Table 1). It typically takes about two months to obtain approval.

IONIZING RADIATION MEDICAL EXPOSURE REGULATIONS APPROVAL

IRMER approval is required if the study involves the use of radiation (radionuclide materials, diagnostic or therapeutic ionizing or non-ionizing radiation) over and above those required for the normal clinical investigation or care of the participant.

CONCLUSION

Starting a clinical study will involve considerable time and patience. This article is intended to provide insights and tips for young researchers on how to efficiently and successfully negotiate their way through the complexities of various regulatory bodies. It is important to remember that application to the various bodies can be done simultaneously, so that the processes will run in parallel and thus minimize waiting times.

USEFUL WEBSITES

- Administration of Radioactive Substances Advisory Committee (ARSAC), for clinical trials involving administration of radioactive substances: www.advisorybodies.doh.gov.uk/arsac/index.htm
- British Heart Foundation (BHF), for details on funding research in heart disease: www.bhf.org.uk
- Central Office Research Ethics Committee (COREC), for clinical trial ethical application and the latest updates: www.corec.org.uk
- Diabetes UK, for details on funding research in diabetes: www.diabetes.org.uk
- European Clinical Trials Database (EudraCT), for obtaining EudraCT number for clinical trials which is essential for MHRA approval: <http://eudract.emea.europa.eu/>
- Medical Research Council (MRC), for details on how to obtain funding for clinical trials in the UK and all over the world: www.mrc.ac.uk

- Medicines and Healthcare products Regulatory Agency (MHRA), for the latest updates on obtaining MHRA approval for clinical trial: www.mhra.gov.uk
- NHS R&D form: www.rdform.org.uk
- Wellcome Trust, for details on funding research to improve human and animal health in the UK: www.wellcome.ac.uk

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