RESEARCH ETHICS

Non-commercial clinical trials of a medicinal product: can they survive the current process of research approvals in the UK?

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Over recent years, considerable attention has been paid to the National Health Service (NHS) research governance and ethics approvals process in the UK. New regulations mean that approval from the Medicines and Healthcare Products Regulatory Agency (MHRA) is now also needed for conducting all clinical trials. Practical experience of gaining MHRA and sponsorship approval has yet to be described and critically explored in the literature. Our experience, from start to finish, of applying for these four approvals for a multicentre randomised controlled trial of two licensed drugs for opiate detoxification in the prison setting is described here. In addition, the implications of the approvals process for research projects, particularly clinical trials, in terms of time and funding, and also indirect implications for NHS patients are discussed. Inconsistencies are discussed and suggestions that could improve and streamline the overall process are made. The current approvals process could now be hindering non-commercial clinical trials, leading to a loss of important evidence-based medical information.

to grant approval⁶ have all created problems for researchers when applying for research governance approval. Research governance procedures have made multicentre research increasingly difficult to conduct.⁷

Approval from an NHS Research Ethics Committee has to be sought for any UK study that includes NHS patients, staff or premises.¹ A large volume of literature has critically discussed the process of gaining NHS ethical approval in the UK,⁸ including the variation in how applications are processed to meet the differing requirements of the local research ethics committees.⁹ Recently, however, attempts have been made to streamline the process.¹⁰ The implementation of one common research ethics application form,¹¹ for example, has reduced the administration procedure for researchers who previously had to complete multiple sets of different forms for the same study if it was taking place across multiple areas. Ethics committees are still criticised on many issues, particularly for their focus on methodological rather than ethical matters.¹²⁻¹³ Indeed, the recent report on the operation of ethics committees¹⁰ recommended that ethical approval should not be another process of scientific review. Rather, the peer review process before ethical submission should be accepted in all but exceptional cases.¹⁰

From 1 May 2004, the European Union Clinical Trials Directive¹⁴ was fully implemented in the UK. The directive was intended to simplify and harmonise clinical trials across European Union member states by creating a single legal framework.¹⁵ Every clinical trial taking place now has to gain full MHRA approval, by obtaining a clinical trials certificate. Owing to the recent introduction of this requirement, discussion and comment regarding this has yet to have an effect on the academic literature. The length and complexity of the clinical trials certificate application form as well as the time-consuming nature of the application, however, have been remarked on.¹⁶⁻¹⁷ In addition, there has been a call for differentiation to be made between trials of drugs tested for first use in humans and trials of drugs that are already licensed and marketed, to avoid the "needless bureaucracy" of trials of the drugs that are already marketed.¹⁸ This

Clinical trials of medicinal products, conducted in the UK, are now subject to a substantial approvals process before they can begin. This process encompasses four distinct and separate levels: National Health Service (NHS) research governance approval, NHS research ethics approval, sponsorship approval and Medicines and Healthcare Products Regulatory Authority (MHRA) approval.

A wealth of literature, discussion and comment exists on the research governance and ethics approvals processes. Since 2001, research governance approval is required from every NHS Trust where research is taking place.¹⁻² The purpose of research governance is to improve the quality of NHS research while protecting the patients.¹⁻² Research misconduct, such as the Alder Hey scandal³ in which organs of dead children were removed and retained without parental approval, highlighted the need for introducing more rigorous systems. Variations in the applications process between NHS Trusts,⁴⁻⁵ differing levels of efficiency between the research and development departments of different NHS Trusts and disparity in time taken

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Abbreviations: LEEDS, Leeds Evaluation of Efficacy of Detoxification Study; MHRA, Medicines and Healthcare Products Regulatory Agency; MREC, multicentre research ethics committee; NHS, National Health Service; RCT, randomised controlled trial

distinction has not been made and trials of drugs used in everyday practice are now subject to a full MHRA approvals process.

Clinical trials now also have to be approved by the sponsor of the study. The sponsor is usually the institution that funded the research, or the institution employing the chief investigator. The sponsor has a duty to ensure safety and scientific quality alongside adherence to appropriate standards, systems and policies.¹⁹ Indeed, the sponsor now has to approve a clinical trial before an application to the MHRA can be made. This can lead to a more cumbersome approvals process.

The author team is keen to emphasise their full support to the concept of the approvals process as safeguarding patient safety and ensuring that no exploitation of research participants takes place. We understand the need for the approvals processes to exist and be respected, but comment on the way in which it has been implemented and organised, and its functioning at an everyday level.

The Leeds Evaluation of Efficacy of Detoxification Study (LEEDS) Prisons Project is a multicentre open-label randomised controlled trial (RCT) with 340 participants. This is the third phase of a well-established research portfolio, being conducted after two other randomised trials conducted by the project team, one with drug users in primary care²⁰ and the other with drug users in a single prison, HMP Leeds. Both trials had received the approval of the research ethics committee, with minimal changes to the trial protocols and supporting materials.

LEEDS evaluates the efficacy of the drugs buprenorphine and methadone for opiate detoxification within the prison setting. Both these drugs are licensed and marketed for opiate detoxification, and are not being tested for any new indication in the LEEDS trial. The rationale for a formal comparison and evaluation of these drugs arises from the fact that neither the scientific evidence base nor the UK national guidelines recommend a drug of choice for successful detoxification.²¹ This decision is left largely to the prescribing clinicians' discretion, with little evidence to guide them on which drug is most pharmacologically efficacious, in such a setting as the prison, where many opiate detoxifications are routinely carried out.

There is an extreme paucity of RCTs evaluating detoxification agents conducted within UK prisons. One study evaluated the withdrawal severity of the detoxification agents methadone and lofexidine;²² yet, the rates of completion were not sufficient to detect a statistically significant difference between the two regimens. Methodologically, LEEDS is important in encouraging clinical research into the prison setting. Further, it increases awareness about the importance of performing RCTs in this environment. LEEDS will contribute to the evidence base and best practice surrounding opiate detoxification, and we hope that an important precedent will be set in showing that RCTs can be performed in the prison setting.

Prisoners are recognised as a vulnerable population under the Declaration of Helsinki,²³ and the research team is aware of the inherent ethical concerns when recruiting prisoners to clinical trials. Specifically, informed consent is critical when including people who are in withdrawal from opiates or are intoxicated. Severe intoxication or withdrawal constitutes the exclusion criteria for the trial, as informed consent cannot be guaranteed in these conditions. Confidentiality is intrinsically important in the prison environment, especially with regard to the post-detoxification urine test, as prisoners can face penalties if an opiate-positive urine test is disclosed to prison authorities. Literacy problems are also prevalent within this population. As a research team working with illicit drug users both in the community and the prison, we

are particularly aware of the ethical concerns regarding this research population.

Previous academic discussion of the approvals process has largely centred on research governance and ethics. This article will widen the debate to include the recent additional sponsor and MHRA approvals that are necessary before clinical trials can begin. In doing so, the whole process from start to finish will be described to provide a holistic account of the LEEDS experience of gaining all necessary approvals.

THE APPROVALS PROCESS

We provide an outline of the work required and discuss the amount of time taken and the human resource needed to complete this approvals process. Our accounts have an extensive record of all written and emailed correspondence with the approvals bodies, and a summarised log of all telephone correspondence. Table 1 provides a concise summary of the approvals process and gives information of when the approvals were administered, submitted and approved.

Research governance

We prepared and submitted an 11-page application form, which included the signatures of the data protection controller, Caldicott Guardian, the clinical director (head of prison healthcare), the principal investigator and the authorised pharmacist (prison pharmacist). All these people had to read and agree to the trial protocol before they signed. This process took almost a month to coordinate, as most of these people are busy healthcare professionals and research activity forms only a small part of their work. At a minimum, the research assistant made 12 phone calls and sent six emails to obtain the signatures that were needed before submission. The research governance organisation required the application form, trial protocol, patient information sheet, consent form, curriculum vitae of the chief investigator and other supporting documents. The application was sent on 2 December 2004 and approval was granted on 20 December 2004.

Research ethics

After five phone calls and varied conflicting information, we discovered that LEEDS required approval from a multicentre research ethics committee (MREC) as local research ethics committees do not consider prison studies, even if they are locally based. Only four MRECs spread across the country review studies within prisons. A 45-page application form was completed, which required the signatures of an "appropriate" prison health professional and the prison governor. All supporting documents (including participant information sheet, consent form, trial randomisation envelope and data outcomes sheet), the protocol (six copies), a statement of indemnity arrangements, the comments of peer reviewers, curriculum vitae of the chief investigator and a diagram of the protocol also had to be sent. Most of this information had already been reviewed by the research governance organisation. Completing the application form and collating all the necessary documents took the research assistant (LS) around 3 working days, spread over 3 weeks, as tight timescales for other projects precluded committing such a block of time within the same working week. Some questions on the application form required hours of further clarification and revising from other members of the project team, particularly the clinical lead (NW). Our application was submitted on 3 February 2005 to meet the ethics committee deadline for their meeting on 11 March.

We attended the NHS MREC committee meeting to answer queries about the study. The committee issued a written statement on 16 March and requested amendments to be made to the patient information sheet. Among other more

Table 1 Summary of the approvals process

Type of approval	Body granting approval	Date when the approvals process began	Date of submission	Date granted
Research governance	Bradford South and West PCT	8 November 2004	2 December 2004	20 December 2004
Ethics	MREC Northern and Yorkshire	11 January 2005	3 February 2005	5 July 2005
Sponsorship	University of Leeds	11 March 2005	11 May 2005	28 June 2005
Clinical trials authority certificate*	Medicines and Healthcare Products Regulatory Authority	11 March 2005	11 July 2005	28 September 2005
International standard randomised controlled trials number	www.controlled-trials.com	27 June 2005	16 August 2005	15 September 2005 (backdated to 16 August 2005)

*Clinical trials authority certificate application requires sponsorship approval before submission.

minor amendments, further clarification of confidentiality arrangements and revisiting the calculation and justification of the sample size were also requested. The committee was concerned about our power calculations for the sample size and that we had not included “stopping rules”. A different MREC that had approved the pilot study for LEEDS, however, had asked us to remove our stopping rules criteria. The committee also asked the project team to resubmit the whole application form because we had failed to tick a box stating that we were carrying out a trial that “involves testing a medicinal product”. This meant completing an additional six-page section of the application form, mostly regarding biochemical data of the drugs to be tested. We believed when completing the application that we were not “testing a medicinal product” as both buprenorphine and methadone are licensed for the purpose of opiate detoxification. Therefore, by definition we were not conducting a phase I trial of the efficacy of a new product. Although some may consider the failure to tick a box to be an oversight on our part, we would argue that the guidance notes provided no information to suggest otherwise. Rather, we would argue that the ethical process may be perceived as being over-regulated if it fails to make separate provision for the approval of (for example) phase I versus phase IV trials. For drugs that are already licensed for their purpose and are used in everyday clinical practice, it would seem unnecessary to provide data on these substances to the ethics committee. Buprenorphine and methadone have been extensively independently evaluated in the community, as shown by recent *Cochrane Reviews* summarising their effectiveness.^{24 25}

MREC also stated that MHRA approval would be required because the European Union Clinical Trials Directive¹⁴ that has recently come into force applies to every clinical trial, regardless of whether the drugs are licensed in the UK. The project team had assumed that we would be able to apply for a Doctors and Dentists Exemption certificate for LEEDS because we were not testing previously untried drugs.

We replied to the chairperson of the committee on 9 June, after making all amendments and seeking statistical opinion. Approaching an external statistician, asking her to review our sample size and making appropriate recommendations took 3 weeks, mostly because of the already heavy workload of the statistician. Again, the several days that were needed to make all the amendments required had to be fitted in around tight deadlines for other projects. After making changes to our sample size calculation owing to the committee's concerns, it was later agreed that our original sample size calculation was both appropriate and justified. We were requested to revert back to this. After some email correspondence with the chairperson, final approval from the research

ethics committee was granted on 5 July 2005. From first submission to final approval, the process of gaining this approval took 5 months.

Sponsor

MHRA application guidelines state that for the investigators of a project to submit an application, a letter from the sponsor permitting this is required. This entails the sponsor's representative reviewing the trial protocol and all supporting documents. After ascertaining who the sponsor's representative was, a meeting took place on 25 April 2005. The sponsor's representative reviewed the MHRA application form and the trial protocol, and requested minor changes to be made to both. No changes were made to supporting documents. It took 2 days to make the changes required and the application was resubmitted on 11 May. The sponsor's representative approved the study on 28 June 2005 for the purposes of the MHRA application. Subsequently (on 24 August 2005), the sponsor's representative requested that a substantial amendment be made to MREC and MHRA to change the wording of the patient information leaflet to make it clear to participants that their medical records could be accessed by the sponsor as part of a random audit.

MHRA

The trial had to be registered with the European Clinical Trials Directive Database²⁶ (by obtaining a EudraCT number) for the relevant MHRA application paperwork to be accessed. A 47-page application form was completed and signed by the chief investigator. This took around 3 working days to complete and required hours of help from the sponsor's representative to understand the terminology and acronyms used on the form, as the guidance notes were unclear. A signed paper copy of the application form was submitted, along with a copy on a floppy disk. The MHRA also required the trial protocol, a summary of product characteristics for all drugs included, fee payment for the application to be processed (in our case £140) and the letter from the sponsor. By this stage, the trial protocol had already been reviewed by three approvals bodies: the research governance organisation, the ethics committee and the sponsor's representative acting on behalf of the sponsor. The complete application was submitted on 11 July 2005 and the trial was provisionally approved on 18 August, subject to further clarification. Final approval was issued on 26 September.

International Standard Randomised Controlled Trials Number

The research team was aware that an International Standard Randomised Controlled Trials Number would need to be sought to ensure that the trial was officially registered. We

completed the online application form on 16 August and made the statutory payment of £100. Registration of International Standard Randomised Controlled Trials Number was granted on 15 September, but backdated to the date of our initial submission. Interestingly, as of 13 September 2005, all RCTs have to be registered on an international database before recruitment begins. Registration might help combat publication bias, as authors now have a responsibility to ensure that negative as well as positive results are published.²⁷ Consequently, unregistered trials will have their scope for publication in peer-reviewed journals jeopardised.²⁷⁻²⁸ Previously this process was optional, but now its compulsory status has led to yet another layer of registration. Such a compulsion can clearly add value to the validity of the international evidence base; we believe that such a registration can also be an integral part of a research governance process to help streamline the approvals procedure.

DISCUSSION

The application process for LEEDS began in November 2004 and was completed in September 2005. By the time all relevant approvals were granted, LEEDS had been subject to four separate reviews with excessive duplication of work.

Any person responsible for reviewing the protocol and supporting documents could (and did) at any stage ask for amendments to be made, and this caused extra workload in negotiating and making the changes as well as in informing other committees that the changes had been made. For instance, the sponsor's representative suggested that changes were made to the protocol and patient information materials. We were keen to ensure that all materials were of the highest quality, but the practicalities were that there could even have been the danger of withdrawal of the offer of funding because of the time delay associated with making these changes. We wanted to ensure that all comments were taken into consideration and did not jeopardise the approval for the project from the sponsor; hence, the suggested amendments were made. Additionally, a substantial amendment to MREC and MHRA regarding a change in wording on the patient information sheet was made on the advice of the sponsor. MREC also had to be informed of the minor amendments made to the protocol. If either MREC or MHRA had substantial problems with the sponsor's suggested changes, then the whole project may not have not been feasible. Although this was not the case for LEEDS, this situation could potentially happen to others, meaning that researchers had to return to the beginning of the process of approval.

One way to prevent such a situation from occurring would be by respecting the external peer review process. Most externally funded studies have already been subject to extensive peer review⁶ before the approvals process. Consequently, we suggest that minor amendments are not made to protocols after initial peer review unless there is a clear and pressing need. Internally funded studies are often peer reviewed at the time of the research governance application and this peer review should consequently be respected.

Public money has been used to undertake the approvals process necessary for LEEDS. This includes payment for the research assistant's time to administrate and organise the relevant applications, the time and subsequently the cost of the other members of the project team in assisting this process, the salaries and expenses of all other associated personnel, such as committee members and administrators, and all consumables. Consequently, the approvals process is diverting funds away from the actual research projects.⁸ This is particularly acute when the project has been secured through charitable funding.²⁹ We understand why Boshier *et*

*al*⁴ took the step of employing a full-time coordinator for research and development for a year before their multicentre trial. LEEDS is funded by the Department of Health of England and Wales; yet, one condition of funding is that all approvals are gained before money is released. The research assistant who completed the approvals process was funded to work on a programme of research regarding substance use. The LEEDS approvals process was undertaken alongside the grant-funded work. This type of necessary preparation is increasingly difficult in the UK, unless funding is available for a researcher from 6 to 12 months preceding the date when the project should start.⁶ A possible repercussion of this lengthy process is that, increasingly, clinical trials will be conducted outside the UK, in countries with less lengthy and complex procedures.³⁰ At the least, in the UK, trial work may have to be conducted only by the relatively few research teams with considerable existing administrative support to complete the overwhelming amount of paperwork. The lengthy approvals process may now be discouraging the sole clinician or small clinical teams, many with valid and useful research ideas, from carrying out research.^{8, 13-17} Teams conducting trials for pharmaceutical companies, however, are unlikely to suffer, as their already existing infrastructure and private investment will still permit the completion of the lengthy approvals process. Independent trials, conducted in the public sector, however, will be jeopardised. Consequently, UK trial regulations will lead to an implicit bias in favour of research conducted by organisations with a commercial interest in the results of their research.

In the UK, a major problem with the implementation of the European Union Clinical Trials Directive¹⁴ is that there is no distinction made between clinical trials that are phase I (trials for drugs that have not previously been tested in humans and are not licensed) and phase IV (trials that simply assess effectiveness and safety of treatment for already licensed drugs). This means that a drug yet to be tested on humans is subjected to the same degree of scrutiny and regulation in the approvals process as a drug that is already fully licensed for its indication and may have been used for years for thousands of patients worldwide. Previously, an exemption could be made under the Clinical Trials of Marketed Products scheme so that full MHRA application was not necessary for phase IV trials. Correspondence with the MHRA disclosed that this exemption has been abolished as of 1 May 2004 and now every clinical trial conducted in the UK has to submit an application for full approval. The potential for such a requirement to impede publicly funded clinical trials has already been noted.¹⁴ Applying this "one size fits all" approach to all clinical trials might be damaging academic medical research, especially for trials that simply assess the effectiveness of already licensed drugs.³¹ In our example, LEEDS is a phase IV trial of two commonly used drugs, already tested and licensed for opiate detoxification. Clearly, the policy towards clinical trials needs to change, as all trials are now being treated as equal in terms of risk assessment. Comparisons of standard treatments represent a relatively low risk,⁹ whereas invasive procedures, radiation and untried drugs do not.³² The UK appears to have a clear example of over-regulation when treatments can be used interchangeably within clinical practice at the prescriber's discretion; yet, their formal comparison requires a lengthy application process. We suggest that the exemption clause is reinstigated for drugs already licensed for purposes for which they are being used in a trial.

More positively, specific research networks such as the Cancer Research Network,³³ the Mental Health Research Network³⁴ and the Prison Health Research Network³⁵ have been established to promote multicentre working and

collaboration. We welcome this approach, specifically the approach of the Mental Health Research Network, which is now able to provide the facilitation and administration skills necessary for completion of governance and ethics applications to member research teams in their network. This will considerably reduce the burden on separate research teams, as the applications processes will be completed by coordinators who are specialised in the governance and ethics process.

Finally, as researchers, we have reported our experience of what we consider to be a burdensome and duplicative application process. As our experience appears to be in keeping with those of others, we believe that it would be timely for the Department of Health to initiate a consultation exercise to explore how this process is now affecting clinical trials research within the UK. Such a consultation exercise would confirm our experience regarding the cumbersome over-regulated and wasteful current approvals process and provide opportunities for researchers to provide policy makers with recommendations for improvement for the benefit of everyone concerned.

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