*Clinical Medicine* 2010, Vol 10, No 2: 127–29

# How the NHS research governance procedures could be modified to greatly strengthen clinical research

Richard Haynes, Louise Bowman, Kazem Rahimi and Jane Armitage

**ABSTRACT – Randomised controlled trials are the gold standard for testing the efficacy and safety of health interventions, especially medications, and researchers in the UK are required to gain approval from ethics committees, the regulatory body (Medicines and Healthcare products Regulatory Agency) and local NHS research governance departments for such trials. Although research governance is important to reassure trial participants that their rights and interests are protected, current practice is impeding research and presents a genuine threat to the UK and to the NHS's ability to deliver high-quality evidence on which doctors can base clinical decisions and improve the delivery of care. This article discusses recent experience of running large-scale clinical trials and suggests measures that could improve the current situation.**

**KEY WORDS: clinical trials, regulation, research governance**

Randomised controlled trials (RCTs) are the gold standard for testing the efficacy and safety of health interventions, especially medications. Before an RCT can commence in the UK, researchers are typically required to gain approval from research ethics committees (RECs), the Medicines and Healthcare products Regulatory Agency (MHRA) and local NHS research governance bodies (via hospital or primary care trusts). Applications to the MHRA and RECs are well described and transparent, as well as constrained by timelines that both parties must adhere to. However, problems with these systems have been highlighted in a recent publication and subsequent correspondence.[1]

In contrast, the focus of this article is on the research governance approvals which are the third major approval required for an RCT. Research governance procedures are not streamlined, well coordinated or clearly thought through and this is a particular problem for multicentre studies. Research governance demands are inconsistent, often inappropriate and commonly very time consuming. These bureaucratic procedures, as currently interpreted, present a genuine threat to the UK and to the NHS's ability to deliver high-quality evidence on which doctors can base clinical decisions and improve the delivery of care. At a time when clinical research networks are trying to encourage and facilitate good quality research it is particularly unfortunate that trusts are making clinical trials so difficult. Unless these issues can be resolved, sponsors – both academic and commercial – will move the running of clinical trials to countries with more amenable regulatory environments; the trend that has started will accelerate. By highlighting particular areas that have caused problems, it is hoped that NHS policy makers will rethink some aspects of the research governance framework and take into consideration the problems encountered by researchers conducting multicentre studies.

It is accepted that within trusts research governance has an important role in overseeing clinical research, and ensuring that trial participants can be reassured that their interests are protected and that the research is scientifically and ethically valid. The problems arise when there is duplication of process between different bodies, slavish adherence to poorly understood rules and a lack of understanding of respective roles of sponsor and local site. Much of what follows is based on recent experience of running large academically-sponsored multicentre RCTs in the UK, two of which have started within the last few years.

The first RCT is a study conducted mainly by mail which uses general practice and hospital records to identify and invite potentially eligible patients to take part. In order to abide by current requirements this has necessitated seeking research governance approval from every primary care trust (PCT) in England, health board in Scotland and local health board in Wales, as well as over 40 acute hospital trusts. The second is a multicentre, hospital-based randomised trial for which local clinics are set up typically within hospital trusts and requires signed contracts, local staff being employed and space being provided. The research governance needs of these studies therefore are somewhat different.

## Pre-trial application procedures

Some welcome steps have recently been taken to rationalise the application process for research governance. In 2007 the site specific information (SSI) form was introduced which allows researchers to complete the application for local REC and research governance approval simultaneously and avoid duplication. In theory, it should be possible to submit a SSI form and a standard set of supporting documentation to a trust research and development (R&D) office for consideration. However, experience has been that many trusts still insist on completion of their own local forms despite the almost complete overlap with the SSI form. Furthermore, despite requiring evidence of ethics committee approval and clinical trial authorisation,

**Richard Haynes,** clinical research fellow; **Louise Bowman,** clinical research fellow; **Kazem Rahimi,** clinical research fellow; **Jane Armitage,** professor of clinical trials and epidemiology

Clinical Trial Service Unit, University of Oxford

© Royal College of Physicians, 2010. All rights reserved.

many R&D offices seek information about issues which have already been considered by the trial's multicentre REC and/or the MHRA and clearly do not fall under the remit of trust research governance. Resolving and explaining these issues can be very time consuming.

The Integrated Research Application System (IRAS) and National Institute for Health Research Coordinated System for Gaining NHS Permission (NIHR CSP) should also simplify the application process and it is hoped that it will be integrated into all trust research governance systems rapidly. Other encouraging developments are that some PCTs have grouped themselves into research consortia thus providing a single point of access for applications which each individual PCT then considers separately. More usefully still, some consortia provide a single decision-making body which members of the consortium sign up to. Both of these situations make it easier for researchers and provide a model which could be usefully employed more widely.

## No agreed timelines

Once an application has been accepted, however, there are no centrally agreed timelines for giving a decision. Whereas some trusts respond within days, others may take many months (Table 1) causing delays and costs. Similarly, when acute trusts are signing contracts for clinic-based studies, some respond rapidly to resolve outstanding issues and complete the process while others have allowed applications to drag on for months. With no nationally agreed timelines, researchers have no leverage to ensure timely consideration of applications. After submitting 55 applications to acute trust R&D departments over the last 18 months, the average time between submission of application and receipt of agreed signed contract was 3.8 months with the range being 0.8 to 9.0 months.

## Confusion over roles and responsibilities

The mail-based study was granted a site specific assessment (SSA) exemption by MREC because the local impact of the study was considered to be minimal and the requirement for local REC (LREC) approval was lifted. Local research governance approval was therefore being sought only to enable the identification and invitation of study participants. The rest of the study was conducted by the coordinating centre in direct contact with the participant and so local research governance has no clear role. Ideally such pre-research activity should not require R&D approval at all but definite guidance about this was not forthcoming at the time and so approval was sought. One consequence of the SSA exemption was that a local investigator was not required for the study in every trust. One particular trust refused to grant study approval simply because there was no local investigator, citing the lack of a local investigator as a reason to doubt that trial participants had the same rights to NHS care as any other patient, and that the presence of such an individual would allow participants to report disabling events which they would not be able to do in their absence (although the reporting mechanism for such events would be the same whether a local collaborator was present or not, ie direct to the coordinating centre).

In the same study, 10 R&D departments requested guarantees of continued funding throughout the entire study before granting approval, even though the study was fully funded at that time (being still only in the middle of the first grant period). RCTs may take many years to complete and funding agencies will typically only guarantee up to five years funding in one go. It is therefore not always possible to demonstrate that sufficient funding for the entire duration of the study is available at the beginning. One trust even went as far as to offer to approach the charity which was funding the trial to seek a guarantee of extended funding, clearly an extremely inappropriate course of action.

Following the unfortunate loss of confidential data by a number of government departments, research governance departments are now involving their information governance colleagues when considering applications. Trial applications are then considered by people with no particular knowledge of research governance or the system of approval which leads to inevitable delays and even refusal to allow studies to proceed. Indeed, one information governance department suggested that data transfer regulations were being contravened by asking patients to complete a questionnaire and return it in the post.

**Table 1. The distribution of time taken to inform the coordinating centre of the primary care trust (PCT) research governance opinion for applications sent in September 2007 to 71 PCTs.**

| Time from initial application to confirmed response | Number of PCTs (%) |
|---|---|
| <8 weeks | 15 (21) |
| 8–<16 weeks | 26 (37) |
| 16–<26 weeks | 16 (23) |
| ≥26 weeks | 14 (19) |

## Conditions of approval

R&D approval is often granted by means of a standard letter typically listing a number of conditions of approval. We have found these often include a requirement to report all adverse events (usually undefined in the letter) sometimes within 24 hours. Not only does the research governance framework not require this, but its inclusion demonstrates a total lack of understanding of the regulatory requirements for clinical trials and what sort of adverse events do or do not require reporting. They do not distinguish between 'serious' adverse events, which are precisely defined by the International Conference on Harmonisation of Good Clinical Practice (ICH GCP) standards, and 'non-serious' adverse events; nor between events


© Royal College of Physicians, 2010. All rights reserved.

attributed to the intervention (usually termed adverse reactions) and other events which might be just part of the disease process and therefore very common. Even if information was provided, the R&D department would not be aware of a participant's randomised treatment allocation, or the rate of events in other trial sites, and therefore the data are essentially un-interpretable, and the whole process is a waste of time and resources both for the researcher and the R&D department. In line with the ICH GCP and the Medicines for Human Use (Clinical Trials) Act 2004 (and subsequent amendments) reporting requirements are well defined and the monitoring of serious adverse events should be left to the trial sponsor and any independent Data Monitoring Committee who might review interim unblinded analyses of all events.

## Progress reports

After a trial has started it is typical to receive frequent requests from R&D offices to complete trial progress or monitoring forms. The latter type of form implies it is the R&D department's role to monitor the study, whereas the Medicines for Human Use (Clinical Trials) Act 2004 and the ICH GCP's guidelines make it clear that this is the responsibility of the trial's sponsor and monitors appointed by the sponsor. This may in part reflect the difference between a single-centre study for which the trust may be acting as sponsor, and multicentre trials when they are typically not the sponsor. Many R&D departments request trial progress reports every six months. The purpose of these is not clear and such requests considerably delay the progress of the trial by distracting the trial administrators from other aspects of running the study. Sponsors are already obliged to provide the ethics committee with annual progress and safety reports (which a minority of R&D departments will accept in lieu of their own report) and duplication of this seems unnecessary.

## Conclusion and recommendations

Although many of these points may seem trivial in isolation the combined effect is to consume substantial amounts of administrative time and money to resolve. Since budgets are always limited, costs incurred in this way require finding savings elsewhere. This will often impact recruitment leading to smaller and therefore less informative studies.

Rational research governance processes should be fully supported, and all those involved in developing policies are called upon to look at the highlighted areas.[2] Simple changes which would help include:

- ensuring that trusts use nationally recognised forms for applications
- imposing nationally agreed timelines for the handling of applications that are no longer than the present ones for MHRA and ethics committee applications
- recognising that externally sponsored, multicentre studies need to be handled differently from smaller internal studies for which the trust may have day-to-day responsibility
- ensuring that any requests for progress reports are necessary and not duplicating ethics committee or other reports
- ensuring that only relevant adverse events (eg suspected unexpected serious adverse reactions in a local patient) are subject to their reporting requirements and that copies of reports required by the MHRA and MREC would suffice.

The current system threatens to stifle clinical research in the UK, contrary to the current strategic aims of the MRC, NIHR and UK Clinical Research Network.[3–5] Clinical research has led to countless improvements in medical care (either by proving therapies to be effective or demonstrating the lack of efficacy, or even harm, of well-intentioned strategies), so preventing such research therefore poses a real risk to public health.

## References

1 Stewart PM, Stears A, Tomlinson JW, Brown MJ. Regulation – the real threat to clinical research. *BMJ* 2008;337:a1732.
2 Hackshaw A, Farrant H, Bulley S, Seckl MJ, Ledermann JA. Setting up non-commercial clinical trials takes too long in the UK: findings from a prospective study. *J R Soc Med* 2008;101:299–304.
3 Kielmann T, Tierney A, Porteous R *et al.* The Department of Health's research governance framework remains an impediment to multicentre studies: findings from a national descriptive study. *J R Soc Med* 2007;100:234–8.
4 Sheard L, Tompkins CN, Wright NM, Adams CE. Non-commercial clinical trials of a medicinal product: can they survive the current process of research approvals in the UK? *J Med Ethics* 2006;32:430–4.
5 Al-Shahi Salman R, Brock TM, Dennis MS *et al.* Research governance impediments to clinical trials: a retrospective survey. *J R Soc Med* 2007;100:101–4.

**Address for correspondence: Professor J Armitage, Clinical Trial Service Unit and Epidemiological Studies Unit, Richard Doll Building, Old Road Campus, Oxford OX3 7LF. Email: jane.armitage@ctsu.ox.ac.uk**

© Royal College of Physicians, 2010. All rights reserved.