

Research for Patient Benefit Programme

Director's Message No.5

Submitting Randomised Controlled Trials

March 2008

There was no explicit mention of randomised controlled trials (RCTs) in early presentations of examples of projects likely to be funded by the NIHR Research for Patient Benefit Programme (RfPB). At the planning stage, some argued that RCT proposals would be likely in the main to be out of scope - associated with knowledge generation, not with the applied focus of the programme. Others felt that a key feature of RfPB should be to offer opportunities to pursue applied health research capable of reducing uncertainty and generating patient benefit without necessarily meeting the acknowledged gold standard of RCT evidence. Many considered that within the constraints - a funding limit of £250,000 and a time frame of three years - it would just not be possible to conduct a definitive trial. RfPB would be a source for pilot work and perhaps for a limited number of small, local RCTs.

RfPB is unlikely to become a major source of funding for definitive trials given the relatively small size of the grants. However, RfPB is always likely to have RCTs in its portfolio. More than one third of the 52 projects from the first two competitions currently reaching final contract stage and being listed on the website involve RCTs. It is always helpful to consult this list and also gain a sense of the wider picture of health research opportunities and the place of RfPB within this before making an application. Many applications for RCTs, however, have not been successful. I initiated a conversation with four of the committee experts on clinical trials and statisticians to see what might be learned from experience across the first three meetings of the Programme in its ten regions and feedback to potential applicants.

Some proposals are ruled out at preliminary stage as basic science. It is crucial that all applicants understand the applied research remit of RfPB and the first in this series of Director's Messages was devoted to this topic. *Overambition* was identified as the overarching problem with many of the trials proposals that remained. Research teams, understandably perhaps, often want to go too far, too fast. Trials which require co-operation of multiple centres to recruit, or where outcomes require repeated measurement or measurement over a long time frame will not fit easily into the constraints. Pragmatic trials where the intervention is multifaceted or where usual practice is highly variable or unclear can generate doubt. Clearer arguments as to why the method fits the question help to avoid this. Committee members have often commented that an application for pilot work might have been a wiser strategy.

Many applications, however, were not over-complex or overambitious given the Programme rules. Here, five areas of questioning have been recurrent themes and between them have provided most of the reasons for rejection.

1. Is now the right time for a full-scale trial?

Have similar trials been conducted already, and if so, how convincing is the rationale for this one? Like other NIHR funders, RfPB committees like to see that a systematic review of the evidence has been conducted and that a trial has been identified as a research priority. (RfPB can also fund a systematic review as a project.) Perhaps, however, the

intervention is a complex one and requires several steps in its development. It may be, for example, that variability in clinician practice or differences in patient understandings of the intervention need to be explored in a qualitative study first. It may be that measures, recruitment strategies and acceptability of the randomisation process need piloting for their feasibility and robustness. It is always a plus for a trial design if evidence, for example, of likely recruitment rates and losses can be demonstrated. A revision of the MRC's guidance on complex interventions, first issued in 2000, is due for publication shortly, and will be particularly helpful on these matters.

2. Does this team have a real chance of success with an RCT?

The lead idea for an application to RfPB often comes from those providing and those receiving care. This is as it should be, but there is no reason to suppose that initiators will have detailed knowledge, for example, of the pros and cons of cluster randomisation, of CONSORT guidelines, of the principles of clinical equipoise, of open label trials and other such matters. Support and advice from trials methodologists is crucial. Research and Development Support Units, soon to become the new Research Design Service, are a first port of call. Much time can be saved with an early stage contact. There is now a national network of accredited Clinical Trials Units which may be able to help in designing and managing RCTs. Persuading researchers with a track record in this area to be co-applicants can strengthen things further. As one of the committee members pointed out: "It's a specific package of expertise, just like economics, statistics, etc." Statistical support is another essential. A last minute phone call to a statistician for a power calculation is unlikely to be enough.

At times, committee members have stressed the potential for bias where there is too little distance between the clinical team delivering an intervention and the conduct of the trial. One member gave a list of examples seen: randomisation processes that could too easily be subverted, lack of a truly independent assessment of outcomes, lack of an acceptably blind analysis and absence of independent oversight and accountability (more on this one below).

3. How well-defined is the intervention and the outcome?

Faced with RCT designs, committees have frequently found themselves criticising lack of clarity in the precise content of the intervention and insufficiently explained or poorly justified primary outcomes. Over-ambition often comes in here – applicants could often be more selective about the list of objectives and the array of outcomes if they are to stand a realistic chance of success. Opting for a trial at the wrong time (question 1) can also be a factor. But again it is vital that there are team members with an understanding of the debates which have taken place about complex interventions and that advice has been taken where necessary on the most up to date and relevant outcome measures.

4. Have common pitfalls concerning data collection and data analysis been addressed?

The majority of members on Regional Funding Committees are researchers themselves. They will look hard at the trial protocol. They will ask, for example, about eligibility criteria, examine how realistic a recruitment strategy is, whether the blinding strategies will work, and how far the team has thought through exactly how they will go about data analysis. Detail on all of these is crucial. A project can fall just as much on practicalities in this area as on technicalities.

"Research needs dedicated time," warned one of our committee members. He explained:

"If you rely on busy clinicians to do things like recruit, supply data, etc, when they already have a day job, you are asking for trouble. You need trial co-ordinators and research assistants whose job is to deliver aspects of your study - even if it is largely chasing those clinicians to sign the form, hand over data or whatever..."

He also suggested that applicants are often far too optimistic about matters such as numbers of patients with the condition who will be seen in the time frame, numbers really eligible, numbers willing, numbers concordant with the treatment, dropouts, loss to follow-up and so on.

5 Are the arrangements for trial governance satisfactory?

All research in the NHS is subject to the requirements of the Research Governance Framework as far as ethical approval and sponsorship are concerned, for example. Alongside this sits a highly developed regulatory framework for trials, including mandatory EU requirements. A drug trial, for example, requires MHRA authorisation before it can go ahead. It must have a monitoring committee able to check side effects and adverse events and with the power to bring the research to a halt. A detailed procedure must be brought into play to deal with any amendments to the protocol. There will also be an independently chaired steering committee. MRC trial guidance is one source for further detail on this. There is a growing debate about whether the full complexity of these arrangements is required for every RCT, including small-scale trials and trials, for example, of alternatives in service design. What is not in debate, however, is that governance arrangements should be spelled out and that the underlying issues of safety and risk for participants, and of potential bias in research procedures should be fully addressed. Here again, RDSUs and Clinical Trials Units should be able to help.

Those wishing to conduct programmes of trial work and large-scale trials will be more likely to look to the NIHR programme run by the NIHR Evaluation and Trials Coordination Centre including the new Efficacy and Mechanism (EME) Programme, launched in April 2008. The EME programme will be funded by the MRC and administered by the NIHR. Other funders include charities.

Finally, some readers will be asking where pilot work fits in all of this. That will be the subject of Director's Message No.6. To keep up to date with this and with the latest developments, visit www.nihr.ac.uk.

Acknowledgements

I would like to thank the following committee members who responded to a request for thoughts on pitfalls in RCTs they had seen for the RfPB programme and also offered comments on a draft of this Director's Message: Cindy Cooper, Graham Dunn, Paul Ewings and Ray Fitzpatrick. Comments on the text from Chairs and from Janet Darbyshire have also been helpful.

Professor Celia Davies