

MRC

Clinical
Trials
Series

Clinical trials for tomorrow
An MRC review of randomised control trials

2003

The importance of clinical trials

For more than 50 years the UK has led the world in the development of randomised controlled trials (RCTs). During that time the results of publicly funded RCTs have helped to avoid illness and early death in millions of people. For example, controlled trials led to the development of modern treatments for tuberculosis and HIV, new treatments for cancers, including dramatic improvements in the treatment of children with leukaemia, and the discovery that something as simple and widely available as aspirin reduces heart attacks and strokes.

What are randomised controlled trials?

Randomised controlled trials (RCT) are studies designed to compare two or more forms of healthcare intervention. These interventions may be drugs, medical devices, screening programmes, surgical procedures, physical and psychological therapies or a combination of these. They all need to be assessed as objectively as possible and compared with any alternative treatments. We need to find out which are the most effective, in which circumstances, and for which kinds of people and patients.

The most scientifically rigorous, unbiased way of comparing alternative healthcare interventions is through randomised controlled trials, in which people are chosen for one or other treatment using a process based on chance. This ensures that people assigned to receive the forms of care being compared will be as alike as possible. In this way, any subsequent differences in the health of the people in the comparison groups is likely to be due to the effects of the different treatments, rather than to differences between the individuals receiving the treatments.

Contents

Clinical Trials for Tomorrow – the review process	1
Key outcomes of the Review	2
Innovations in MRC funding of trials	4
Management of trials	6
Promoting public engagement	7
Conclusions – the way ahead	9
Acknowledgements	10
Review Panel members	10

Clinical Trials for Tomorrow

The Medical Research Council (MRC) has been supporting publicly funded randomised controlled trials (RCTs) for over sixty years, and remains the UK's largest public funder of these important studies. In January 2002, the MRC set up a review - Clinical Trials for Tomorrow - to consider its positioning as a funder of RCTs, both relative to other public sector and charity funders in the UK, and in the light of an important new initiative, the National Cancer Research Network, which has been established to promote and support cancer research. In addition, the Review offered an opportunity to take a fresh look at MRC's approach to the assessment, management and oversight of RCTs, particularly in the light of a rapidly evolving ethical and regulatory framework.

Wide-ranging consultation

Consultation was a key element of Clinical Trials for Tomorrow. We approached over 1000 organisations, groups and individuals, all of whom have an interest in publicly-funded trials and evidence-based approaches to healthcare. Each was invited to complete a questionnaire covering four key areas:

- The MRC's strategy on funding and prioritisation of trial.
- Issues relating to the design and delivery of trials.
- Challenges presented by early phase (safety and efficacy) trials.
- Ways of promoting consumer engagement and understanding.

The Public Health Resource Unit in Oxford analysed feedback based on a total of 221 questionnaires, and presented the results to the four subgroups of review panel for Clinical Trials for Tomorrow.

Based on this evidence, and on input from other experts in the field, the subgroups developed recommendations about how the MRC might improve its policy and approach to RCTs to meet the changing needs of participants, health professionals, researchers and various end users of research findings. The recommendations of the subgroups, supported by information from the MRC's clinical trials portfolio, were

then finalised by the full review panel before submission to the MRC Council in March 2003. The Council accepted the Clinical Trials for Tomorrow review panel's report in full, and agreed that its recommendations should become MRC policy. The following pages give details of many of the report's findings and of the new approaches that the MRC is adopting as a result.

Key outcomes of Clinical Trials for Tomorrow

Approaches to research

Encouraging challenging research

Over the past fifty years the MRC has supported a number of pivotal trials that have had major implications for the treatment of a diverse range of conditions. For example, cancer, cardiovascular disease, HIV and pre-eclampsia. The breadth of the range of areas we support will not change following Clinical Trials for Tomorrow. However, the MRC is keen to promote trials in areas that may pose methodological challenges, but in which the interventions studied could have an important impact on the public's health. The MRC will place particular emphasis on RCTs of complex interventions; for example, trials in which the interventions being assessed are intended to change the behaviour of patients or practitioners.

To help to promote this type of study, the Council is introducing a ring-fenced fund to support the developmental stages of RCTs (see below). Not only will this enable investigators to explore how the proposed intervention can be developed and delivered, but it will also provide information to inform subsequent applications for substantive studies. This innovation will help to put trials of complex interventions on a more even footing with those involving drugs, where relevant pharmacological information is usually already available.

Including qualitative research Randomised controlled trials provide the most reliable framework for obtaining unbiased estimates of the effects of new or existing healthcare interventions. The MRC will be continuing to support these important studies, but it believes that qualitative research has a potentially more important role to play than it has in the past. For example, qualitative research can help to understand the perspectives of participants and professionals involved in studies. The MRC believes that qualitative information should increasingly be used to improve the design, conduct and interpretation of RCTs. This might be particularly relevant when very different forms of intervention are being compared (surgery with physiotherapy, for example).

Trials in priority areas

RCTs have led to important discoveries about the effects of interventions for prevention, treatment and rehabilitation, but they can also help to promote a positive and proactive attitude towards evaluative research trials among health professionals and patients. The MRC's track record of support in the area of childhood leukaemia is an example of this. Following 'Clinical Trials for Tomorrow', the MRC Council has agreed to commit to long-term support for trials in one or two strategically important areas. There are a number of ways in which the MRC could provide such targeted support, but initially it will earmark special funds for pilot studies in the important area of mental health.

Making it easier for trialists to access NHS costs

When MRC trials are carried out in the National Health Service, the costs are split between the MRC and the NHS. The MRC is responsible for the costs of the research, while the NHS covers the costs of the treatments being compared, and the time of the practitioners who provide the treatments. The Department of Health makes about £40m available each year to underpin the costs of research in the NHS; part of this budget is expected to cover the NHS costs of clinical trials, which are often a major component of the

total package of support. However, accessing the NHS costs involves a complex process, particularly in the case of multicentre studies. Clinical Trials for Tomorrow made clear that this is a major issue for researchers, who feel that the system lacks transparency and is cumbersome and inefficient. The process also takes up large amounts of investigator time and effort and often delays the progress of research. The MRC has begun discussions with the Department of Health and other stakeholders to help to find solutions to these problems.

Incentives for health professionals to take part

There is little, or no, financial incentive for healthcare institutions to host publicly-funded trials. Trials can also mean extra work for the health professionals who deliver treatments to the people participating in RCTs. Following Clinical Trials for Tomorrow, the MRC will start a drive to raise the profile of clinical trials in the public healthcare sector, working directly with practitioners, and using its contacts in the Royal Colleges and training bodies. Our aim will be to promote a view that, when the relative merits of alternative forms of healthcare are not clear, offering patients the opportunity to participate in RCTs is an important professional responsibility, and should be recognised as such in staff appraisals. Clinical Trials for Tomorrow also highlighted the fact that the University Research Assessment Exercise could obstruct this aim, as it has done little to promote the collaboration among academic centres which is essential to address some important research questions. The review also showed the need for better communication between the MRC and the Chief Executives of NHS Trusts, for example, through more formal acknowledgement when a Trust has made a major contribution to an MRC study.

An MRC communications initiative headed by Sir Iain Chalmers will take forward this work, with the support of other public sector partners.

Innovations in MRC funding of trials

Trial development grants

In future the MRC will provide funding for discrete development studies (proof of concept, or early phase trials) to inform the preparation of applications for trials involving complex interventions. The MRC aims to make the application process as streamlined as possible, with quick response times, and will develop it in consultation with our independent Research Boards. It is likely that an initial annual budget of £250,000 will be set aside for this scheme.

Ensuring feasibility

Large controlled trials usually involve a significant long-term investment by the MRC. This means that for each trial that fails or requires additional financial support, the MRC loses the opportunity to support other, potentially more successful research projects. The most common reason for failure is poor recruitment or inability to retain participants. To help manage these risks and to ensure that partnership with participants in trials is put to the best possible use, the MRC is introducing a mandatory feasibility stage for all of the RCTs it funds.

As part of their applications, investigators will be required to provide a project plan showing key milestones, particularly recruitment and retention targets, and stating an early feasibility checkpoint. These indicators of progress will be agreed with applicants during the MRC's assessment of proposals. Researchers will report back to the MRC at the end of the feasibility stage. If the trial meets the agreed targets, it can proceed to the next stage. Failing studies will either be given an additional probationary period, or terminated, with a requirement that the data obtained should be archived.

Speeding up response

Many respondents in the Clinical Trials for Tomorrow consultation told us that the MRC took too long to make decisions about applications for support. Since 1997, applicants have had to submit an outline proposal for assessment by the MRC Trials Cross Board Subgroup. If the study is thought to have merit and be competitive at this stage,

the applicant is invited to submit a fully developed proposal. The aim of this approach has been to save applicants, referees and assessors time and effort by 'sifting out' studies that are unlikely to be funded. Between 50% and 75% of all applications are rejected at this initial stage. If an applicant is successful and invited to submit a full proposal, the MRC usually makes its final decision about 12 months after receiving the initial outline.

Despite the length of time to reach decisions, there is strong support for these arrangements, and they will continue to be the MRC's standard approach. Many investigators say that the current arrangements prevent wasted time and effort, and provide valuable feedback, which they can take into consideration when developing a full proposal. Some investigators, however, find the current timescale frustratingly long. A simple way of reducing it would be to allow applicants to submit full proposals, without going through the initial 'sift-by-outline' phase. The MRC has decided that applicants will be allowed to submit full proposals at the outset. This will not be our preferred route, however, and we will be taking steps to ensure parity in assessing the two types of application. The fact that one involves a more developed proposal at the initial assessment stage will not influence the MRC's decision about the potential value of the research.

Support with regulatory issues

Clinical Trials for Tomorrow showed that the increasingly complex regulations surrounding clinical trials have become a major disincentive for potential trialists. This is particularly the case for investigators who are not based at large trials units, which often have the infrastructure and resources needed to deal with regulatory matters. To help address this problem, the MRC plans to develop a central facility providing regulatory support to investigators. This support facility may be housed in the MRC Clinical Trials Unit in London; it may also have responsibility for training in good clinical trials practice.

Management of trials

The role of the Trial Steering Committee

Under the terms of the MRC Good Clinical Practice guidelines, each trial must have an independent Trial Steering Committee (TSC) to oversee the study. However, in practice, the TSC usually acts as an 'independent advocate' for the study. While this is understandable, given that TSC members give freely of their time, it can mean that the committee is not always able to make sufficiently objective decisions about the trial's feasibility, its continuing wider relevance, and whether it remains a good use of MRC resources. To promote clarity and the most effective use of limited resources, MRC is revising its guidelines about the role and remit of TSCs. As noted earlier, we will introduce feasibility checkpoints for all studies, to help ensure that the MRC supports trials that are likely to succeed in meeting their objectives.

Support and training for trial managers

Managing a clinical trial is a complex and challenging task and the experience and abilities of the trial manager can have a major impact on the success of a study. Because there is a shortage of suitably experienced, trained individuals for this role in the UK, the MRC set up a Trial Managers' Network some years ago, to help increase the numbers of well-trained trial managers. With support provided through the NHS Health Technology Assessment programme, the Network has recently been expanded to include Department of Health trial managers, and the MRC is developing plans for its further expansion. The Network will be coordinated from the MRC Clinical Trials Unit in London.

Promoting public engagement

The MRC is committed to involving patients (consumers) in all aspects of the clinical trials it funds. However, the Review has shown that the extent to which this has been achieved has differed greatly from trial to trial. In future the MRC will:

- Require applicants for funding to give details of the extent to which they will involve consumers, and why they think this level of involvement is appropriate for their study.
- Require applicants to agree at the beginning of the study how they will inform participants in a trial about its results.
- Encourage research on the effects of consumer involvement in clinical trials, so that evidence-based good practice guidelines about consumer engagement can be developed.
- Set up a communications and discussion forum on randomised controlled trials, involving patients, practitioners, researchers, and others. The forum will engage with the public and media to explore perceptions of RCTs, provide information about them, and raise their profile. With support from the Department of Health, the MRC has appointed Sir Iain Chalmers to take this initiative forward.

Conclusion and future challenges

Clinical Trials for Tomorrow leaves no doubt that the MRC's role in clinical trials remains as vital as ever. The Council has restated its commitment to this important area of research, which complements our investments in basic biomedical science. Clinical trials will therefore remain a key element in our funding strategy, and particularly those trials that address important questions in challenging areas of healthcare.

Focussing on quality at every stage

The response to our consultation during the Review has also helped to confirm that the MRC should continue to focus on supporting the highest quality research among the proposals submitted to it by investigators, rather than commissioning research, as other funders do. Although assessing quality has always been an essential part of the MRC funding application process, the Review has highlighted areas in which the MRC can help to promote quality throughout the life of trials. These include the introduction of a mandatory feasibility stage, with particular emphasis on recruitment and retention; revised guidelines for Trial Steering Committees; and improved support and training for trial managers through expansion of the Trial Managers Network.

Supporting trialists

The Review also identified a number of ways we can improve our services to trialists and help them cope with an increasing bureaucratic workload, for example, through:

- Provision of pilot funding.
- Faster decision-making about awards.
- Development of a central facility providing support with regulatory issues.
- Working with the Department of Health to improve trialists' access to NHS costs.
- Fostering better partnership working with the Health Departments and others.

Finally, as the ultimate objective of any trial is to provide patients with better options in healthcare, the MRC is committed to working with the public to promote understanding of and engagement with clinical trials. Not only will this help to ensure that RCTs address important questions successfully, it will also help the MRC's campaign to protect the future of publicly funded trials in the UK.

An issue that could have a major impact on the future of publicly funded clinical trials in the UK is the European Directive on Good Clinical Practice in Trials of Medicinal Products. Many of the Directive's proposed regulations may be appropriate for commercial trials of new drugs without marketing licences, but far less relevant for publicly funded trials. The latter often address important questions about whether new drugs offer any advantages compared with older drugs, the beneficial and unwanted effects of which are better known. In May 2003, an MRC-led steering group submitted its assessment of the impact of the Directive to the Medicine and Healthcare Products Regulatory Agency. The group set out its major concerns about the inflexibility of the Directive, which it felt could delay and sometimes prevent important publicly funded controlled trials.

The MRC decided that Clinical Trials for Tomorrow should not attempt to cover clinical trials in developing countries. These are an important component of the MRC's research portfolio, but they often present very specific logistical and ethical challenges. We plan to carry out a comparable exercise to Clinical Trials for Tomorrow, focussing on trials in developing countries, drawing on our experience of implementing the recommendations of this review.

Acknowledgements

We are very grateful to the many individuals, groups and organisations that contributed to the Clinical Trials for Tomorrow review.

Review Panel Members

Professor Alan McGregor (Chair), Kings College Hospital, London

Professor Genevra Richardson (Deputy Chair), Queen Mary & Westfield & MRC Council member

Sir Iain Chalmers, UK Cochrane Centre, Oxford (now James Lind Initiative)

Professor Ray Fitzpatrick, Oxford, MRC Health Services & Public Health Research Board & MRC Council member

Dr John Feussner, Veterans Administration, USA

Dr Yvonne Greenstreet, Clinical R&D, GlaxoSmithKline

Ms Ailsa Harrison, MRC Consumer Liaison Group

Professor Adrian Grant, Health Services Research Unit, Aberdeen

Professor Alessandro Liberati, Mario Negri Institute, Milan

Dr Paul Little, Primary Care, Southampton

Professor Ian Roberts, Epidemiology, London School Hygiene & Tropical Medicine (LSHTM)

Professor Kent Woods, Health Technology Assessment Programme, Department of Health.

Further information online

The Clinical Trials for Tomorrow consultation questionnaire:
www.....

Recommendations by the Review Panel:
www.....

Public Health Resource Unit analysis of the consultation: www
.....

MRC clinical trials portfolio analysis
.....