

MRC
*Clinical
Trials
Series*

MRC
**GUIDELINES FOR
GOOD CLINICAL
PRACTICE IN
CLINICAL TRIALS**

MRC
Medical Research Council

MRC GUIDELINES FOR GOOD CLINICAL PRACTICE IN CLINICAL TRIALS

This document provides guidelines for good clinical practice (GCP) in MRC trials. During 1998 it will be sent to all the Principal Investigators of MRC trials. The guidelines will be re-issued during 1999 incorporating necessary modifications from feedback received.

Trials sponsored by industry are required to follow the International Conference on Harmonisation's Good Clinical Practice Guideline (ICH GCP). However, there are many other funders of clinical trials in the public and charity sectors who will have an interest in maintaining standards of GCP in their trials. Clearly there is an opportunity to produce a single set of guidelines for this purpose and during 1998 the MRC will consult widely with these organisations with a view to agreeing a unified approach. The present document has already been drafted in close consultation with the NHS Research and Development Programme.

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ABOUT THE MEDICAL RESEARCH COUNCIL (MRC)

The MRC is the largest public sector organisation in the UK responsible for directly funding research relating to human health. It is funded mainly by the UK government, but is independent in its choice of which research to support. The aim of the MRC is to improve health by funding research across the spectrum of biomedical science. It supports research in three main ways: through its research establishments, via response-mode awards to universities and through training and career development awards. The competition for funds is vigorous and the portfolio of research supported, which has all been the subject of rigorous independent peer review, is therefore of high quality.

The MRC recognises the importance of the randomised controlled trial as the optimum methodology for assessing the effects of particular interventions on defined outcome measures. Its portfolio includes a large number of trials aimed at the assessment of health interventions used in the promotion of health, the prevention and/or treatment of disease and in rehabilitation or long-term care.

AIM OF THESE GUIDELINES

As a funder of research, the MRC needs to be assured that those who conduct research it has funded involving human participants agree to adhere to guidelines that safeguard study participants and ensure that the data gathered are of high quality. This needs to be done without destroying the essential element of trust that underpins all research funding, or adding a cumbersome layer of bureaucracy that stifles legitimate research activity. The guidelines are based on the thirteen principles laid down in the ICH Harmonised Tripartite Guideline for Good Clinical Practice agreed in May 1996¹.

The scientific integrity of the trial and the credibility of the data produced depend primarily on the trial design and not solely on the accuracy of the data collected. A properly randomised trial will ensure no foreknowledge of the random treatment allocations, no bias in patient management, unbiased outcome assessment, and no post-randomisation exclusions. The appropriateness and quality of the trial design will be carefully considered at the peer-review stage and this document does not attempt to provide detailed guidelines on trial design. However, it does provide guidelines on appropriate conduct of a trial to ensure the accuracy of the data gathered.

introduction

MRC GUIDELINES FOR GOOD CLINICAL PRACTICE IN CLINICAL TRIALS 1998

The Council expects that this framework for good practice will be implemented in all MRC-funded trials that involve human participants, including all trials involving medicinal products. MRC trials involving investigational medicinal products in which the resulting data are likely to be pivotal in a subsequent licensing application may also need to follow the ICH Guideline. Under these circumstances it is expected that there will be an industrial partner who will fund the extra costs involved.

SCOPE OF THESE GUIDELINES

Most MRC trials are large comparative studies of established therapies, but these guidelines are designed to be used in any prospective study involving human participants and the administration of a treatment or type of management, including diagnosis or the provision of lifestyle (eg, dietary) advice. However, the MRC also funds non-trial-research involving human participants and the detailed guidance contained in this document may be overly complex for the methodologies used in this type of research. The MRC is therefore drafting separate guidelines for this type of non-trial-research and decisions on which guidelines to follow will be made at the peer-review stage.

RESPONSIBILITY FOR THE CONDUCT OF MRC-FUNDED TRIALS

Most MRC trials are funded through grants awarded to host institutions (universities, medical schools, hospital trusts) in response to applications submitted by a principal investigator(s) (PIs) who has(ve) designed and will ultimately run the trial. This document details the responsibilities of those involved in MRC-funded trials, and provides guidelines on appropriate mechanisms to oversee the trial. A brief summary of their roles is given below.

The MRC Role - Before awarding a grant to support a trial, the MRC will ensure that: the proposed trial design is of the highest scientific quality; due consideration has been given to ethical and safety issues; the PI and Host Institution agree to conduct the trial to the standard of GCP; and appropriate arrangements for the day-to-day management and independent supervision of the study have been proposed. Once the trial is underway the MRC will monitor progress of the trial through consideration of annual reports and may wish to carry out random audits of individual studies.

The Host Institution Role - When a trial is funded through a grant, the organisation receiving the grant is known as the Host Institution. As the organisation in receipt of the funds for conducting the trial and as the employer of the PI, the Host Institution has a responsibility for ensuring that the trial is run to the highest standards as laid out in these guidelines. This responsibility is accepted by the Host Institution when it accepts the terms and conditions of the MRC award. Although the exact level of involvement will depend on the trial and the institution involved, it is expected that Department Heads and Deans of Medicine should ensure that the arrangements for trial management include an element of independent advice. In addition, and as a minimum, they should: a) be aware of trials run through their departments; b) be aware of progress in each of these trials; c) be aware of any problems and complaints associated with these trials; and d) work with the PIs and MRC to resolve these problems and complaints. For trials funded through MRC Units or Trials Offices, the MRC is the Host Institution.

The Principal Investigator's Role - The Principal Investigator has overall responsibility for the design, conduct, analyses and reporting of the trial.

The Investigator's Role - The Investigator has responsibility for the conduct of the trial in his/her participating centre.

Independent Supervision of the Trial - Arrangements for the management of trials will vary according to the nature of the study proposed. However, all should include an element of expert advice that is entirely independent of the Principal Investigators and the Host Institution involved. This will normally take the form of a Trial Steering Committee (TSC) and an independent Data and Monitoring and Ethics Committee (DMEC). It is recognised that these arrangements may not always be appropriate and structures may need to vary according to the nature of the study and the Host Institution involved. Thus, the arrangements for supervision should be detailed and justified in the trial proposal and the MRC should satisfy itself that these are appropriate in the light of the risks involved.

When TSCs and DMECs are appropriate:

The Trial Steering Committee Role - The role of the TSC is to provide overall supervision for the trial. It should also provide advice through its independent Chairman to the PI(s), the MRC and the Host Institution on all aspects of the trial. Involvement of independent members who are not directly involved in other aspects of the trial provides protection for both trial participants and PIs.

The Data and Ethics Monitoring Committee Role - The DMEC is the only body involved in the trial that has access to the unblinded comparative data. The role of its members is to monitor these data and make recommendations to the Steering Committee on whether there are any ethical or safety reasons why the trial should not continue. In addition, the DMEC may be asked by the TSC or MRC to consider data emerging from other related studies. If funding is required above the level originally requested, the DMEC may be asked by the PI, TSC or MRC to provide advice and where appropriate information on the data gathered to date in a way that will not unblind the trial. Membership of the DMEC should be completely independent of the PIs, TSC and Host Institution.

These guidelines are designed to be used by: MRC Officers and members of their Boards; Host Institutions in receipt of funding for clinical trials; members of Trial Steering and Data Monitoring and ethics committees; Principal Investigators and those involved in MRC-funded trials. They provide details of where responsibility for different aspects of trial conduct lie.

A statement acknowledging receipt of these guidelines and accepting the responsibilities laid out in them must be signed by a representative of the Host Institution and by the Principal Investigator before funds are made available.

1. GLOSSARY

1.1 Applicable Regulatory Requirements

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

1.2 Audit

A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.3 Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the Principal Investigator/co-ordinating centre on each trial participant.

1.4 Confidentiality

Prevention of disclosure, to other than authorised individuals, of a participant's identity.

1.5 Host Institution

University or hospital that is in receipt of a grant from the MRC for the purposes of running a trial. In the case of trials funded through MRC Units or Trials Offices the Host Institution will be the MRC itself.

1.6 Investigator

The person responsible for conducting a trial at one of the trial sites.

1.7 Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted and recorded in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.8 Multicentre Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

1.9 Principal Investigator(s)

The person(s) who is/are responsible for: a) initiating the trial by applying to the MRC for support; and b) conduct of the trial on a daily basis.

1.10 Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout these Guidelines the term protocol refers to protocol and protocol amendments.

1.11 Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

1.12 Quality Assurance (QA)

All those actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with these guidelines for Good Clinical Practice (GCP) and the applicable regulatory requirements.

1.13 Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.14 Randomisation

The process of assigning trial participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.15 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, **or**
- is a congenital anomaly/birth defect.

1.16 Sponsor

That person/organisation taking responsibility for the initiation, management and financing of a trial. Sponsorship of MRC trials is shared between the Principal Investigator (initiation and management) and the MRC (finance).

1.17 Participant/Trial Participant

An individual who participates in a clinical trial, either as a recipient of the investigational procedure or product(s) or as a control.

1.18 Trial Management Group

A group set up by the PIs to manage the trial on a day-to-day basis

1.19 Trial Site

The location(s) where trial-related activities are actually conducted.

1.20 Trial Steering Committee

A Committee formed to provide overall supervision for the trial. Membership should include one or two PIs, one or two independent experts and an independent Chair as well as observers from the MRC and Host Institution

2. THE PRINCIPLES OF GOOD CLINICAL PRACTICE FOR MRC-FUNDED TRIALS

The principles for Good Clinical Practice in MRC-funded trials are the same as those laid down in the ICH Harmonised Tripartite Guideline for Good Clinical Practice agreed in May 1996¹. However, the principles have been qualified to allow for exceptional circumstances pertaining to the nature of publicly funded research and the health system in the UK.

- 2.1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (appendix 1) and are consistent with GCP and the applicable regulatory requirement(s).
- 2.2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial participant and society. A trial should be initiated and continued only if the benefits justify the risks.
- 2.3. The rights, safety and well-being of the trial participants are the most important consideration and should prevail over interests of science and society.
- 2.4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed trial.
- 2.5. Clinical trials should be scientifically sound and described in a clear detailed protocol.
- 2.6. A trial should be conducted in compliance with the protocol that has received prior Ethical Committee favourable opinion.
- 2.7. The medical care given to, and medical decisions made on behalf of, participants should always be the responsibility of a qualified physician or, when appropriate, a qualified dentist.*
- 2.8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- 2.9. Freely given informed consent should be obtained from every participant prior to clinical trial participation**.

- 2.10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
- 2.11. The confidentiality of records that could identify participants should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- 2.12. Investigational products should be manufactured, handled, and stored in accordance with Good Manufacturing Practice (GMP)^{***}. They should be used in accordance with the approved protocol.
- 2.13. Systems with procedures that ensure the quality of every aspect of the trial should be implemented.

** In the UK there may be situations where it would be appropriate for other qualified health care professionals, such as midwives etc to be responsible for patient care.*

*** Situations do exist in which fully informed consent may not possible (eg emergency settings). In these cases, procedures agreed in existing guidelines (see text) should be followed, provided favourable opinion has been given by the appropriate independent ethics committee.*

**** Or the appropriate guidelines for the manufacture of medicinal products.*

3. THE MEDICAL RESEARCH COUNCIL

3.1 PEER REVIEW OF SCIENTIFIC, ETHICAL AND MANAGEMENT ARRANGEMENTS

- 3.1.1 The MRC procedures for peer-review of proposals for trials require that an application is submitted in a structured format (see Appendix 2) that ensures that all the information required to judge whether a trial will be conducted according to the principles detailed in 2 above will be provided. In peer reviewing the proposals for a new trial the MRC should satisfy itself based on the information available that:
- 3.1.2 The proposed trial is scientifically sound, designed to produce results which are sufficiently reliable for the purposes of the trial, clearly described and feasible
- 3.1.3 Any foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial participant and society and the benefits of the proposed trial justify the risks;
- 3.1.4 The principal investigator(s) are competent to undertake the proposed trial. The applicants for any proposed trial should be able to demonstrate an adequate track record appropriate to their role in the trial;
- 3.1.5 The proposals include details of the trial team that includes the key disciplines necessary for all aspects of the design and implementation of the trial, as well as the clear allocation of responsibilities within the trial;
- 3.1.6 Arrangements for the management of trials should include an element of expert advice that is entirely independent from the Principal Investigator(s) and the Host Institution. The model presented in these guidelines is for a Trial Steering Committee with an independent Chair and an independent Data Monitoring and Ethics Committee. However, it is recognised that the exact arrangements for supervision may need to vary according to the nature of the study, the Host Institution and the risks involved. Therefore, detailed arrangements for trial management should be presented as part of the proposal for funding and the MRC should satisfy itself that these are appropriate to the trial proposed;

- 3.1.7 The proposals include appropriate resources (including facilities) to conduct and complete (including adequate follow up) the research according to the trial protocol, and the monitoring of resource use during the trial;
- 3.1.8 The proposal details the availability of adequate and competent support staff and appropriate facilities for the duration of the trial;
- 3.1.9 The proposal states that all potential trial participants will be informed whenever possible of the possible benefits and known risks of the intervention (or of no intervention or a placebo) and of the possibility that there are unknown risks;
- 3.1.10 The proposal states that freely given informed consent will be sought from every participant prior to clinical trial participation whenever possible. When fully informed consent is not possible (eg, emergency settings), consent procedures should be fully justified, existing guidelines (referred to in 5.4.3) should be followed, and a favourable opinion from the appropriate ethics committee should be supplied;
- 3.1.11 Any necessary approval has been, or will be, obtained from the relevant ethical and regulatory bodies before the trial's implementation (see Note 1);
- 3.1.12 The publication policy proposed will report the results of the trial within an appropriate time scale of the findings being available and that adequate plans are in place to disseminate and implement the results of the proposed trial;
- 3.1.13 The time period proposed by the PI for retention of relevant trial documentation is appropriate.

3.2 AWARD OF FUNDS

If funding is agreed in principle by the MRC, the MRC ensures that the award will be contingent on:

- 3.2.1 A written undertaking being given by the Host Institution and Principal Investigator that they will conduct the trial in accordance with the general MRC terms and conditions of an award and these GCP guidelines.

Note 1: For multicentre trials involving five or more centres, the MRC will require proof of MREC approval. As detailed in these guidelines, it is the responsibility of the PI to ensure that LREC approval has been obtained before the trial is started in individual centres (see 5.5)

3.3 MONITORING AND AUDIT OF PROGRESS

Once the trial has started the MRC may:

- 3.3.1 consider reports from the Host Institution, TSC and DMEC when appropriate;
- 3.3.2 carry out a random audit of a number of randomly selected MRC-funded trials annually.

4. THE HOST INSTITUTION

- 4.1 As the organisation in receipt of the funds for conducting the trial and as the employer of the PI, the Host Institution has a responsibility to ensure that the trial is run to the highest standards as laid out in these guidelines. This responsibility is accepted by the Host Institution when it agrees to accept the terms and conditions of the MRC award. In particular the Host Institution must:
 - 4.1.2 ensure that the trial is conducted in accordance with the general MRC terms and conditions, these GCP guidelines and with the specified protocol, and according to the proposed schedule of resource use and the requirements of other relevant regulatory bodies;
 - 4.1.3 ensure that appropriate arrangements for the management of the research are in place. These should include an element of expert advice that is entirely independent from the PIs and the Host Institution itself. These arrangements will have been proposed by the PI and approved by the MRC. If these arrangements include a TSC, the MRC regards it as good practice for a representative of the Host Institution to be appointed as an observer on the TSC;
 - 4.1.4 make a commitment to maintain, for the trial's duration, the key disciplines for all aspects of the design and implementation of the trial;
 - 4.1.5 permit monitoring, auditing and inspection (see section 8 below);
 - 4.1.6 provide appropriate facilities for all the relevant documentation as laid out in section 7, to be kept for the appropriate period;
 - 4.1.7 ensure that a Report is submitted to the MRC annually.

- 4.1.8 It is expected that Department Heads and Deans of Medicine should as a minimum requirement: a) be aware of trials run through their departments; b) be aware of progress in each of these trials; c) be aware of any problems, complaints or claims associated with these trials; and d) work with the PIs and MRC to resolve these problems, complaints or claims. However, the level of direct involvement required from the Host Institution in any one trial may vary and will depend on the type of trial and the institution involved.
- 4.1.9 In the case of trials funded through MRC Units or Trials Offices the Host Institution will be the MRC itself.

5. THE PRINCIPAL INVESTIGATOR AND PARTICIPATING INVESTIGATORS

This section details the responsibilities of those involved in the running of the trial on a day-to-day basis. The practices detailed here should be followed by all those involved in the recruitment and follow-up of trial participants. With respect to multicentre trials, the Principal Investigator has overall responsibility for the conduct of the trial and this role is specified accordingly.

The Principal Investigator has overall responsibility for design of the proposed trial and co-ordination and the day-to-day management of the trial. The PI must ensure that: 1) the trial is run in accordance with these guidelines; and 2) all the investigators involved are aware and adhere to these guidelines.

5.1 TRIAL MANAGEMENT

- 5.1.1 The PI is responsible for the day-to-day running of all aspects of the trial and for managing the trial budget.
- 5.1.2 The PI should ensure that all the investigators involved in the trial conduct the trial in accordance with the proposal funded by the MRC and the specified final protocol (as approved by the TSC), and according to the proposed schedule of resource use as submitted in the original application.
- 5.1.3 The PI should ensure that all Participating Investigators are aware of their responsibilities as laid out in these guidelines and that the trial follows these guidelines in all the participating centres.

- 5.1.4 The PI should ensure that appropriate systems and procedures that assure the appropriate quality of every aspect of the trial are in place.
- 5.1.5 The PI should ensure that all the persons involved in implementing the protocol are adequately informed about the protocol, the nature of the intervention and their trial-related duties.
- 5.1.6 The PI should ensure that all trial-related functions are clearly defined, allocated and documented and that the responsibilities of participating investigators are clearly understood. It is good practice for the PI to produce a standard investigator agreement that lays out the terms and conditions of centre participation and is signed by the Participating Investigator.
- 5.1.7 The PI should ensure that clear lines of communication are established between investigators.
- 5.1.8 It is good practice for the PI to nominate a dedicated trial co-ordinator with clearly defined duties, in particular to ensure that recruitment targets are met.
- 5.1.9 The PI should manage the resources for the trial in a way that maximises the chances of the trial finishing within the available funding.
- 5.1.10 The PI should call meetings of the TSC (or the agreed alternative source of independent advice) when there are any matters arising from the conduct or management of the trial that might require their advice.
- 5.1.11 The PI should submit an annual report to the MRC. This should be endorsed by the TSC (or alternative source of independent advice).
- 5.1.12 The PI should ensure that, on completion of the study, the results are analysed, written up, reported and disseminated. All MRC trials should be registered at the time of approval and publication with a current trial register. Trials should be submitted to a peer-reviewed journal irrespective of the result of the trial.

5.2 COMPLIANCE WITH PROTOCOL

- 5.2.1 The trial should be conducted in accordance with the proposal funded by the MRC (and the protocol approved by the TSC) and favourably reviewed by the relevant ethics committees. It is the ultimate responsibility of the Principal Investigator to ensure that this happens. Any material amendments or alterations to or deviations from the protocol which affect the scientific or ethical basis of the trial, which could affect the personal integrity and/or welfare of trial participants, or which could have resource implications must have approval of the relevant ethics committees and the Trial Steering Committee (or the agreed alternative source of independent advice) before their implementation. The MRC should be notified of all material changes.

5.3 MEDICAL CARE OF TRIAL PARTICIPANTS

- 5.3.1 The current revision of the Declaration of Helsinki (Appendix 1) is the accepted basis for clinical trial ethics and must be known and implemented by those engaged in research involving human participants. The personal integrity and welfare of the trial participants is the ultimate responsibility of the doctor responsible for their care.
- 5.3.2 The medical care given to, and medical decisions made on behalf of, participants should always be the responsibility of a qualified doctor or, when appropriate, a qualified dentist or other qualified health care professional. It is the responsibility of the PI to ensure that the trial is organised in a way that ensures that appropriately qualified staff are responsible for patient care.

5.4 RESPECT FOR TRIAL PARTICIPANTS AND INFORMED CONSENT

- 5.4.1 The principles of informed consent in the current revision of the Helsinki Declaration (Appendix 1) and those laid out in the 13 principles at the beginning of this document should be implemented in all RCTs.
- 5.4.2 Whenever possible, all participants, or their representative(s), must give their consent to participate in the trial on the basis of appropriate information and with adequate time to consider this information and ask questions. The participant's consent to

participate should be obtained through signing an appropriate consent form and should be available, if necessary, for verification. Situations do exist in which fully informed consent is not possible (eg, emergency settings). In these cases, procedures agreed in the guidelines referred to in 5.4.3 should be followed after favourable opinion from the appropriate ethics committee. If any changes to the protocol are made (ref 5.2.1 above), then the need for changes to the patient information leaflet should be considered and, if appropriate, implemented without delay.

- 5.4.3 In the case of children up to the age of 18, mentally incapacitated individuals who cannot give full informed consent and the unconscious, particular considerations apply. The Council's guidance on these is set out in the relevant MRC Ethic Series publications². The Health Department, LREC and Royal College of Physicians Guidelines also cover these topics.
- 5.4.4 If the investigators are aware that participant samples or information for the trial may be used subsequently for other specific purposes beyond the aims of the current study, the participants' consent should also be obtained for such uses.
- 5.4.5 The participants, (or their representative(s)) must be made aware before consenting to participate that they are free to withdraw without obligation at any time and that such an action will not adversely affect any aspect of their care.
- 5.4.6 Appropriate information should be provided in a form which is readily accessible (see Note 2) and at a level which will enable an **informed** decision by the trial participants or their representative(s) regarding participation in the trial. It is good practice and can prove helpful to seek advice from consumers/lay people when drafting this information.
- 5.4.7 The written information about the trial that is to be provided to the participants will usually have been considered by the MRC as part of the overall assessment of the trial, and always by relevant ethics committees, and it is the responsibility of the Principal Investigator(s) to ensure that it is used as approved and that any necessary amendments are made without delay.

Note 2: Where necessary, patient information should be available in different languages to ensure that it can be clearly understood by all expected participants.

- 5.4.8 During the course of the trial results from related studies or interim results from the trial may become available. If these have implications for the ongoing trial, and following consultation with the TSC, the patient information should be changed and trial participants and collaborating investigators should be notified where appropriate. Where feasible, trial participants should also be notified of progress with the trial and the eventual outcome of the trial.
- 5.4.9 Participants and their GPs should be given a long-term contact point/ source of information about the trial.
- 5.4.10 It may be appropriate for the Principal Investigator(s) and/or the responsible clinician to inform other clinicians in contact with the participant of their participation in the trial, with appropriate information about relevant aspects of the study.
- 5.4.11 Participants should have access to information on the complaints procedure outlined in 6.10.1.
- 5.4.12 The participant should have access to information about the procedures for obtaining compensation and treatment following harm through negligence or non-negligence as a direct result of participating in the trial.

5.5 COMMUNICATION WITH LREC/MREC

- 5.5.1 The MRC has published its own ethics guidelines on aspects of research involving human participants and these should be applied generally in the context of all randomised controlled trials². The following publications are of particular relevance:
- Responsibility in investigations on human participants and material and on personal information
 - The ethical conduct of research on the mentally incapacitated
 - Responsibility in the use of personal medical information for research - principles and guide to practice
 - The ethical conduct of research on children
 - The ethical conduct of AIDS vaccine trials
 - Principles in the assessment and conduct of medical research and publicising results

5.5.2 All MRC support is contingent on approval being obtained from the relevant Multicentre Research Ethics Committee (MREC), where appropriate, and all Local Research Ethics Committees (LREC) from all Health Authorities in which the trial will be implemented. Centres can only begin recruiting when both the MREC and LREC approvals have been obtained.

5.5.3 Documentation of MREC approval should be submitted to MRC Head Office, and for multicentre trials should also always be available, along with LREC approval, for verification at the co-ordinating centre for the trial.

5.5.4 During the trial the PI should notify, and where necessary seek favourable opinion of, the appropriate MREC/LRECs and the MRC of any material modifications to the trial protocol and patient information leaflet.

5.6 INVESTIGATIONAL PRODUCTS

5.6.1 If investigational products are part of the trial intervention they should be manufactured, handled, and stored in accordance with the appropriate guidelines for the manufacture of medicinal products. They should be used in accordance with the approved protocol. Where appropriate, the PIs should seek advice from a suitably experienced pharmacist when planning the trial.

5.7 RANDOMISATION PROCEDURES

5.7.1 The PI should ensure that any randomisation procedures are rigorously designed, and identify any possible sources of bias. He/she should ensure that the randomisation procedures are rigorous and strictly controlled and adhered to by all the investigators. If the trial is blinded, investigators should promptly document and explain any premature unblinding.

5.8 SAFETY REPORTING

5.8.1 All serious adverse events (SAEs) should be reported to the trial co-ordinating centre in a timely manner in accordance with the protocol and reported regularly to the TSC and DMEC. Where appropriate, and in keeping with the applicable regulatory requirement(s) related to the reporting of serious adverse reactions, these should be reported to the regulatory authorities and, as appropriate, to ethics committees.

- 5.8.2 Clear procedures should be developed and implemented for the purpose of SAE reporting.

5.9 DATA HANDLING AND RECORD KEEPING

- 5.9.1 The primary objective of good data handling and record keeping is to ensure that data collected on participants in the trial are accurate and complete and unbiased with respect to the study treatment allocation. The procedures and documentation used to ensure that the data contained in the final clinical trial report agree with original observations should be made explicit by, and are the responsibility of, the PI and would normally require some degree of monitoring at the clinical site by the PI.
- 5.9.2 The PI should ensure that the Case Report Forms (CRF) are designed to capture the required data at all multicentre trial sites and that the information gathered is appropriate to the aims of the trial and will not adversely affect recruitment.
- 5.9.3 The PI should ensure that the procedures to be followed to ensure that the data are of high quality and accuracy at the point of collection and the integrity of the data during processing are set out. The level of clinical site monitoring necessary will vary from trial to trial and should be agreed between the PI and TSC.
- 5.9.4 All data and documentation associated with the trial should be readily accessible for independent inspection and validation (see below, Section 8). Ensuring such availability is the responsibility of the Principal Investigator.
- 5.9.5 The PI should take responsibility for drafting the annual report to the MRC in the format requested for approval by the TSC. The PI and Chairman of the TSC should approve and sign the final report of the trial.
- 5.9.6 It is essential that data on personal health are treated confidentially and held securely. Where such data are held on computer, the Data Protection Act places legal obligations on those who 'control' such data (eg, the local and principal investigators). In 1995 the EC issued a Directive³ which will be incorporated into UK law as a new Data Protection Act. The Council has issued guidance on the use of personal information in its Ethics Series.²

For NHS patients, DH guidance was updated in 1996⁴ and there is guidance from the DH and others (eg, the BMA⁵) on computer security systems⁶. These references give further information in a complex area, and new guidelines may follow new legislation in 1997/98.

- 5.9.7 The PI should ensure that data are recorded and stored in a way that ensures that they are: a) secure and cannot be tampered with, (eg, limited access, lock and key); and b) unlikely to be damaged (eg, appropriate environmental conditions).
- 5.9.8 The appropriate time period for which patient identification codes should be retained will vary depending on the nature of the study. The PI should justify the proposed retention period in the proposal to the MRC for agreement by the Board.

6. INDEPENDENT SUPERVISION OF THE TRIAL

6.1 INDEPENDENT ADVICE

- 6.1.1 Arrangements for the management of trials will vary according to the nature of the study proposed. However, all should include an element of expert advice that is entirely independent from the Principal Investigators and the Host Institution involved. This will normally take the form of a Trial Steering Committee and an independent Data and Monitoring and Ethics Committee. It is recognised that these arrangements may not always be appropriate and structures may need to vary according to the nature of the study and the Host Institution involved. Thus, the arrangements for supervision should be detailed and justified in the trial proposal and the MRC should satisfy itself that these are appropriate to the risks involved.

6.2 THE TRIAL STEERING COMMITTEE

6.2.1 Membership of Trial Steering Committee

Applicants should submit a proposal for membership for the TSC with their full application to the MRC who will agree the final membership. The membership should be limited and include an

independent Chairman (not involved directly in the trial other than as a member of the TSC), not less than two other independent members plus one or two Principal Investigators. Trial co-ordinators, statisticians etc. should attend meetings as appropriate. An observer from the MRC and Host Institution should be invited to attend all Steering Committee meetings.

6.3 Steering Committee Meetings

- 6.3.1 A meeting of the TSC should be organised by the PI before the start of the trial to approve the final protocol, which should then be sent to the MRC. After that the TSC should meet at least annually although there may be periods when more frequent meetings are necessary and maybe called either by the Chairman of the TSC or the PI. Responsibility for calling for and organising Steering Committee meetings lies with the Principal Investigators. However, there may be occasions when the MRC will wish to organise and administer these meetings for particular trials. Papers for meetings should be circulated well in advance of the meeting rather than tabled and an accurate minute of the meeting should be prepared by the PI and agreed by all members.

6.4 Data Monitoring

- 6.4.1 Applicants should submit their proposed arrangements for overseeing of the trial and for membership for the DMEC with their full application to the MRC, who will consider whether the proposed arrangements are appropriate to the trial and approve membership proposed. The Data Monitoring and Ethics Committee (DMEC) should be established to report to the TSC and when appropriate the MRC. Membership of the DMEC should be completely independent of the trial. Detailed terms of reference and guidance notes are given at annex 3. DMEC meetings should be called for and organised by the PIs with the DMEC Chair. However, attendance by Investigators or Principal Investigators at these meetings should only be at the invitation of the DMEC Chair.

6.5 Trial Steering and Management

- 6.5.1 The role of the TSC is to provide overall supervision of the trial and ensure that the trial is conducted to the rigorous standards set out in these MRC Guidelines for Good Clinical Practice. In particular, the TSC should concentrate on progress of the trial,

adherence to the protocol, patient safety and the consideration of new information. Day-to-day **management** of the trial is the responsibility of the investigators. The PI(s) may wish to set up a separate Trial Management Group to assist with this function.

6.6 Patient Safety

- 6.6.1 In all the deliberations of the TSC the rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society. The TSC should ensure that the protocol demands freely given informed consent from every trial participant. The TSC should look closely at the patient information provided and advise the investigators on its completeness and suitability.

6.6 Progress of the Trial

- 6.6.1 It is the role of the TSC to monitor the progress of the trial and to maximise the chances of completing it within the time scale agreed by the MRC. At the first TSC meeting, targets for recruitment, data collection, compliance etc. should be agreed with the PIs. These targets should not be "set in stone" but are designed to permit adequate monitoring of trial progress. The TSC should agree which data, based on the targets set, should be presented at each TSC meeting (template attached at appendix 3).
- 6.6.2 The PI is required to submit an annual report to MRC based on the template provided. This report should be endorsed by the TSC and should stand alone and contain sufficient data to allow the relevant MRC Board to judge progress in the trial without the need to refer back to the original grant proposal, and inform the MRC of any new information that has a bearing on safety or ethical acceptability of the trial or any significant complaints arising, with a justification of any decisions taken on the matter.
- 6.6.3 In exceptional circumstances, Council will consider proposals for the extension of grants for clinical trials. In these cases, the Boards will require evidence from TSCs that all practicable steps have been taken to achieve targets and keep within the agreed tenure of the grant. In these cases an analysis of the data collected to date that does not unblind the trial may be requested.

If progress of the trial suggests that an extension may be necessary, the TSC should notify MRC officers at the earliest opportunity.

6.7 Adherence to Protocol

- 6.7.1 The TSC should ensure that there are no major deviations from the trial protocol. A full protocol should be presented as an agenda item at the first TSC meeting. If the PIs need to make any material changes to the protocol during the course of the trial, approval should be sought from the TSC and the LREC/MREC and the MRC should be informed.

6.8 Consideration of New Information

- 6.8.1 The TSC should consider new information relevant to the trial including reports from the DMEC and the results of other studies. It is the responsibility of the PIs, the TSC Chairman and independent members of the TSC to bring to the attention of the TSC any results from other studies of which they are aware that may have a direct bearing on future conduct of the trial.
- 6.8.2 On consideration of this information, the TSC should recommend appropriate action, such as changes to the trial protocol, additional patient information, or stopping or extending the study. The rights, safety and well-being of the trial participants (present and future) should be the most important considerations in these deliberations.
- 6.8.3 It is the responsibility of the investigators to report regularly the extent of serious adverse events to the TSC and DMEC. In the case of unexpected SAEs, the Chairman of the TSC should be notified and, where appropriate, the regulatory authority.

6.9 Dissemination and Implementation of Results

- 6.9.1 The TSC should ensure that appropriate efforts are made to ensure that the results of the trial are adequately disseminated and due consideration is given to the implementation of the results into clinical practice.

6.10 Complaints Procedure and Compensation for Participants

- 6.10.1 The TSC should ensure that participants in a trial should have access to information that clearly explains that if they are unhappy with any aspect of the conduct of the trial they can

pursue their grievance by taking the matter up with the clinician responsible for their care. Following this, if the problem remains unresolved, they should take it up with the authority responsible for their care. In some circumstances they may wish to take it up with the Chairman of the Trial Steering Committee and, if there is still no resolution, the Chief Executive of the MRC.

6.10.2 The MRC as funder of a trial accepts responsibility for its sponsorship of the trial, and as such would give sympathetic consideration to claims for any non-negligent harm suffered by individuals as a result of participating in the trial. (This would not extend to non-negligent harm arising from conventional treatment where this is one arm of a trial.) Like other publicly funded bodies, the Council is unable to insure and thus cannot offer advance indemnity cover for participants in MRC-funded studies.

6.10.3 Where studies are carried out in a hospital, the hospital continues to have a duty of care to the patient being treated within that hospital, whether or not that patient is participating in an MRC-supported study. Therefore the MRC does not accept liability for negligence on the part of employees of, or staff engaged by, hospitals. This applies whether the hospital is an NHS Trust or not. The MRC cannot be held liable for any breach in the hospital's duty of care.

7. DOCUMENTATION

7.1 The documentation for the trial relates to all records in any form describing the methods and conduct of the trial, factors affecting the trial and action taken. These include, as appropriate, all versions of the protocol and agreed amendments, copies of submissions and approvals from relevant authorities and ethics committees, consent forms, monitor reports, audit reports, relevant letters, reference ranges, raw data such as laboratory reports etc, completed case report forms and the final report. Documentation of the ethics committee approval for the conduct of the trial should be retained by the PIs. In multicentre trials, this may be co-ordinated centrally. Similarly, evidence of informed consent should be available for verification. Written procedures for the scientific basis, design,

conduct, organisation and verification of all trials are required. This should be the ultimate responsibility of the Principal Investigator. For those trials using medicinal products where it is clear at the start of the trial that the data may be required for a licensing application, the documentary requirements outlined in the ICH GCP Guideline should be followed. In the majority of MRC trials, in which this is not the case, the actual requirements will vary according to the trial, the type of intervention and whether or not medicinal products are involved. Appendix 4 provides guidance on the retention of key documentation under these circumstances.

- 7.2 The scientific basis of the trial will usually be in the form of a clear and concise protocol which will also include information on the design, conduct and organisation of the trial. Many of these issues will have been considered in the original proposal for the trial which was submitted for funding. The application procedure for MRC funding for trials now requires submission of full proposals in a structured proforma. Full details are given at appendix 2
- 7.3 The case report form is the record of the relevant information and data collected during the trial on each participant in the trial as defined by the protocol. The level of detail of information recorded will be defined by the trial in question, with the fundamental principle being to ensure the collection of adequate, relevant and accurate data which are not excessive in quantity and/or detail. Often data are collected on each patient unnecessarily and the quality of the recorded data can be adversely affected as a consequence. In addition, particularly for multicentre trials, collection of excessive data can seriously discourage collaboration and jeopardise the trial overall by undue complication of the trial procedures (while also wasting limited resources). Copies of case report forms after completion should be stored centrally and, if required, should be available for verification. This is the responsibility of the Principal Investigator, who should ensure that these records are retained for the period agreed by the MRC.

8. QUALITY ASSURANCE AND AUDIT

- 8.1 In order to reassure itself of the reliability of the data gathered and the ethical conduct of its trials, the MRC may audit a randomly selected number of MRC-funded trials.
- 8.2 Audits will be carried out by individual(s) entirely independent of the trial and the MRC will define the level of audit required on a case-by-case basis depending on the nature of the trial concerned.
- 8.3 Reports of the audits will be reviewed by the MRC and, if necessary, by the relevant Research Board. Principal Investigators will be given the opportunity to comment on the audit before it is passed on to the relevant Board or TSC. Copies of the reports, together with the comments of the PIs and assessment by the MRC/Board, will be made available to the Principal Investigator and, where relevant, Chairmen of the Steering and Data Monitoring Committees.

REFERENCES

1. International Conference on Harmonisation (ICH) guideline (1996)
2. MRC Ethics Series: Grants and Training Awards: Terms and Conditions of Award
 - Responsibility in investigations on human participants and material and on personal information
 - The ethical conduct of research on the mentally incapacitated
 - Responsibility in the use of personal medical information for research – principles and guide to practice
 - The ethical conduct of research on children
 - The ethical conduct of AIDS vaccine trials
 - Principles in the assessment and conduct of medical research and publicising results
3. EC Directive on Data Protection (1995)
4. The Protection and Use of Patient Information. Department of Health (1996)
5. Security in Clinical Information Systems. British Medical Association (1996)
6. The NHS Security Reference Manual. NHS (1996)

DECLARATION OF HELSINKI

Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects.

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and amended by the 29th World Medical Assembly, Tokyo, Japan October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983 and the 41st World Medical Assembly, Hong Kong, September 1989 and in South Africa, October 1996.

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subjects must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of his official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with the national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I.2.).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (NON-CLINICAL BIOMEDICAL RESEARCH)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

MRC PROFORMA APPLICATION FORM

MRC CONTROLLED TRIALS 1997 -1998

PROFORMA FOR FULL PROPOSALS

Please structure Annex 1 of your application form using the headings listed below

- Please make an entry under every heading
- Do not exceed 9 sides of A4 (10 point)

1 FULL TITLE OF TRIAL

- 1.1 ACRONYM (only if applicable – this is not a requirement)
- 1.2 CONTACT APPLICANT (name, address, tel, fax, e-mail)

2 THE NEED FOR A TRIAL

- 2.1 WHAT IS THE PROBLEM TO BE ADDRESSED?
- 2.2 WHAT IS THE HYPOTHESIS TO BE TESTED?
- 2.3 WHY IS A TRIAL NEEDED NOW?
- 2.4 HAS A SYSTEMATIC REVIEW BEEN CARRIED OUT AND WHAT WERE THE FINDINGS?
- 2.5 HOW WILL THE RESULTS OF THIS TRIAL BE USED?
(eg, inform clinical decision making /improve understanding)
- 2.6 PLEASE DETAIL ANY RISKS TO THE SAFETY OF PARTICIPANTS INVOLVED IN THE TRIAL

3 THE PROPOSED TRIAL

- 3.1 WHAT IS THE PROPOSED TRIAL DESIGN?
(eg, randomised or observational, open, double or single blind-
ed, etc)
- 3.2 WHAT ARE THE PLANNED TRIAL INTERVENTIONS?
(both experimental and control)
- 3.3 WHAT IS THE PROPOSED DURATION OF TREATMENT PERIOD?
- 3.4 WHAT ARE THE PLANNED INCLUSION/EXCLUSION CRITERIA?

- 3.5 WHAT ARE THE PROPOSED OUTCOME MEASURES?
PRIMARY:
SECONDARY:
- 3.6 WILL HEALTH SERVICE RESEARCH ISSUES BE ADDRESSED?
(Please justify inclusion/exclusion of health economics and quality of life measures. If these measures are to be included full details should be given including power calculations)
- 3.7 WHAT IS THE PROPOSED FREQUENCY /DURATION OF FOLLOW-UP?
- 3.8 HOW WILL THE OUTCOME MEASURES BE MEASURED AT FOLLOW-UP?
- 3.9 WHAT ARE THE PROPOSED PRACTICAL ARRANGEMENTS FOR ALLOCATING PARTICIPANTS TO TRIAL GROUPS?
(eg, Randomisation Method)
- 3.10 WHAT ARE THE PROPOSED METHODS FOR PROTECTING AGAINST OTHER SOURCES OF BIAS? (eg, blinding or masking)
- 3.11 WHAT IS THE PROPOSED SAMPLE SIZE AND WHAT IS THE JUSTIFICATION FOR THE ASSUMPTIONS UNDERLYING THE POWER CALCULATIONS?
(include both control and treatment groups, a brief description of the power calculations detailing the outcome measures on which these have been based, and give event rates, means and medians etc as appropriate)
- 3.12 WHAT IS THE PLANNED RECRUITMENT RATE?
- 3.13 ARE THERE LIKELY TO BE ANY PROBLEMS WITH COMPLIANCE?
- 3.14 WHAT IS THE LIKELY RATE OF LOSS TO FOLLOW-UP?
- 3.15 HOW MANY CENTRES WILL BE INVOLVED?
(details can be given on the final sheet)
- 3.16 WHAT IS THE PROPOSED TYPE OF ANALYSES?
- 3.17 WHAT IS THE PROPOSED FREQUENCY OF ANALYSES?
- 3.18 ARE THERE ANY PLANNED SUBGROUP ANALYSES?
- 3.19 HAS ANY PILOT STUDY BEEN CARRIED OUT USING THIS DESIGN?

4 TRIAL MANAGEMENT

- 4.1 WHAT ARE THE ARRANGEMENTS FOR DAY-TO-DAY MANAGEMENT OF THE TRIAL? (eg, randomisation, data handling, and who will be responsible for co-ordination)
- 4.2 WHAT WILL BE THE RESPONSIBILITIES OF THE APPLICANTS? (Please give below details of the roles of the named applicants).
- 4.3 WHAT WILL BE THE RESPONSIBILITIES OF THE STAFF EMPLOYED ON THE GRANT? (Please give below details of the roles of the staff requested on the grant).
- 4.4 WHAT WILL BE THE ROLES OF THE NAMED COLLABORATORS? (Please give below details of the roles of the named collaborators).
- 4.5 WHO IS THE TRIAL STATISTICIAN?
- 4.6 TRIAL STEERING COMMITTEE (Please give names and affiliations of the proposed trial steering committee to include – independent Chairman, independent members, principal investigators – see guidance notes)

5 FINANCIAL DETAILS OF THE TRIAL?

Please complete the financial sections of the application form as normal.

In addition in the body of the application form please provide the following information:

- 5.1 Financial Summary (please summarise the total cost of the trial in a table)

| Year | 1997/98 | 1998/99 | 1999/2000 ^(etc) | TOTAL |
|-----------------------|---------|---------|----------------------------|-------|
| Research Costs | | | | |
| Treatment Costs | | | | |
| Service Support Costs | | | | |
| TOTAL | | | | |

NB Please see the note on NHS service support in the attached guidelines and the summary of definitions

- 5.2 Justification for support requested (Please give full justification for the resources requested (excluding those described under 4.3 above).

TRIAL STEERING COMMITTEE (TSC)

It is MRC policy that for all its trials a Trial Steering Committee (TSC) should be set up with the following terms of reference:

A) TERMS OF REFERENCE

1. to monitor and supervise the progress of the trial [“title of trial”] towards its interim and overall objectives;
2. to review at regular intervals relevant information from other sources (eg, other related trials);
3. to consider the recommendations of the Data Monitoring and Ethics Committee;
4. in the light of 1, 2 & 3, to inform the Council and relevant Research Boards on the progress of the trial;
5. to advise Council on publicity and the presentation of all aspects of the trial.

B) MEMBERSHIP

Applicants should submit a suggested membership with their full application. The relevant Board(s) will decide on the final membership of the TSC. The membership should be limited and include an **independent** Chairman (not involved directly in the trial other than as a member of the TSC), not less than two other independent members and one or two Principal Investigators. Where possible membership should include a lay/consumer representative. Trial co-ordinators, statisticians etc should attend meetings as appropriate. Observers from the MRC and Host Institution should be invited to all meetings.

C) GUIDANCE NOTES

Meetings

A meeting of the TSC should be organised by the PI before the start of the trial to finalise the protocol, which should then be sent to the MRC. After that the TSC should meet at least annually although there may be periods when more frequent meetings are necessary. Meetings should be called for organised by the PI. Papers for meetings should be circulated well in advance of the meeting rather than tabled and an accurate minute of the meeting should be prepared by the PI and agreed by all members.

Trial Steering and Management

The role of the TSC is to provide overall supervision of the trial on behalf of the MRC. In particular, the TSC should concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information. Day-to-day **management** of the trial is the responsibility of the Principal Investigators. The Principal Investigators may wish to set up a separate Trial Management Committee to assist with this function.

Patient Safety

In all the deliberations of the TSC the rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society. The TSC should ensure that the protocol demands freely given informed consent from every trial participant. The TSC should look closely at the patient information provided and advise the investigators on its completeness and suitability.

Progress of the Trials

It is the role of the TSC to monitor the progress of the trial and to maximise the chances of completing the study within the time scale agreed by the Board. At the first TSC meeting, targets for recruitment, data collection, compliance etc. should be agreed with the investigators. These targets should not be "set in stone" but are designed to act as a gauge of trial progress. The TSC should agree a set of data, based on the targets set, that should be presented to each TSC (template attached).

The PI is required to submit an annual report to Council based on the standard template attached. This report should be endorsed by the TSC and should be **stand alone** and contain sufficient data to allow the relevant Research Board to judge progress in a trial without the need to refer back to the original grant proposal and inform the MRC of any new information that has a bearing on safety or ethical acceptability of the trial or any significant complaints arising, with a justification of any decisions taken on the matter.

In exceptional circumstances, Council will consider proposals for the extension of grants for clinical trials. If progress on the trial suggests that an extension may be necessary, the TSC should notify MRC officers at the earliest opportunity (for a large study it may take a year before approval of further funding can be given). In these cases, the Boards will require evidence from TSCs that all practicable steps have been taken to improve recruitment and keep within the agreed duration of

the grant. In these circumstances the DMEC should be asked to advise the TSC and may be required to provide information on the availability of data collected to date (from this and other studies) and advice on the likelihood that continuation of the trial will allow detection of an important effect. This should be done using methods that do not unblind the trial.

Adherence to Protocol

The full protocol should be presented as an agenda item at the first TSC meeting to be agreed. If the investigators need to make any changes to the protocol during the course of the trial, approval should be sought from the TSC, LREC/MREC and, if necessary, the MRC.

Consideration of New Information

The TSC should consider new information relevant to the trial including reports from the DMEC and the results of other studies. It is the responsibility of the PI and the Chairman and other independent members of the TSC to bring to the attention of the TSC any results from other studies that may have a direct bearing on future conduct of the trial.

On consideration of this information the TSC should recommend appropriate action, such as changes to the trial protocol, additional patient information or stopping of the study. The rights, safety and well-being of the trial participants should be the most important considerations in these deliberations.

It is the responsibility of the investigators to notify the TSC and DMEC and relevant regulatory authority (if applicable) of any unexpected serious adverse events during the course of the study.

Data Monitoring and Ethics Committee

The TSC should, at its first meeting, establish a Data Monitoring and Ethics Committee (DMEC) that meets regularly to view the data and the results of any interim analyses. The terms of reference and guidelines for DMECs are attached. Members should be independent of both the trial and TSC.

MRC GCP

The TSC should endeavour to ensure that the trial is conducted at all times to the rigorous standards set out in the MRC Guidelines for Good Clinical Practice.

CLINICAL TRIALS FUNDED BY THE MRC

DRAFT TEMPLATE FOR STEERING COMMITTEE AGENDAS AND REPORTS

The Medical Research Council requires that independent Steering Committees are set up for every major trial it funds and that these committees should meet at least once a year and submit a report to the relevant Research Board. Presented below are guidelines on the information that should be provided by triallists for discussion at Steering Committee meetings and included in the Steering Committee's annual report. It is suggested that the headings listed below should provide a basis for the agenda of the meetings and form the template for the report. These headings may not be appropriate at every stage of an individual trial or for all trials.

| | Target (date target set) | Achieved (date achieved) |
|---|-----------------------------|-----------------------------|
| 1) Name of Trial | | |
| 2) Grant No. | | |
| 3) Sample size sought | | |
| 4) Date recruitment started | | |
| 5) Proposed date for recruitment end | | |
| 6) Actual recruitment rate versus target rate (by month/quarter) | | |
| 7) Acceptance rate, as a proportion of i) those invited to participate and ii) if known all eligible participants | | |
| 8) Quarterly/monthly forecasts of recruitment for the planned remainder of the trial | | |

| Target (date target set) | Achieved (date achieved) |
|--|-----------------------------|
| 9) Losses to follow-up, i) as a proportion of those entered, and ii) per month/quarter | |
| 10) No. for whom follow-up has been completed successfully (or still being successfully followed-up) | |
| 11) Completeness of data collected | |
| 12) Any available results (pooled) | |
| 13) Any organisational problems | |
| 14) Issues specific to individual trials (to be specified by the Steering Committee) | |

DATA MONITORING & ETHICS COMMITTEE (DMEC)

A) TERMS OF REFERENCE

1. to determine if additional interim analyses of trial data should be undertaken
2. to consider the data from interim analyses, unblinded if considered appropriate, plus any additional safety issues for the trial [“title of trial”] and relevant information from other sources
3. in the light of 2., and ensuring that ethical considerations are of prime importance, to report (following each DMEC meeting) to the Trial Steering Committee and to recommend on the continuation of the trial
4. to consider any requests for release of interim trial data and to recommend to the TSC on the advisability of this
5. in the event of further funding being required, to provide to the TSC and MRC appropriate information and advice on the data gathered to date that will not jeopardise the integrity of the study.

B) MEMBERSHIP

The membership should be proposed as part of the proposal to the MRC and approved by the Board.

Members

The membership of the DMEC will usually be small: *3-4 members and the members will be independent;

* expert(s) in the field (eg, clinician with experience in the relevant area)

*expert trial statistician(s)

Invited to attend

The trial statistician may be invited to attend for part of the DMEC meeting to present the most current data from the trial, unblinded if appropriate.

c) GUIDANCE NOTES

- The DMEC should meet at least annually, or more often as appropriate, and meetings should be timed so that reports can be fed into the Trial Steering Committee (TSC) meetings. Meetings should be called for and organised by the Principal Investigator of the trial in association with the Chairman of the DMEC. Dates for DMEC meetings should be agreed in advance and only altered with agreement of all members. All significant communications between the Principal Investigators and the DMEC should be in writing, or if they have to be oral, they should be backed up by written records.
- The role of the DMEC is to look at the [unblinded] data from an ethical standpoint, the safety, rights and well being of the trial participants being paramount.
- The PIs (normally the trial statistician) should prepare a comprehensive report for the DMEC. This should be prepared and circulated well in advance of the meeting to allow DMEC members time to study the data. Content of the report should be agreed in advance with the DMEC Chairman. The trial statistician may be invited by the Chairman to attend part of the meeting to present the data; otherwise, no one involved with the trial or TSC should be present to see the unblinded data.
- A full confidential report should be made in writing by the Chairman of the DMEC providing advice to the Trial Steering Committee (and PI) on whether the trial should continue or not. If the the DMEC recommends that the trial should be stopped at any point, the funding body should be notified. It will be the responsibility of the TSC to decide whether or not to act upon the information received from the DMEC.
- If at any stage an extension to the grant is needed the DMEC may be requested by the Board to provide information on the data gathered to date (from this and other studies) and advice on the likelihood that continuation of the trial will allow detection of an important effect. This should be done using methods that do not unblind the trial.

Before reporting on the results of the trial the DMEC will consider not only the interim results as presented by the trial statistician, but also any major new information from other sources thought to be relevant to the trial. It follows that the DMEC will not automatically follow pre-assigned statistical rules, although it will be guided by statistical considerations.

- Information provided by the DMEC is likely to fall into the following categories:
 - (a) Information that might lead to the TSC stopping the trial prematurely in the event of a clear outcome, if this is deemed to be appropriate in the light of the accumulating data from the study, or on the basis of information available from other sources;
 - (b) Information that might lead to the TSC modifying the design of the trial, if this is deemed to be appropriate in the light of the accumulating data from the study, or on the basis of information available from other sources.

ESSENTIAL DOCUMENTS THAT SHOULD BE HELD BEFORE THE CLINICAL PHASE OF THE STUDY BEGINS

For those trials using medicinal products where it is clear at the start of the trial that the data may be required for a licensing application, the documentary requirements outlined in the ICH GCP Guideline should be followed. In the majority of MRC trials in which this is not the case the actual requirements will vary according to the trial, the type of intervention and whether or not medicinal products are involved. The table below provides guidance on the retention of key documentation under these circumstances.

| Document | Principal investigator/ coordinating centre | Participating investigator | MRC |
|--|--|-------------------------------|------------|
| Final protocol, including <ul style="list-style-type: none"> • Patient information • Consent form • Case record forms • Instructions on handling trial product | Yes | Yes | Yes |
| Investigator agreement on final protocol (Participation form or Agreement) | Yes | - | - |
| Investigator's Brochure | If applicable | If applicable | - |
| Local variation on <ul style="list-style-type: none"> • Patient information • Consent form • Advertising | yes | yes | - |
| Ethics approval and composition of committee | Yes (MREC) | Yes (LREC) | Yes (MREC) |
| CTX approval | If applicable | If applicable | - |
| Investigator's qualifications (CV) | Yes (known consultant/GP post acceptable) | Yes | - |
| List of Investigators | Yes | Yes | - |
| List of pharmacy contacts | If applicable | If applicable | - |
| Normal Ranges | If applicable | If applicable | - |
| List of signatures | If applicable | If applicable | - |
| Sample label | If applicable | If applicable | - |

ESSENTIAL DOCUMENTS THAT SHOULD BE HELD ONCE CLINICAL PHASE OF THE STUDY HAS BEGUN

For those trials using medicinal products where it is clear at the start of the trial that the data may be required for a licensing application, the documentary requirements outlined in the ICH GCP Guideline should be followed. In the majority of MRC trials, in which this is not the case, the actual requirements will vary according to the trial, the type of intervention and whether or not medicinal products are involved. The table below provides guidance on the retention of key documentation under these circumstances.

| Document | Principal investigator/ coordinating centre | Participating investigator | MRC |
|---|--|-------------------------------|-----|
| Protocol revisions: | Yes | Yes | Yes |
| <ul style="list-style-type: none"> ● Amendments ● Case record forms ● Patient information ● Case record forms | | | |
| Ethics approvals necessary for any protocol revision | Yes | Yes | Yes |
| Investigator's Brochure: | Yes | Yes | – |
| <ul style="list-style-type: none"> ● Any updates | | | |
| New investigator's qualifications (CV) | Yes (known consultant/GP post acceptable) | Yes | – |
| List of new investigators | Yes | – | – |
| Changes to normal ranges | If applicable | If applicable | – |
| Changes to list of signatures | If applicable | If applicable | – |
| Monitor visit reports | Yes | Yes | – |
| Record of communications with sites: letters, telephone calls | Yes | Yes | – |
| Signed consent forms | – | Yes | – |
| Completed CRFs: | Yes (original) | Yes (copy) | – |
| <ul style="list-style-type: none"> ● includes SAE reports from that site | | | |
| CRF corrections | Yes | Yes | – |
| SAE reports of unexpected events from pharmaceutical company | Yes | Yes | – |
| Annual reports to ethics committees if required | Yes, if required | Yes | – |
| Screening log/Trial register | – | Yes | – |
| Record of stored blood or tissue samples, if any | Yes | Yes | – |

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comments contact:**

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