

MRC Clinical Trials Series

MRC GUIDELINES FOR MANAGEMENT OF GLOBAL HEALTH TRIALS

Involving Clinical or Public Health
Interventions

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INTRODUCTION

ABOUT THE MEDICAL RESEARCH COUNCIL (MRC)

The MRC funds 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. The MRC has a strong history of supporting Global Health research, in partnership with other Research Councils and Low and Middle Income Countries (LMICs), and aligned with global initiatives.

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 early phase clinical trials, global health trials and trials of public health interventions.

The MRC endorses the broad definition of clinical trials used by the World Health Organization (WHO) and International Committee of Medical Journal Editors (ICMJE), which includes all interventional studies involving human participants: *“any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.”*

SCOPE OF THESE GUIDELINES

This document provides guidelines for good clinical practice (GCP), trial oversight and management for MRC-funded clinical trials conducted in lower and middle income countries (LMICs), also called ‘global health trials’.

Most MRC-funded global health trials are large comparative studies of established therapies, however this guideline can be applied to any prospective evaluation of a healthcare intervention, including methods for diagnosis, treatment, disease prevention or management of service provision. This guideline outlines principles for good clinical practice and trials management that apply to all trials of clinical and public health interventions.

Clinical trials in the UK or EU are not covered in these guidelines. Clinical trials of investigational medicinal products (CTIMPs) within the UK and EU member states fall within the scope of the UK Medicines for Human Use (Clinical Trials) Regulations 2004. The lead organisation for funding late-phase clinical trials within the UK is the National Institute for Health Research (NIHR). NIHR supports the [Clinical Trials Tool Kit](#)¹ which provides information about the regulations and requirements for conducting clinical trials in the UK.

Additional guidance documents relevant to MRC-funded research involving human participants can be downloaded from the [MRC website](#).² Practical guidance in meeting regulatory governance and ethics requirements in research can be obtained from the [MRC Regulatory Support Centre](#).³

¹ <http://www.ct-toolkit.ac.uk/>

² <http://www.mrc.ac.uk/research/policies-and-resources-for-mrc-researchers/#ethics>

³ <http://www.mrc.ac.uk/regulatorysupportcentre>

AIM OF THESE GUIDELINES

These guidelines are designed to be used by MRC Head Office staff and members of their Boards; MRC research units; Host Institutions in receipt of funding for clinical trials; members of Trial Steering Committees and Data Monitoring Committees; Chief and Co-Investigators; and others involved in MRC-funded trials.

As a funder of research, the MRC wishes to be assured that those who conduct research involving human participants adhere to guidelines that safeguard study participants and ensure that the data gathered are of high quality. The scientific integrity of the trial and credibility of the data produced depend primarily on the trial design and this will be carefully considered at the peer-review stage. This document provides guidelines on the appropriate management of a trial to safeguard research participants, optimise the accuracy of the data gathered and ensure that trial outcomes are reported.

Investigators in MRC trials involving medicinal products in which trial data are likely to be part of a licensing application (or marketing authorisation) are advised to follow the [International Conference on Harmonisation \(ICH\) Good Clinical Practice \(GCP\) Guideline](#)⁴.

MRC expects investigators involved in global health trials funded through the MRC to have regard to this framework for good clinical practice and trials management.

Please note: The MRC has withdrawn previous guidance entitled 'MRC Guidelines for Good Clinical Practice in Clinical Trials' (1998).

⁴ www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html

GLOSSARY

Audit	A systematic and independent examination of trial-related activities and documents to determine whether these were conducted, and data recorded, analysed and reported accurately and according to the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirement(s).
Adverse event (AE)	Any untoward medical occurrence affecting a research participant in the trial. This does not necessarily suggest a causal relationship. Some adverse events are defined as 'serious' (see below).
Adverse drug reaction (ADR)	An unexpected reaction that is attributable to the administration of a drug.
Case Report Form (CRF)	A printed, optical, or electronic document designed to record all data to be collected for the trial.
Co-Investigator (Co-I)	Co-investigators collaborate and work with the Principal Investigator, who has overall responsibility for the trial. A co-investigator may be responsible for conducting the trial at one of the trial sites/centres in a multi-centre trial.
Clinical Trial (CT)	For the MRC, this means any prospective evaluation of a health care intervention involving human participants, including the administration of a treatment or type of management, diagnosis or the provision of lifestyle (e.g. dietary) advice.
Community Engagement	This describes practices intended to support interaction and a participatory relationship between the community and researchers involved in a trial. The community is a group of people with a shared social identity or characteristics.
Confidentiality	Prevention of disclosure, except to authorised individuals, of a participant's identity, trial data and results before publication.
Co-ordinating Centre	The centre involved in setting up, managing, closing and analysing the trial.

Data Monitoring Committee (DMC)	The Data Monitoring Committee is a committee that is independent of the investigators, sponsors and funders. The role of its members is to monitor trial progress, safety data and critical efficacy endpoints, then make recommendations to the Sponsor and Trial Steering Committee on whether the trial should continue, stop or be modified.
Good Clinical Practice (GCP)	Good Clinical Practice (GCP) is a standard for the design, conduct performance, monitoring, auditing, analyses and reporting of clinical trials. The guideline provides assurance that the data and reported results are credible and accurate, and the rights and confidentiality of trial participants are protected.
Host Institution	The University, hospital or other institution that is in receipt of a grant from the MRC for the purposes of running a trial.
Independent Ethics Committee (IEC)	An independent committee usually constituted of medical/scientific professionals and non-medical/scientific (lay) members, whose responsibility is to ensure the protection of the rights, safety and wellbeing of human participants in research. The ethics committee will make a decision based on the trial protocol, suitability of investigators, facilities, and the methods and information materials to be used in obtaining informed consent from participants.
Investigators	A collective term to describe the Chief and Co-Investigators and additional participating clinicians at sites.
Monitoring	The act of overseeing the progress and quality of a clinical trial, and of ensuring that it is conducted, recorded and reported in accordance with the protocol, Standard Operating Procedures, Good Clinical Practice and any applicable regulatory requirement(s).
Multicentre or multisite Trial	A clinical trial conducted according to a single protocol but at more than one site, and therefore involving more than one investigator.
Principal Investigator (PI)	For MRC-funded global trials, this means the person who is responsible for: a) initiating the trial by applying to the MRC for support; and b) has overall responsibility for the design, conduct, management, analyses and reporting of the trial.

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.
Protocol Amendment	A written description of change(s) to or clarification of a protocol.
Quality Assurance (QA)	All systems that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with the protocol, Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.
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.
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.
Serious Adverse Event (SAE)	For the purposes of this guidance, any untoward medical occurrence that: <ul style="list-style-type: none"> • results in death • is life-threatening • requires in-patient hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability/incapacity, or • is a congenital anomaly/birth defect.
Sponsor	The Sponsor is the individual, or organisation (or group of individuals or organisations) that takes responsibility for confirming there are proper arrangements to initiate, manage, monitor, and finance a study. Where MRC is the funder, the Host Institution is normally the Sponsor.

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.
Trial Management Group (TMG)	A group set up by the Principal Investigator to manage the trial on a day-to-day basis.
Trial Site/Centre	The location(s) where trial-related activities are actually conducted.
Trial Steering Committee (TSC)	An independent committee formed to provide overall supervision for the trial. The TSC is led by an independent Chair and membership should include at least two independent experts, the Principal Investigator, one or two Co-Investigators, and as well as observers from the MRC and Host Institution and Sponsor (if different). At least 50% of members should be independent (i.e. not members of the trial team nor employed by the same institutions that employ the trial team members).

1 PRINCIPLES OF GOOD CLINICAL PRACTICE

The principles for Good Clinical Practice (GCP) in MRC-funded trials are those laid down in the ICH Guideline for GCP (May 1996⁵). The ICH GCP principles are embedded in clinical trials legislation of the UK, European Union, Japan and United States. It is important for investigators in low- and middle-income countries to meet the GCP standard as far as possible as this will ensure participants are adequately protected and trial results are more readily accepted as reliable.

- 1) The conduct of clinical trials should have regard to the ethical principles of the Declaration of Helsinki, and any applicable regulatory requirement(s).
- 2) Before a trial is initiated, any 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 potential benefits justify the risks.
- 3) The rights, safety and well-being of the trial participants are the most important consideration and should prevail over the interests of science and society.
- 4) The available non-clinical and clinical information on an investigational product should be adequate to support the proposed trial (i.e. there should be sufficient information about the investigational product to confirm that the type of trial proposed is appropriate).
- 5) Clinical trials should be scientifically sound and described in a clear detailed protocol.
- 6) A trial should be conducted in compliance with the protocol that has received approval from an Independent Ethics Committee.
- 7) A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
- 8) Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- 9) Freely given informed consent should be obtained from every participant prior to participation⁶.
- 10) All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
- 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).
- 12) Investigational medicinal products or other investigational products should be manufactured, handled, and stored in accordance with Good Manufacturing Practice (GMP) or equivalent guidelines. They should be used in accordance with the approved protocol.
- 13) Systems with procedures that ensure the quality of every aspect of the trial should be implemented.

⁵ <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html>

⁶ In some situations fully informed consent may not be possible (e.g. emergency settings, loss of capacity, minors). In these cases, procedures approved by the independent ethics committee should be followed.

2 ETHICS APPROVAL AND PARTICIPANT CONSENT

2.1 Independent Ethics Review

All MRC support is contingent on approval being obtained from an Independent Ethics Committee (IEC). Trials with a UK site require ethics approval from a committee in the UK, which may be an NHS or university ethics committee. For global trials, ethics approval should be sought in the UK *and* in the country where the trial will take place.

Specific issues which may be of relevance in global health research settings include consideration of:

- Culturally appropriate approaches to obtaining consent;
- Standard of care to be offered to individuals in the non-intervention arm of a trial;
- Appropriateness of any proposed compensation or incentives to be offered;
- Whether the research addresses the needs and priorities of the community taking part;
- Whether interventions developed or tested within the trial, will continue to be available to participants or the community after the trial;
- The responsibility for post-trial management and care of participants in the longer-term, including implications for local health policy.

It is the responsibility of the Sponsor(s) to ensure that the trial has received a positive opinion from a relevant Independent Ethics Committee.

During the trial the Principal Investigator (PI) should notify, and where necessary seek approval from the Independent Ethics Committee and any relevant regulatory bodies, for any substantial amendments to the trial.

2.2 Standards of Care

The standard of care offered to the control group in a clinical trial must be critically assessed and justified in the research protocol and ethics application.

Various factors must be considered in making the decision about the standard of care that is appropriate for an individual trial, including the:

- research design (this may require a specific standard of care);
- severity of the condition and treatments;
- existence of an evidence-based universal standard of care;
- standards of care for the target condition in the host and sponsor countries;
- standard of care for the target that can be afforded by the host and sponsor countries;
- standard of care that can be effectively delivered and provided on a sustainable basis by the host country.

The standard of care⁷ may be:

- Non-universal – the best available (defined as the standard in national best practice guidelines)
- Universal – the best available anywhere in the world. Although it has been argued that providing this standard is the responsibility of researchers and sponsors, and avoids exploitation, it may not be feasible to offer this standard of care.

MRC expects that the standard of care offered to a control arm is, as a minimum, the standard that the host country provides according to national policy.

2.3 Information that should be provided to participants

Appropriate information should be provided in a format which is readily accessible and appropriate to the needs of participants, as well as feasible to provide within the context of the trial environment. Possible formats include written and oral communications, printed and digital material (including the use of portable devices such as mobile phones or tablets). If necessary, participant information should be available in different languages.

Information provided should be sufficient to enable an informed decision by the trial participant or their representative about participation in research. It is good practice and can prove helpful to seek advice from participant communities or representative groups when preparing this information, including deciding whether to present information in written or oral formats, or via devices such as mobile phones.

The information about the trial that is to be provided to the participants will usually have been considered by the Trial Steering Committee as part of the overall assessment of the trial, and always by relevant ethics committees. It is the responsibility of the Principal Investigator to ensure that the participant information used is as approved and that any necessary amendments are made without delay.

The participants, or their representative(s), should be made aware before consenting to participate that they are free to withdraw at any time. Researchers should ensure, as far as possible, that withdrawal does not adversely affect a participant's care.

If the investigators are aware that participant samples or information from 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.

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, following consultation with the TSC and with relevant ethics and regulatory approvals, the patient information sheet should be updated. Trial participants and collaborating investigators should be notified where appropriate.

⁷ *The Ethics of Research Related to Healthcare in Developing Countries*. London: Nuffield Council on Bioethics, 2002.

Trial participants should also be notified of progress with, and the eventual outcome of the trial, if they wish to be informed. Information might be provided through public meetings, mobile phones, trial websites or printed materials, such as posters and leaflets.

Participants and their usual doctors, where applicable, should be provided with up-to-date information about the trial and a point of contact for the trial team.

If other clinicians are in contact with a participant in a trial, it may be appropriate for the Principal Investigator and/or the usual doctor to supply these clinicians with relevant information about the study.

Participants should have access to information about a complaints procedure and the procedures for obtaining compensation and treatment following harm through negligence or non-negligence (if an ethics committee deems this necessary) as a direct result of participating in the trial. It is the Sponsor(s) responsibility to ensure that these arrangements are in place. Where the MRC is the Sponsor, further details about the arrangements for compensation are available from the MRC or the [MRC website](#).⁸

In certain situations provision of information prior to obtaining consent is not possible (e.g. emergency settings). In these cases, the process must be agreed by an Independent Ethics Committee and applicable regulatory requirements should be met.

2.4 Participant Consent

Informed consent is a decision to participate in research, taken by a competent individual who has received the necessary information, adequately understood the information and has arrived at a decision without having been coerced, induced or intimidated. It must always be complemented by independent ethical review of research proposals.

Whenever possible, all participants, or their representative(s), should give their consent on the basis of appropriate information given to them before the start of the trial, and with adequate time to consider this information and ask questions. Each individual should be given as much time as is needed to reach a decision, including time for consultation with family members or others, and a participant should not take part until consent has been obtained.

An investigator should not take consent from a participant if they do not understand the language of the participant, unless a witness who does understand the language is present.

2.4.1 Recording consent

It is common to take written consent, and for each participant to sign a consent form. The participant should be given a copy of the completed consent form and another copy kept by the trial investigators and available for verification. If the prospective participant cannot sign their name, then they can mark the consent form and the person taking consent may write in their name. The witness should also sign the form to confirm that they have observed that the participant has been provided with adequate information, has understood this and had any questions answered, and has freely given consent.

⁸ <http://www.mrc.ac.uk/research/facilities-and-resources-for-researchers/regulatory-support-centre/sponsorship-indemnity/>

Written consent may not be appropriate, for example if a participant cannot read or write, or if there is not a written form of the language. In these cases, verbal consent or other methods may be considered.

If verbal consent is taken, then an impartial witness should be present and the communication recorded and available for verification.

Other formats of recording consent, for example using digital devices, may be used if more appropriate. A record of the consent should be available for verification.

The proposed methods for obtaining and recording consent must be approved by an independent ethics committee.

2.4.2 Children and young people

If the participant is a child or young person, and a minor in law, then an adult parent or guardian may be asked to consent on behalf of the participant. A child who is not able to give consent can still be involved in the decision-making process therefore consideration should be given to providing age-appropriate information about the study to the child or young person. It may also be appropriate to seek their assent (or agreement) to participation as part of the consent process.

2.4.3 Vulnerable participants

Vulnerable individuals are those who are incapable of protecting their own interests, which may be due to a lack of power, education, resources, strength, or other reasons. This may limit their capacity or freedom to confirm or decline consent. Vulnerable groups may include refugees or displaced persons, nomads, homeless people, prisoners, some ethnic minority groups, individuals who are politically powerless, and members of communities that are unfamiliar with modern medical concepts.

If the vulnerable participant is unable to give informed consent then their representative should also give permission, in addition to the participant's own agreement to take part.

Involving vulnerable individuals in a trial should be justified and their rights and welfare must be protected. Ethics committees should be assured that the research cannot be carried out with less vulnerable individuals, and that participants (i) will benefit from the research findings as a patient group or individually, (ii) will not be exposed to excess risk, and, as far as possible, (iii) will continue to be provided with any interventions or treatments that are of benefit after the trial.

2.4.4 Specific cultural considerations

In some cultures, it is not appropriate for an investigator to enter a community to approach participants for individual consent without obtaining permission from a community leader, council of elders, or similar. Such customs should be respected, however individual consent is considered best practice⁹ and the permission of a community leader is not a substitute for this.

⁹ In rare cases, when the study participants are a group or community then it may be appropriate to seek 'group' or community' consent without individual consent.

2.5 Return of Research Results

The research design should include plans for providing results from the trial to participants or communities involved. These may be general or summary research findings or individual research results that have health implications for an individual participant. For individual research results, it is important to consider which results will be communicated to participants, or to justify a policy of not returning any results. If the results provided have health implications, then the policy for returning individual results should include the further provision of clinical investigation or management. Participants should be given an option to opt out of receiving results.

2.6 Incidental or Health-Related Findings

During a trial involving human participants, it is possible that researchers may make a finding that has potential health or reproductive implications for an individual participant.

A [framework](#)¹⁰ developed by the MRC and Wellcome Trust, provides guidance to help researchers design and implement a policy on feeding back findings that arise during the course of a study. MRC recommends that a feedback policy is developed before the study begins recruitment and that information about the policy is given to participants prior to consent. Participants should be given an option to opt out of receiving results.

3 COMMUNITY ENGAGEMENT

In developing and conducting clinical trials or other health research in LMIC settings, investigators should seek to establish partnerships with local communities whom they wish to involve. Community engagement in research should aim to improve the protection of, and benefits available to, the individuals and communities involved. Consideration should be given to involving community stakeholders at an early stage in order to build local capacity in trial design and conduct, and ethical review of research.

UNAIDS/WHO¹¹ provide explicit guidance for HIV Prevention Trials, however much of this guidance is relevant to any clinical or public health intervention studies and trials involving human participants,

“researchers and trial sponsors should consult communities through a transparent and meaningful participatory process which involves them in an early and sustained manner in the design, development, implementation, monitoring, and distribution of results of [clinical] trials”.

Early engagement with the community will help identify relevant local partners and inform decisions about ethical trial design in a LMIC setting, including:

- protocol development;
- approaches to seeking and documenting consent;

¹⁰ <https://www.mrc.ac.uk/documents/pdf/mrc-wellcome-trust-framework-on-the-feedback-of-health-related-findings-in-researchpdf/>

¹¹ UNAIDS/WHO. *Ethical considerations in biomedical HIV prevention trials*. Geneva: United Nations Joint Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO), 2007 (updated 2012).

- conducting the research, e.g. employing or training community members;
- reimbursing the community for additional costs or use of resources, e.g. researcher accommodation, water, power, etc (where appropriate);
- access to data and samples resulting from the trial;
- understanding how best to disseminate research findings to maximise the benefit to the community.

Sponsors and investigators should develop culturally appropriate ways to communicate the information that is needed by individuals for the informed consent process, for example about scientific concepts such as randomisation or placebo. Proposed recruitment and consent processes should be described in the research protocol and adequate resources allocated to supporting community engagement to facilitate recruitment and consent and ensure ethical trial design.

In some trials the intervention may be provided by community health workers, therefore engagement with the community may be primarily through identifying, training and working with these individuals. However in other communities, it may not be appropriate for a researcher to conduct research or engage individuals as participants or members of the wider study team without first seeking approval from a community leader or similar authority. Some examples of community participation in HIV/AIDS trials are provided in a report from UNAIDS¹² and an e-learning package is available from the Global Health Network (see Appendix 1).

4 REPRODUCIBILITY AND RESEARCH TRANSPARENCY

The MRC strongly promotes the principles of research transparency and aims to make the research process and findings as open, understandable and reproducible as possible.

The MRC supports data sharing initiatives to increase the availability of study data for re-use. Sharing data from research can enhance the use of existing data, avoid duplication of research effort and stimulate new discoveries.

The [MRC policy on open research data](#)¹³ applies to clinical trials, clinical intervention studies, public health intervention studies and observational studies involving human participants, including global health trials.

The policy includes guidance on:

- Registering the trial on a public [WHO-approved registry](#)¹⁴, such as the [ISRCTN Registry](#)¹⁵;
- publishing the study protocol and statistical analysis plan;
- publishing trial findings (within 12 months of completion);
- MRC Open Access policies;
- sharing participant data (including individual-level data);

¹² UNAIDS, AVAC. *Good participatory practice: Guidelines for biomedical HIV prevention trials 2011*. Geneva: UNAIDS, 2011.

¹³ www.mrc.ac.uk/documents/pdf/mrc-policy-on-open-research-data/

¹⁴ <http://www.who.int/ictrp/en/>

¹⁵ <http://www.isrctn.com/>

- data access processes;
- secondary use of data.

Bull *et al*¹⁶ have published a discussion paper on best practices for sharing individual-level patient data in LMIC settings.

5 TRIAL MANAGEMENT: ROLES AND RESPONSIBILITIES

In their written acceptance of an award from the MRC, the Principal Investigator and Host Institution agree to the applicable Terms and Conditions before funds are made available. In doing this, they are accepting the responsibilities specified in these guidelines.

A brief summary of the roles and responsibilities of those involved in MRC-funded trials is given below.

5.1 MRC

The role of the MRC is as **research funder**.

Before awarding a grant, the MRC will ensure that:

- the proposed trial design is of the highest scientific quality (usually determined through peer review);
- the Principal Investigator, Host Institution and Sponsor(s), agree to conduct the trial in accordance with the applicable regulatory requirements (dependent on the type of trial) and the standards set out in this guidance; and
- appropriate arrangements for the day-to-day management and independent supervision of the trial have been proposed.

Once the trial is underway, the MRC will monitor progress through annual reports or minutes of the Trial Steering Committee, and may wish to attend the Trial Steering Committee as an observer, and/or audit individual studies.

5.1.1 Peer Review of Scientific, Ethical and Management Arrangements

The MRC procedures for peer-review of trial proposals require an application in a structured format that includes all the information needed to assess whether a trial will be conducted according to the principles detailed above. In reviewing a proposal for a new trial the MRC will satisfy itself based on the information available that:

- The proposed trial is scientifically sound, designed to produce results which are sufficiently reliable for the purposes of the trial, clearly described and feasible and, where possible, based on a systematic review of the current evidence;

¹⁶ Bull S *et al*. Best Practices for Ethical Sharing of Individual-Level Health research data from Low- and Middle-Income settings. *Journal of Empirical Research on Human Research Ethics* 2015;10(3):302-13. DOI: 10.1177/1556264615594606

- The potential benefits of the proposed trial justify the potential risks for the individual participant and society ;
- The investigators are competent to undertake the proposed trial, for example applicants demonstrate an adequate track record appropriate to their role;
- The proposal includes details of the trial team that includes the key disciplines necessary for the design and implementation of the trial, and a clear allocation of responsibilities within the trial;
- The proposal details the availability of adequate and competent support staff and appropriate facilities for the duration of the trial (or requests funds to provide them);
- Arrangements for oversight of trials should include expert advice that is independent from the trial investigator(s) and the Host Institution, e.g. a Trial Steering Committee with an independent chair;
- The proposal includes trial management and data monitoring plans that are proportionate to the risks inherent in the trial;
- The proposal includes appropriate resources (including facilities) to conduct and complete the research (including adequate follow up) and to meet regulatory requirements, including registration of the trial, trial monitoring and archiving;
- The proposal states that all potential trial participants will be informed whenever possible of the potential benefits and known risks of the intervention (or of no intervention or a placebo) and of the possibility that there are unknown risks;
- The publication policy includes reporting the results of the trial within an appropriate time frame, and that plans are in place to disseminate, including to participants, and implement results;
- The time period proposed by the Principal Investigator for retention of relevant trial documentation is appropriate;
- The proposal contains plans for preserving and sharing primary data at the end of the trial in accordance with MRC policy and guidance (see above);
- Tissue and other biological samples collected in the course of a clinical trial is a valuable resource. Researchers must ensure that any such collection is in accordance with applicable legislation and MRC guidance (see Appendix 1). As with data, plans for the ultimate storage or disposal of tissue should be included in the proposal. Consideration should be given to potential further uses of tissue.

5.1.2 Award of Funds

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

- All applicable approvals being obtained from the relevant ethical and regulatory bodies before any participants are recruited to the trial;
- The MRC being informed of any significant changes to the proposal resulting from these regulatory and ethical reviews;
- Registration of the trial on the ISRCTN register and award of a unique identifier.

5.1.3 Monitoring and Audit of Progress

Once the trial has started:

- A representative of the MRC will attend meetings of the Trial Steering Committee (in the role of funder representative);
- MRC expects to receive minutes of Trial Steering Committee meetings (which will be held on file as a record of trial progress);
- The MRC may wish to consider additional reports from the Host Institution or Data Monitoring Committee;
- The MRC Reserves the right to audit any MRC-funded trial.

5.2 THE TRIAL SPONSOR

The Sponsor is the individual, or organisation (or group of individuals or organisations) that takes responsibility for confirming there are proper arrangements to initiate, manage, monitor, and finance a study.

The Sponsor is responsible for ensuring that:

- the trial is appropriately assessed and resourced;
- the trial is conducted to the required standards and conforms with regulatory requirements, including financial;
- there is adequate provision for compensation and indemnity in the event of harm to research participants.

Where the MRC is the funder, the Host Institution employing the Principal Investigator is usually the Sponsor.

When the MRC is the funder and Sponsor of a trial, arrangements are in place to allow for compensation of participants in that trial, where appropriate. The [MRC statement on indemnity](#)¹⁷ can be accessed from the MRC website.

5.3 THE HOST INSTITUTION

When a trial is funded through a grant, the organisation receiving the grant is known as the Host Institution. The Host Institution is often the employer of the Principal Investigator and Sponsor of the trial, and therefore has a responsibility for ensuring that the trial is run to the highest standards and meets all applicable regulatory and research governance requirements. This responsibility is accepted by the Host Institution when it accepts the terms and conditions of the MRC award. The Host Institution should ensure that there are systems in place to manage sponsorship requirements. The MRC, as the funder, must be informed of the name of the Sponsor(s) of the trial and the arrangements for independent oversight.

¹⁷ <https://www.mrc.ac.uk/documents/pdf/mrc-statement-on-indemnity/>

In particular the Host Institution must:

- Ensure that there are systems in place to arrange or manage relevant sponsorship requirements;
- Inform the MRC of the Sponsor(s);
- Ensure that the trial is conducted in accordance with the general MRC terms and conditions, these guidelines and with the specified protocol, and according to the proposed schedule of resource use and all applicable regulatory requirements;
- Ensure that appropriate arrangements for oversight of the research are in place. These arrangements will have been proposed by the Principal Investigator and approved by MRC;
- Make a commitment to maintain, for the trial's duration, the key expertise for all aspects of the design and implementation of the trial;
- Permit auditing by the MRC or Sponsor(s) and inspection;
- Provide appropriate facilities for the storage and retention of all relevant documentation (the MRC expects research data from clinical studies to be retained for 20 years after the study has been completed);
- Ensure that a report (or a copy of all Trial Steering Committee minutes) is submitted to the MRC annually.

5.4 THE PRINCIPAL INVESTIGATOR, CO-INVESTIGATOR(S) AND OTHER TRIAL STAFF

- **Principal Investigator** -The Principal Investigator (PI) has responsibility for the design, conduct, management, analyses and reporting of the trial. He or she is likely to be the Principal Applicant on the MRC application.
- **Co-Investigator** - A Co-Investigator (Co-I) has responsibility for the conduct of the trial in a participating site/centre.

This section details the responsibilities of those involved in the running of the trial on a day-to-day basis and 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 responsibility for the design, conduct, management, analyses and reporting of the trial.

The Principal Investigator must ensure that: 1) the trial is run in accordance with the protocol, and applicable regulations and guidelines; and 2) all investigators involved are aware and of, and adhere to these guidelines.

The MRC considers it good practice that a study web site dedicated to providing up-to-date information for participants, researchers and the public, is established and maintained. It should provide information on:

- the unique identifier for the trial and provide a link to its entry on a clinical trial registry;
- the scientific rationale for the trial (such as the underpinning systematic review of the available evidence);

- the current version of the protocol, (e.g. a summary that respects intellectual property rights, etc.);
- the current status of the trial; and
- the results of the study and any publications.

5.4.1 Trial Management

The Principal Investigator is responsible for the day-to-day conduct of all aspects of the trial and for managing the trial budget. It is good practice for the Principal Investigator to appoint a dedicated trial manager/co-ordinator with clearly defined duties, in particular to ensure that recruitment targets are met.

The Principal Investigator should ensure that:

- all the investigators involved in the trial, conduct the trial in accordance with the proposal funded by the MRC and the approved final protocol, and according to the proposed schedule of resource use as submitted in the approved funding proposal;
- All members of the trial team are adequately qualified and trained to undertake their roles and are familiar with the principles of GCP;
- all Co-Investigators at participating centres are aware of their responsibilities and all applicable guidance and regulations are followed in all the participating centres;
- appropriate systems and procedures to assure the quality of every aspect of the trial are in place. It is recommended that the systems are tailored to the specific risks inherent in the trial;
- all the persons involved in implementing the protocol are adequately informed about the protocol, the nature of any intervention and their trial-related duties;
- all trial-related functions are clearly defined, allocated and documented and that the responsibilities of participating investigators are clearly understood. It is good practice to put in place a standard investigator agreement that lays out the terms and conditions of centre participation and is signed by each Co-Investigator, or a standard contract with the relevant institution;
- clear lines of communication are established between investigators;
- resources for the trial are managed in a way that maximises the chances of the trial finishing within the available funding;
- the final protocol has been agreed by the Trial Steering Committee and Data Monitoring Committee before the start of the trial, this is commonly undertaken at an initial meeting of the Trial Steering Committee;
- the Trial Steering Committee and Data Monitoring Committee (or the agreed alternative source of independent advice) meet according to the agreed schedule (normally at least annually) *and* when there are any matters arising from the conduct or management of the trial that might require their advice;
- accurate records of Trial Steering Committee meetings are retained and made available to MRC on request;

- an annual report is submitted to the MRC. This should be endorsed by the Trial Steering Committee (or alternative source of independent advice);
- on completion of the study, the results are analysed, written up, publicly reported and disseminated (at a minimum results should be made publicly available on the trial registry).

5.4.2 Compliance with Protocol

The trial should be conducted in accordance with the proposal funded by the MRC, and the approved protocol which has been favourably reviewed by a research ethics committee. It is the ultimate responsibility of the Sponsor(s) 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, any relevant regulatory body, the Trial Steering Committee, and the Data Monitoring Committee (or the agreed alternative source of independent advice) before their implementation. The MRC should be notified of any significant changes to the funded proposal.

5.4.3 Medical Care of Trial Participants

Investigators should have regard to the principles within the Declaration of Helsinki regarding medical care of human participants involved in clinical trials. The welfare of the trial participants is the ultimate responsibility of the clinician responsible for their care. The medical care offered, and medical decisions made on behalf of, participants should be the responsibility of a qualified medical doctor or, when more appropriate, a qualified dentist or other qualified health care professional. It is the responsibility of the Principal Investigator to ensure that the trial is organised in a way that ensures that appropriately qualified staff are responsible for patient care.

5.4.4 Investigational Products

If the clinical trial involves medicinal products then all applicable requirements for the trial and product manufacture and handling should be met. Where appropriate, the Principal Investigator should seek advice from a suitably experienced pharmacist, or other appropriate professional, when planning the trial.

If the trial involves an investigational product that is not medicinal, the products used should be manufactured, handled, and stored to appropriate quality standards. They should be used in accordance with the approved protocol.

If the clinical trial of an investigational medicinal product (IMP) includes a UK site, it is within the scope of the UK Medicines for Human Use (Clinical Trials) Regulations 2004. Guidance for trials in the UK is available from the [Clinical Trials Tool Kit](#).¹⁸

5.4.5 Randomisation Procedures

The Principal Investigator should ensure that any randomisation procedures are rigorously designed and managed so that allocations are completely concealed from investigators prior to randomisation to

¹⁸ www.ct-toolkit.ac.uk

protect against bias. S/he should ensure that the randomisation procedures are strictly controlled and adhered to by all the investigators. If the trial is blinded, investigators should promptly document and explain any premature unblinding.

5.4.6 Safety Reporting

It is the responsibility of the investigators to comply with the requirements specified in the protocol for the notification of serious adverse events (SAEs) to the Principal Investigator or Sponsor. The Principal Investigator is responsible for ensuring that the Trial Steering Committee and Data Monitoring Committee are kept informed of the frequency of those SAEs defined in the protocol as requiring notification. The frequency of reporting of SAEs to the Trial Steering Committee and Data Monitoring Committee should be in accordance with the Data Monitoring Committee Charter (see Section 6.2). In the case of unexpected SAEs, the Chair of the Data Monitoring Committee should be notified and, where appropriate, the regulatory authority.

All applicable regulatory requirement(s) related to the reporting of serious adverse reactions to products should be adhered to. Serious adverse drug reactions (ADRs) occurring in trials of medicines should be reported to the Sponsor, appropriate regulatory authorities and the ethics committee.

Clear standard operating procedures (SOPs) should be developed and implemented for the purpose of safety reporting.

5.4.7 Data Handling and Record Keeping

MRC require that a Data Management Plan is developed for each study and a copy submitted to the MRC during the funding application process.

The primary objective of good data handling and record keeping is to ensure that data collected on participants in the trial are accurate, complete and compatible with the original observations on which they were based. The procedures to ensure the quality of the data in the final clinical trial report are the responsibility of the Principal Investigator. They should be developed according to risk-based principles and be documented.

The Principal Investigator should ensure that the Case Report Forms (CRFs) are designed to capture all necessary data on each study participant and that the information gathered is appropriate to the aims of the trial.

The Principal Investigator should ensure that there are specified procedures to be followed to ensure that the data are of high quality, accurate at the point of collection and their integrity maintained during processing. That would normally require monitoring either centrally at the co-ordinating centre and/or at the clinical trial site. The level and type of data monitoring necessary will vary from trial to trial and should be based on the design of the trial and risk, and be agreed between the Principal Investigator, independent Trial Steering Committee and funder.

All data and documentation associated with the trial – whether held on paper or electronically – should be readily accessible for independent inspection and validation. Ensuring such availability is the responsibility of the Principal Investigator.

The Principal Investigator should take responsibility for drafting the annual report to the MRC in the format requested for approval by the Trial Steering Committee. The Principal Investigator and Chair of the Trial Steering Committee should approve and sign the final report of the trial.

It is essential that all trial participant data are processed, held and transmitted securely to protect participant confidentiality.

The appropriate time period for which trial participant data and essential trial documents should be retained will vary depending on the nature of the study and any applicable regulatory requirements. The Principal Investigator should justify the retention period in the proposal to the MRC.

6 OVERSIGHT OF THE TRIAL

The specific arrangements for trial oversight and management will vary according to the nature of the study but should include an element of expert advice that is independent of the Chief and Co-Investigators, the Host Institution and the Sponsor(s). This will usually take the form of a Trial Steering Committee (TSC) and an independent Data Monitoring Committee (DMC). A Trial Management Group (TMG) should work closely with the Principal Investigator and participating centres to manage the set-up, day-to-day running, and analysis of the trial. These arrangements should be detailed and justified in the trial proposal; the MRC will satisfy itself that these are appropriate in the light of the risks involved.

6.1 THE TRIAL STEERING COMMITTEE

The role of the Trial Steering Committee is to provide overall supervision of the trial and ensure that the trial is conducted in accordance with the standards set out in this guidance. The Trial Steering Committee will formally report to the Sponsor(s).

In particular, the Trial Steering Committee should emphasise

- patient safety;
- progress of the trial;
- adherence to the protocol and statistical analysis plan;
- consideration of new information;
- dissemination and implementation of results; and the
- complaints procedure and compensation for participants.

6.1.1 Membership of the Trial Steering Committee

Principal Investigators should submit a proposed membership for the Trial Steering Committee to the MRC, who will agree the final membership. The membership should include an independent Chair who is not involved directly in the trial, other than as a member of the Trial Steering Committee, does not

have a relationship with the investigators, their funders¹⁹ or sponsors and is not employed by or working within the same institution. There should be no fewer than two other independent members, the Principal Investigator and one or two Co-Investigators, with additional experts if required. At least 50% of members should be independent of the investigators, i.e. not involved directly in the trial nor having any relationship to the investigators, their funders¹⁹ or sponsors, nor employed by the investigators' employing organisations. The trial manager/co-ordinator, Principal Investigator and trial statistician should usually attend meetings. An observer from the MRC and Host Institution, or sponsoring organisation if different, should be invited to attend all Trial Steering Committee meetings. Terms of reference and membership for Trial Steering Committees are given in Appendix 3.

6.1.2 Meetings

A meeting of the Trial Steering Committee should be organised by the Principal Investigator before the start of the trial to approve the final protocol, which should then be sent for review by an independent Ethics Committee, and any other applicable regulatory body. After that the Trial Steering Committee should meet at least annually although there may be periods when more frequent meetings are necessary and may be called either by the Chair of the Trial Steering Committee or the Principal Investigator.

Responsibility for calling for and organising Steering Committee meetings lies with the Principal Investigator, following consultation with Principal Investigators. 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 and an accurate minute of the meeting should be prepared by the Principal Investigator and agreed by all members. The minutes must be available to MRC on request.

The Chair of the Data Monitoring Committee should be invited to the first meeting of the Trial Steering Committee. A joint first meeting of both committees would be good practice.

6.1.3 Patient Safety

In all the deliberations of the Trial Steering Committee 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 Trial Steering Committee should ensure that the protocol demands, where possible, freely given informed consent from every trial participant. The Trial Steering Committee should look closely at the patient information provided and advise the investigators on its completeness and suitability.

6.1.4 Progress of the Trial

It is the role of the Trial Steering Committee 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 Trial Steering Committee meeting, targets for recruitment, data collection, compliance, etc. should be agreed with the Principal Investigator. These targets should not be "set in stone" but are designed to permit adequate

¹⁹ The Chair or TSC members may still be considered independent if they have previously received an award from the same funder as the investigators, as long as this is unrelated to the trial and membership is agreed with the MRC.

monitoring of trial progress. The Trial Steering Committee should agree which data, based on the targets set should be presented at each Trial Steering Committee meeting (template provided in Appendix 5).

The Principal Investigator is required to submit an annual report to MRC based on the template provided. A full copy of all minutes of the Trial Steering Committee will also be acceptable in place of an annual report if this provides the required information. The annual report should be endorsed by the Trial Steering Committee and should contain sufficient data to allow the MRC 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.

In exceptional circumstances, the MRC will consider proposals for the extension of grants for clinical trials. In these cases, the MRC will require evidence from Trial Steering Committees 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 Trial Steering Committee should notify the MRC at the earliest opportunity.

6.1.5 Adherence to Protocol and Statistical Analysis Plan

The full protocol should be presented as an agenda item at the first Trial Steering Committee meeting. The Trial Steering Committee should help ensure that there are no major deviations from the trial protocol and should approve the statistical analysis plan. If the investigators recommend any material changes to the protocol during the course of the trial, approval should be sought from the Trial Steering Committee, the REC, and any appropriate regulatory body; the MRC should be informed.

6.1.6 Consideration of New Information

The Trial Steering Committee should consider new information relevant to the trial including reports from the Data Monitoring Committee and the results of other studies. It is the responsibility of all members of the Trial Steering Committee to bring to the attention of the Trial Steering Committee any results from other studies of which they are aware that may have a direct bearing on future conduct of the trial.

On consideration of this information, the Trial Steering Committee 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.

It is the responsibility of the investigators to comply with the requirements for the notification of SAEs specified in the trial protocol and Data Monitoring Committee Charter.

6.1.7 Dissemination and Implementation of Results

The Trial Steering Committee should ensure that appropriate efforts are made to ensure that the results of the trial are adequately disseminated (including to the participants, should they wish to receive them) and due consideration is given to the implementation of the results into clinical practice.

6.1.8 Complaints Procedure and Compensation for Participants

The Trial Steering Committee 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 organisation responsible for their care or the trial Sponsor.

6.2 DATA MONITORING COMMITTEE

The role of the Data Monitoring Committee (DMC) is to monitor the data emerging from the trial, in particular as they relate to the safety of participants, and to advise the Trial Steering Committee on whether there are any reasons for the trial not to continue. It is the only body involved in the trial that has access to the unblinded (unmasked) comparative data during the trial.

6.2.1 Membership of the Data Monitoring Committee

Applicants should submit their proposed arrangements for trial oversight and the membership of the Data Monitoring Committee with their full application to the MRC, who will consider whether the proposed arrangements are appropriate and the proposed membership should be approved. The Data Monitoring Committee should advise the Trial Steering Committee who in turn report to the Sponsor(s) and MRC, as required. Membership of the Data Monitoring Committee should be completely independent of the trial and any institutions involved in the trial. Any competing interests should be declared by members and documented. Detailed terms of reference and guidance notes are given in Appendix 4.

6.2.2 DMC Charter

The Data Monitoring Committee should establish a Charter (the DMC Charter) that describes the roles and responsibilities of the independent Data Monitoring Committee for the trial. This is likely to include the Data Monitoring Committee terms of reference, timing and format of meetings, reporting to and from the committee, statistical issues and relationships with other committees. The DMC Charter should also state whether the Data Monitoring Committee will be given the opportunity to comment on publications before submission and specify how long members must wait before discussing issues arising from their involvement in the trial.

A template for a DMC Charter has been proposed by the DAMOCLES Study Group (Lancet 2005;365;711-22).

6.2.3 Meetings

The Data Monitoring Committee should meet at least once a year, or more often as appropriate, and meetings should be timed so that reports can be fed into the Trial Steering Committee (TSC) meetings. The frequency of meetings should be agreed in the DMC Charter and the wishes of the Data Monitoring Committee and trial investigators considered in planning each meeting. The Principal Investigator should be allowed to request a meeting if there are concerns that need to be raised.

Meetings may consist of open and closed sessions and the membership of each should be agreed by the Data Monitoring Committee. Usually only Data Monitoring Committee members and those they invite, such as the trial statistician, will attend closed sessions. Open sessions include the Data Monitoring Committee members, as well as the Principal Investigator, trial statistician, other investigators and members of the trial steering group, and representatives of the sponsor, funder or regulator as appropriate. The content of closed and open sessions should be described in the DMC Charter and separate meeting notes should be taken for the different sessions. At the first meeting, members of the Data Monitoring Committee should agree the data monitoring process and rules for stopping the trial and ensure these are in the DMC Charter.

All significant communications between the Principal Investigator and the Data Monitoring Committee should be in writing, or if they have to be oral, they should be backed up by written records.

6.2.4 Role of the statistician

The trial statistician should prepare a comprehensive report for each Data Monitoring Committee meeting. This should be prepared and circulated in advance of the meeting (usually two weeks) to allow Data Monitoring Committee members time to study the data. Content of the report should normally be agreed at the first meeting of the Data Monitoring Committee. The trial statistician may be invited by the Chair to attend the closed session to present the data; otherwise, no one involved with the trial or Trial Steering Committee should be present at the DMC closed session when unblinded data are presented.

6.2.5 Reporting

Following each meeting a written report should be made by the Chair of the Data Monitoring Committee to the Trial Steering Committee (and Principal Investigator), advising whether the trial should continue or be stopped or modified. A time frame for submitting this report should be specified in the DMC Charter (usually within three weeks). If the Data Monitoring Committee recommends that the trial should be stopped at any point, the funding body should be notified. It will be the responsibility of the Trial Steering Committee to decide whether or not to act upon the information received from the Data Monitoring Committee. The DMC Charter should specify how disagreement between the Data Monitoring Committee and Trial Steering Committee will be managed.

If at any stage an extension to the grant is needed, the Data Monitoring Committee may be requested by the MRC Board to provide information on the data gathered to date (from this and other studies) and advise 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 Data Monitoring Committee 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 (compiled by the Principal Investigator or trial team). It follows that the Data Monitoring Committee will not automatically follow pre-assigned statistical rules, although it will be guided by statistical considerations.

Information provided by the Data Monitoring Committee is likely to fall into the following categories:

- No action required and the trial can continue as planned;

- Information that might lead to the Trial Steering Committee stopping the trial prematurely in the event of a clear outcome, if this is deemed to be appropriate in the light of data from the study or information available from other sources;
- Information that might lead to the Trial Steering Committee modifying the design of the trial, if this is deemed to be appropriate in the light of data from the study or information available from other sources.

Other outcomes are possible, such as stopping a single arm of a trial, stopping recruitment within one subgroup, extending recruitment or the duration of follow-up, or recommending protocol changes.

6.3 TRIAL MANAGEMENT

Day-to-day management of the trial is the responsibility of the Principal Investigator and other Investigators. The Principal Investigator may wish to set up a separate Trial Management Group (TMG) to assist with this function. A Trial Management Group is particularly valuable for the co-ordination of multi-centre trials by bringing together all those responsible for site set-up and closure, day-to-day running, monitoring of progress and adherence to the protocol, data management and analysis.

6.3.1 Documentation

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 applicable, all versions of the protocol and agreed amendments, copies of submissions and approvals from relevant authorities and ethics committees, consent forms, monitoring reports, audit reports, relevant communications (e.g. letters, emails, etc), 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 Principal Investigator and Co-Investigators. In multicentre trials, this may be co-ordinated centrally. Evidence of consent should be available for verification at each clinical site, if this is also to be held by a co-ordinating centre, explicit consent for personal identifiers to be seen by someone other than the staff of the healthcare provider, should be obtained. 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.

The following types of trials have specific documentary requirements:

- trials using medicinal products where the data may be required for a licensing application – these should follow documentary requirements outlined in the ICH GCP Guideline
- trials that are within the scope of UK/EU clinical trials legislation should follow EU guidance for non-commercial trials (see the [Clinical Trials Tool Kit](#)).

In the majority of MRC trials, the data will not be required for a licensing application, and the documents will vary according to the trial and the type of intervention.

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 that was submitted for funding. The application procedure for MRC funding for trials requires submission of full proposals in a structured proforma.

The case report form (CRF) 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 depend on the needs of the trial, with the fundamental principle being to ensure the collection of adequate, relevant and accurate data which are not excessive in quantity and/or detail. Unnecessary data are often collected and the quality of the study data can be adversely affected as a consequence. In addition, particularly for multi-centre 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.

6.3.2 **Quality Assurance, Audit and Inspection**

The Sponsor of the trial has the responsibility to ensure that the trial is conducted to the highest quality. As such, the sponsoring organisation(s) may audit research that it/they sponsor.

The MRC, in order to reassure itself of the reliability of the data gathered and the ethical conduct of its trials, may audit MRC-funded trials.

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.

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 report before it is passed on to the relevant Board or Trial Steering Committee. Copies of the reports, together with the comments of the investigators 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.

The Sponsor of trials that are within the scope of UK legislation may be inspected by the relevant regulatory authority. If this is the case, sponsors and individual trials teams will need to demonstrate compliance with this legislation and terms of any licence or permissions.

REFERENCES

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- *Good Practice Principles for Sharing Individual Participant Data from Publicly Funded Clinical Trials*. Tudur Smith C, Hopkins C, Sydes M, Woolfall K, Clarke M, Murray G, Williamson P. April 2015. Available from: <http://www.methodologyhubs.mrc.ac.uk/files/7114/3682/3831/Datasharingguidance2015.pdf>
- UNAIDS, AVAC. *Good participatory practice: Guidelines for biomedical HIV prevention trials 2011*. Geneva: UNAIDS, 2011.
- SPIRIT Statement <http://www.spirit-statement.org/>

APPENDIX 1: MRC POLICIES AND GUIDANCE

MRC Data Management Plan

<https://www.mrc.ac.uk/research/policies-and-resources-for-mrc-researchers/data-sharing/data-management-plans/>

MRC Ethics Publication: Good Research Practice 2012

<http://www.mrc.ac.uk/research/policies-and-resources-for-mrc-researchers/good-research-practice/>

MRC Ethics Publication: Human Tissue and Biological Samples for Use in Research (2014)

<http://www.mrc.ac.uk/publications/browse/human-tissue-and-biological-samples-for-use-in-research/>

MRC Policy on Open Research Data from Clinical Trials and Public Health Intervention Studies

<https://www.mrc.ac.uk/documents/pdf/mrc-policy-on-open-research-data/>

MRC Policy of Sharing of Research Data from Population and Patient Studies

<http://www.mrc.ac.uk/publications/browse/mrc-policy-and-guidance-on-sharing-of-research-data-from-population-and-patient-studies/>

MRC/Wellcome Trust Framework on the Feedback of Health-Related Findings in Research

<https://www.mrc.ac.uk/documents/pdf/mrc-wellcome-trust-framework-on-the-feedback-of-health-related-findings-in-researchpdf/>

APPENDIX 2: LINKS TO ADDITIONAL INFORMATION

Clinical Trials Tool Kit

- Designed for clinical trials in the UK but with some guidance that is more widely applicable.
www.ct-toolkit.ac.uk

CONSORT Statement (Consolidated Standards of Reporting Trials)

- A minimum set of recommendations for reporting randomised trials.
<http://www.consort-statement.org/>

Council for International Organizations of Medical Sciences (CIOMS): International Ethical Guidelines for Health-Related Research Involving Humans (2016)

<http://cioms.ch/ethical-guidelines-2016/WEB-CIOMS-EthicalGuidelines.pdf>

Declaration of Helsinki: Ethical Principles for Medical Research on Human Subjects

- Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and most recently amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.
<http://www.wma.net/en/30publications/10policies/b3/>

Global Health Network (GHN)

- An online resource for researchers undertaking global health trials.
<https://tghn.org/>

Global Health Training Centre (associated with the GHN)

- Provides online e-learning courses and other resources for global health trials, including:
 - GCP
 - trial management
 - roles of the Trial Steering Committee and Data Monitoring Committee
 - data management
 - community engagement
 - ethics issues, e.g. informed consent, return of results and standard of care.

<https://globalhealthtrainingcentre.tghn.org/elearning/>

International Conference on Harmonization (ICH) guideline on Good Clinical Practice (1996)

<http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html>

ISRCTN

- A registry for clinical and public interventional studies involving human participants. Each registered study is assigned a unique ISRCTN number.

www.isrctn.com/

Nagoya protocol

- An international protocol on access to genetic resources and equitable sharing of the benefits arising from the use of these, for example in health research.

https://en.wikipedia.org/wiki/Nagoya_Protocol

SPIRIT Statement (Standard Protocol Items: Recommendations for Interventional Trials)

- SPIRIT is an international initiative that aims to improve the quality of clinical trial protocols by defining an evidence-based set of items to include or address.

<http://www.spirit-statement.org/>

Wellcome Trust/World Health Organisation (WHO)

- The following pages from the Wellcome Trust website provide guidance for research involving people in low- and middle-income countries.

<https://wellcome.ac.uk/funding/guidance/guidance-notes-research-involving-people-low-and-middle-income-countries>

- The WHO and Wellcome Trust commissioned a report on good practice in the management and sharing of health data collected in low resource settings.

https://figshare.com/articles/Sharing_health_research_data_in_low-resource_settings_Supporting_necessary_infrastructure_and_building_on_good_practices/6042047

APPENDIX 3: TRIAL STEERING COMMITTEE (TSC)

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

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 Committee;
- 4) to report to the Sponsor on progress of the trial, and if necessary to MRC as funder.
- 5) to advise Principal Investigator, Sponsor and MRC as funder on publicity and the presentation of all aspects of the trial.

Membership

The proposed membership should be submitted to the MRC.

Members	Invited to attend
<ul style="list-style-type: none"> • At least 50% of members should be independent of the investigators, i.e. not involved directly in the trial nor having any relationship to the investigators, their funders²⁰ or sponsors, nor employed by the investigators' employing organisations. <p><i>Members should include:</i></p> <ul style="list-style-type: none"> • At least two independent expert(s) in the field (for example clinicians with experience in the relevant area) • One member should be an independent expert with experience of conducting trials in low income settings • Policy stakeholders from the Ministry/Department of Health in the proposed setting • Members of relevant stakeholder groups, e.g. local NGOs operating in the field, representatives from user or community groups, other funders if relevant • Senior staff in the trial team, e.g. PI, co-investigators, trial statistician, health economist, etc 	<p><i>Observers should include representative(s) of the:</i></p> <ul style="list-style-type: none"> • Funder (usually the MRC) • Host Institution • Sponsor

²⁰ The Chair or TSC members may still be considered independent if they have previously received an award from the same funder as the investigators, as long as this is unrelated to the trial and membership is agreed with the MRC.

APPENDIX 4: DATA MONITORING COMMITTEE (DMC)

A Data Monitoring Committee should be established with the following terms of reference and membership. The Data Monitoring Committee should be completely independent from the trial. Trialists are advised to consider developing a Data Monitoring Committee Charter (as proposed by the DAMOCLES Study Group, Lancet 2005;365;711-22).

Terms of Reference

- to determine if additional interim analyses of trial data should be undertaken
- 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
- after considering interim analyses and ensuring that the safety, rights and wellbeing of the trial participants are paramount, to report (following each Data Monitoring Committee meeting) to the Trial Steering Committee and to recommend on the continuation of the trial
- to consider any requests for release of interim trial data and to recommend to the Trial Steering Committee on the advisability of this
- in the event of further funding being required, to provide to the Trial Steering Committee and MRC appropriate information and advice on the data gathered to date that will not jeopardise the integrity of the study.

Membership

The proposed membership should be submitted to the MRC.

Members	Invited to attend
<ul style="list-style-type: none">• The membership of the Data Monitoring Committee 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)	<ul style="list-style-type: none">• The trial statistician may be invited to attend for part of the Data Monitoring Committee meeting to present the most current data from the trial, unblinded/unmasked if appropriate.

APPENDIX 5: TRIAL DOCUMENTATION

Clinical trials funded by the MRC should maintain appropriate documentation. Guidance and templates for documents which should be retained are provided below.

The MRC requires notification of any changes to the funding proposal, annual progress reports (or copies of minutes of the Trial Steering Committee), and may request copies of other trial documentation.

TEMPLATE FOR REPORTING TO TRIAL STEERING COMMITTEE, FUNDER AND SPONSOR

Presented below is a list of information that should be provided by investigators for discussion at Trial Steering Committee meetings and included in the Principal Investigator's annual report to MRC. The Principal Investigator may submit full copies of all Trial Steering Committee minutes to the MRC each year instead of an annual report if these include all of the relevant information. It is suggested that meeting agendas and the annual report are based on the headings listed below. These headings may not be appropriate at every stage of an individual trial or for all trials.

	Target (date target set)	Achieved (date achieved)
Title of Trial		
Grant No.		
Sample size sought		
Date recruitment started		
Proposed date for recruitment end		
Actual recruitment rate versus target rate (by month/quarter)		
Acceptance rate, as a proportion of those invited to participate and if known all eligible participants		
Quarterly/monthly forecasts of recruitment for the planned remainder of the trial		
Losses to follow-up, as a proportion of those entered, and per month/quarter		
No. for whom follow-up has been completed successfully (or still being successfully followed-up)		
Completeness of data collected		
Any available results (pooled)		
Any organisational problems		
Issues specific to individual trials (to be specified by the Trial Steering Committee)		

ESSENTIAL DOCUMENTS - BEFORE THE CLINICAL PHASE OF THE STUDY BEGINS

Document	Principal Investigator/ co-ordinating centre/ Sponsor(s)	Co-Investigator(s)
Final protocol, including <ul style="list-style-type: none"> - Patient information - Consent form - Case record forms - Instructions on handling trial product 	Yes	Yes
Investigator agreement on final protocol (Participation form or agreement)	Yes	-
Investigator's Brochure or Summary of Product Characteristics (SMPC)	Yes, if applicable	Yes, if applicable
Local variation on <ul style="list-style-type: none"> - Patient information - Consent form - Advertising 	Yes	Yes
Ethics approval	Yes	Yes (local approval)
NHS R&D Management permission (<i>for trials which are wholly or partially conducted in the UK</i>)	Yes, if applicable	If applicable (local permission)
Clinical Trial Authorisation, and other regulatory approvals	Yes, if applicable	Yes, if applicable
Contract or agreements, e.g. with participating sites	Yes, if applicable	Yes, if applicable
Investigator's qualifications (CV)	Yes (known consultant/GP post acceptable)	Yes
List of Investigators	Yes	Yes
List of pharmacy contacts	Yes, if applicable	Yes, if applicable
Normal Ranges	Yes, if applicable	Yes, if applicable
List of signatures of staff who will be signing study documents	Yes, if applicable	Yes, if applicable
Sample label	Yes, if applicable	Yes, if applicable

ESSENTIAL DOCUMENTS - ONCE THE CLINICAL PHASE OF THE STUDY HAS BEGUN

Document	Principal Investigator/ co-ordinating centre/ Sponsor(s)	Co-Investigator(s)
Protocol revisions: - Amendments - Case record forms - Patient information	Yes	Yes
Ethics approval necessary for any protocol revision	Yes	Yes
NHS R&D Management permission for any related protocol revision	Yes, if applicable	If applicable (local permission)
Regulatory authority approval necessary for any protocol revision	Yes, if applicable	Yes, if applicable
Investigator's Brochure updates or Revisions to the Summary of Product Characteristics (SMPC)	Yes, if applicable	Yes
New Investigator's qualifications (CV)	Yes (known consultant/GP post acceptable)	Yes
List of new Investigators	Yes	-
Change to normal ranges	Yes, if applicable	Yes, if applicable
Change to list of signatures	Yes, if applicable	Yes, if applicable
Monitoring visit reports	Yes, if applicable	Yes, if applicable
Record of communications with sites: - letters, telephone - calls	Yes	Yes
Signed consent forms	If applicable	Yes
Complete CRFs: - Include SAE reports from that site	Yes (original)	Yes (copy)
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

Version Control

Version	Date	Summary of changes	Approved by
1.0	22 Feb 2017	New guidance aimed at global health trials.	MRC Ethics Regulation and Public Involvement Committee (MRC ERPIC)
2.0	14 Jan 2019	Review and update. Changes to Sections 6.1.1 and 6.2.1, Additional Resources (page 34), Annex 3.	Head of Global Health Strategy, MRC
3.0	09 October 2019	Changes to Sections 6.1.1 and annex 3 to clarify 'independent'. New footnotes added to pages 24 and 35.	

