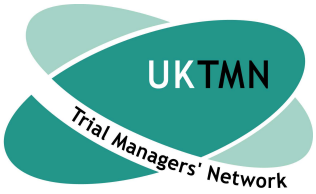


UK Trial Managers' Network

A GUIDE TO EFFICIENT TRIAL MANAGEMENT

Third Edition: 2006

This guide has been compiled to help those involved in managing trials, to make their work more efficient and enjoyable. Guidance can change so please use the links to ensure you have the most up to date information. We welcome suggestions or constructive criticism for the next version, to ensure a constantly improving guide.

This guide has been written and co-ordinated by Barbara Farrell and Sara Kenyon in collaboration with members of the UK Trial Managers' Network Steering Group.

We wish to thank all organisations and individuals who have contributed to this document.

A GUIDE TO EFFICIENT TRIAL MANAGEMENT

Section 1: WHY DO A RANDOMISED TRIAL?

Assessment of the risks and benefits of a new treatment or other intervention needs to be based on reliable evidence. The most reliable evidence is best obtained by carrying out randomised trials to compare outcomes of similar groups of participants either receiving the new intervention or the current standard intervention or if there is no current standard a placebo (or no active treatment). These trials need to be large enough to estimate the effects of an intervention or procedure with a high level of confidence.

The group that does not receive the intervention being evaluated is called the control group. This group may receive the standard intervention or, if there is no standard intervention available, no intervention or a placebo (dummy) intervention

Ethically, equipoise should exist for a randomised trial to be undertaken: that is, genuine uncertainty about the additional benefits and risks of the new intervention over the current standard intervention.

Randomised trials are the gold standard (Pocock, 1983) as they aim to minimise potential biases in the estimation of the effect of the intervention. The two primary ways of minimising bias are randomisation and blinding. Chance effects are minimised by including large enough numbers of participants.

Randomisation & methods

Randomisation

In a randomised trial designed to evaluate a novel intervention versus control with equal numbers in each group (1:1), random allocation of the trial intervention gives all participants the same chance of receiving the new or control intervention. Allocation is independent of the characteristics of the participants (unless the allocation uses stratification or minimisation, see below) and preferences or prejudices of the investigator and participants. This can only be achieved if concealment of intervention allocation is secure such that the investigator and participants are ignorant of, and unable to predict, the next intervention allocation.

Randomisation methods

Simple randomisation – allocation decided by [the equivalent of] a random number table, computer program or by the toss of a coin.

Minimisation – improves balance between the groups in terms of important characteristics, especially in small samples. It is based on the idea that the next participant to enter the trial is more likely to be allocated the intervention that would minimise the overall imbalance of selected characteristics between the groups at that stage.

Blocked (or restricted) randomisation – interventions assigned randomly within blocks to ensure balance within the blocks. Blocks can be of any size but a multiple of the number of trial groups is logical. The block size should be small and variable, and unknown to the investigators, to prevent predictability and maintain concealment.

Stratified randomisation – gives a balance within sub-groups defined by important variables such as centre/country in a multicentre trial. Blocked randomisation must be used within each strata. Stratification is not feasible for small studies or for many variables.

Cluster randomisation – the unit of randomisation is not the individual participant being studied but groups of participants (clusters), such as a GP practice or village community. This design is particularly appropriate when the intervention is at a group level. The overall sample size required is larger because the analysis is based on the cluster unit.

Blinding (also known as masking)

Double Blind

Both investigator and participant are ignorant of the intervention allocation.

Single Blind

Either the participant or the investigator is unaware of the intervention allocated. Usually it is the participant who is 'blind'.

Whether or not it is possible to 'blind' the participant and the care-giver, the outcomes should be well defined and objective and the person assessing the pre-specified outcomes should, whenever possible, be ignorant of (blind to) the intervention allocated.

Placebos

Placebos are dummy interventions often used in drug trials. Although more difficult to organise in non-drug trials of complex interventions, placebos are sometimes both feasible and desirable in this setting. If there is no existing standard intervention then giving the control group no active intervention is ethical, and blinding can be achieved by use of a placebo. The placebo must be (pharmacologically) inactive but identical in appearance, taste etc. to the active intervention.

'Double dummy' placebo

In many trials where there is an existing treatment for a disease it is not appropriate or ethical to withhold treatment from the control group and therefore the comparison is between the new treatment and the standard treatment. In order to blind both the participants and the clinical team various methods can be adopted. Ideally the new treatment and standard treatment would be prepared in such a way that they cannot be distinguished (except by laboratory analysis). This is often not feasible as the two preparations may have very different characteristics. The "double-dummy" technique is often used in these circumstances. Placebo preparations for both treatments are required so that the group allocated to the new treatment receive a placebo matched to the standard treatment and those allocated to the standard treatment receive a placebo matched to the new treatment. One disadvantage of this approach is that participants have to have extra 'trial treatments' and this may reduce compliance.

Sample size
The planned sample size (number of participants needed in the trial) is calculated to ensure a high chance of detecting a clinically important difference at a specified level of statistical significance if one truly exists. In order to calculate the sample size the number of primary events (event rate) in the control group must be known or estimated reasonably accurately so that a realistic estimate of the size of effect of the intervention can be made. It is usually prudent to have a slightly larger than required sample size to allow for dropouts or poor adherence. (Similar calculations can be made for other types of outcomes such as 'means'.) The sample size must be pre-specified but may be reviewed during the course of a trial especially if event rates are not well known. The sample size provides the overall recruitment target for the trial.

Power
The probability that a study of a given size will detect a clinically important difference at a given level of significance, if a true difference of a certain size exists, is known as the statistical 'power'. The greater the 'power', the more certain it is that the trial will be able to detect the difference if it exists, but also the larger the sample size needed.

Confidence intervals
A confidence interval is the range of effect sizes around the estimate for the trial that is likely to include the true value. Commonly a 95% confidence interval is used, giving a 95% chance that the true value is within this interval, but 80%, 90% and 99% are alternatives.

Confounding
Confounding occurs when the interventions to be examined are not the only difference between the groups being compared, so that differences in outcome may not be due to the intervention. A trial comparing participants allocated intervention **A** versus those allocated intervention **A** plus intervention **B** in parallel, is not confounded for the evaluation of intervention **B**, since this is the only difference between the regimens.

Types of trials assessing medicines

Phase I First test of drug in humans. Usually not placebo controlled, small studies.
- to establish safe/tolerable levels
- to establish initial pharmacokinetics
- usually includes healthy volunteers (who may be paid) but may be patients

Phase II May or may not be a randomised and/or placebo controlled study
- includes participants with the disease
- to provide evidence of activity and better evidence of safety
- to define dosage and regimen

Phase III Comparative, controlled trials

- includes participants with the disease
- assess the efficacy, safety and therefore the balance of risks and benefits
- to compare benefits and side effects with those of standard treatment or a placebo or both

Phase IV

Phase IV trials evaluate medicines that are already available for doctors to prescribe, rather than new medicines that are still being developed. Phase IV trials include participants with the disease

Main reasons for conducting phase IV trials are to find out

- more about the side effects and safety of the drug in a larger population
- what the long term risks and benefits are by conducting long term follow-up
- how well the medicine works when used in a broader population or in a combination of treatments

SECTION 2: THE REGULATIONS

WHAT APPROVALS AND PERMISSIONS ARE NEEDED?

All UK research

All clinical research conducted within the NHS must comply with the NHS Research Governance Framework. A Sponsor must be identified and approval obtained from an Ethics Committee and relevant NHS R&D departments. These steps may be done in parallel.

Additional requirements for trials testing or evaluating a medicinal product

For a trial testing or evaluating a medicine (often referred to as a trial of an Investigational Medicinal Product (IMP)) there are a number of additional steps to follow before a trial can commence. The first step is to confirm that the trial falls within the scope of the UK Regulations of Medicines for Human Use (Clinical Trials). The EU Directive on Clinical Trials was transposed into UK law on 1st May 2004 as the UK Regulations of Medicines for Human Use (Clinical Trials). These are the regulations that govern all clinical trials of a medicinal product and they conform to the requirements of the EU Directive.

If the trial does fall within the scope of the regulations, then the trial protocol should be written with the regulations in mind. A EudraCT number must be obtained from European Medicines Agency (EMEA), followed by an application for authorisation from MHRA (Clinical Trial Authorisation) and a favourable opinion (approval) by an Ethics Committee. R&D permission is also required before a trial can commence in any clinical site. The application for the Clinical Trial Authorisation, Ethics Committee Approval and R&D permission can be submitted in parallel.

MHRA have developed an algorithm (below) to help determine whether or not a trial falls within the scope of the UK Regulations of Medicines for Human Use (Clinical Trials).

Note: For international trials the regulations are more complex, generally involving getting approvals and authorisations from each national body, i.e. ethics committee approval, Competent Authority, Ministry of Health.

Algorithm produced by the MHRA

IS IT A CLINICAL TRIAL OF AN IMP?

This algorithm will help you answer that question. Please start in column A and follow the instructions.

If you answer yes to any of the questions below go to column B. If you answer no to all these questions, the activity is not a clinical trial.	If you answer no to the question below go to column C. If you answer yes to this question the activity is not a clinical trial.	If you answer yes to any of the questions below go to column D. If you answer no to all the questions the activity is not a clinical trial.	If you answer yes to any of the questions below go to column E. If you answer no to both these questions the activity is not a clinical trial.	If you answer yes to any of the questions the activity is a clinical trial. If you answer no to all these questions the activity is not a clinical trial.
A	**B**	**C**	**D**	**E**
Is it a medicinal product?	**Is it not a medicinal product?**	**What effects of the medicine are you looking for?**	**Why are you looking for those effects?**	**How are you looking for those effects?**
Are you administering a substance to a human subject?	Are you only administering any of the following substances? - Human whole blood - Human blood cells - Human plasma - Tissues except a somatic cell therapy medicinal product - A food product (including dietary supplements) not presented as a medicine. - A cosmetic product - A medical device	To discover its clinical effects?	To ascertain efficacy of the medicine?	Is the prescription of the medicine linked to the decision to include the patient in the study?
Is the substance presented as a medicine (i.e. for preventing or treating disease.)		To discover its pharmacological effects?	To ascertain the safety of the medicine?	Is the medicine prescribed in a manner outside the terms of the marketing authorisation?
Does the substance function as a medicine i.e. can it be administered, with a view to making a medical diagnosis, to restore, correct or modify physiological functions in human beings or is otherwise administered for a medicinal purpose?		To discover its pharmacodynamic effects?		Does the protocol specify when the patient will take the medicine?
Is it an active substance in a pharmaceutical form?		To identify adverse reactions?		Is any diagnostic or monitoring procedure added to the patients' usual therapeutic strategy?
Is the substance an ingredient in the preparation of a combination of substances administered for a medicinal purpose?				
Is it being used for a medicinal purpose?		To study its absorption, distribution, metabolism or excretion?		Will methods other than epidemiological methods be used to analyse the collected data?

For more information and to obtain a pdf of this algorithm:
http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=723

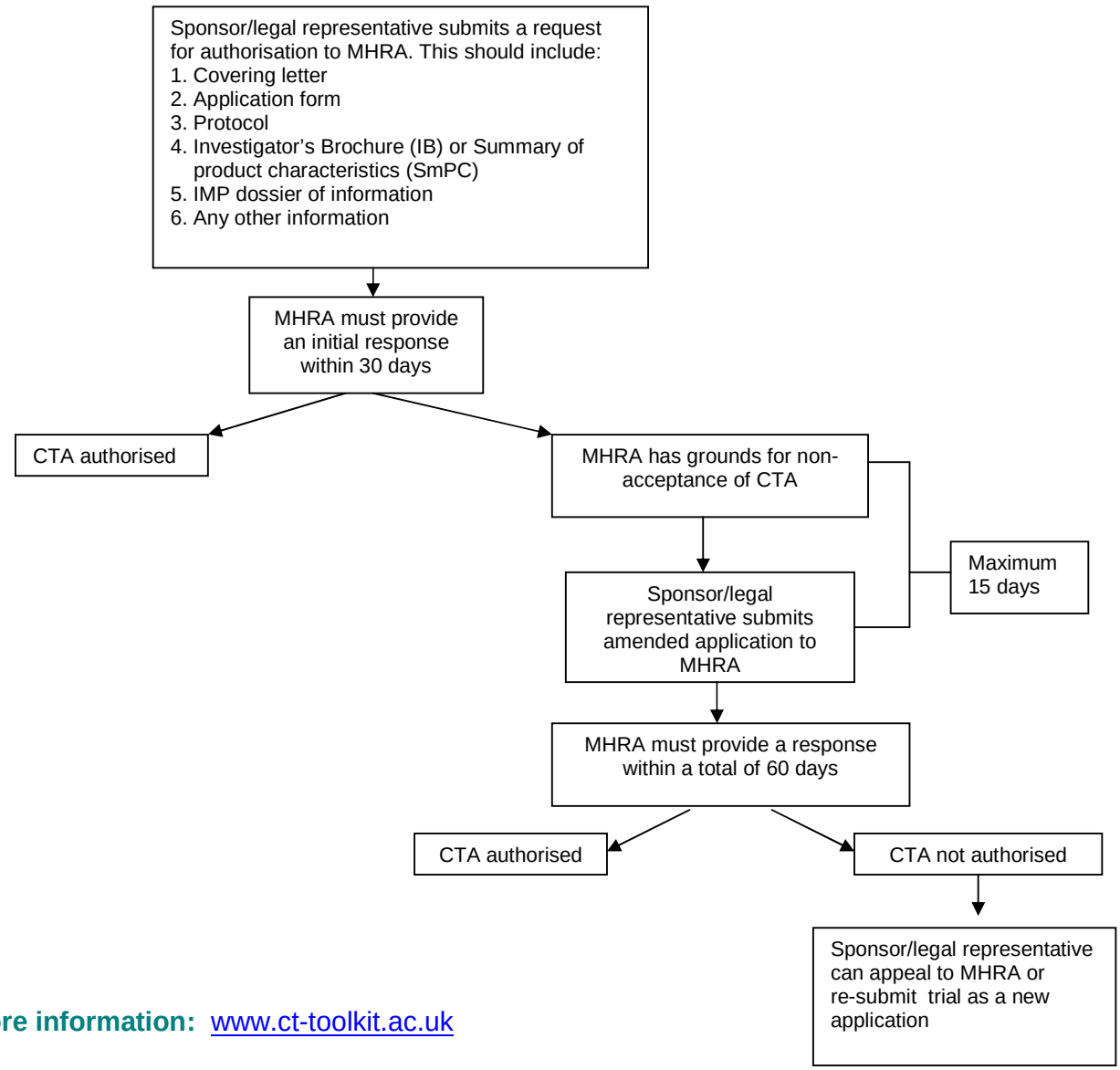
EudraCT Number

It is required that you register your trial, if it is evaluating a medicinal product, on the EudraCT database by obtaining a EudraCT number using the on-line registration system. One number per trial is issued and this becomes the main identifier for the trial and should be used on all correspondence with MHRA, Ethics Committees and when reporting amendments, SUSARs etc.

For more information see: *http://eudract.emea.eu.int/*

CLINICAL TRIAL AUTHORISATION

Obtaining a Clinical Trial Authorisation (CTA)



For more information: www.ct-toolkit.ac.uk

ETHICS APPROVAL AND ETHICS COMMITTEES

Ethics committee approval is required for all clinical trials
An ethics committee is an independent body comprised of medical and lay members whose responsibility is to check that participant's rights, safety, and well being are maintained with regard to confidentiality, informed consent and protection from harm. Ethics committees are guided by the Declaration of Helsinki.

For more information: *http://www.fda.gov/oc/health/helsinki89.htm*
http://www.emea.eu.int/pdfs/human/ich/013595en.pdf

CENTRAL OFFICE FOR RESEARCH ETHICS COMMITTEES (COREC)

All multicentre clinical trials in the UK should obtain ethics committee approval using the centralised system. An up to date, concise, easy to follow guide on how to apply for single and multicentre ethics committee approval has been prepared by COREC and is available on the COREC website.

For more information: http://www.corec.org.uk

PARTICIPANTS' INFORMATION LEAFLETS

The elements to be included in an Information Leaflet provided for participants can be viewed on the COREC website.

Remember to make sure information is

- clear
- relevant
- appropriate to the participant and their situation

The participant information leaflet should contain information about the trial under the headings described below. These headings can be re-worded and re-ordered provided the information leaflet contains all the necessary information to ensure a participant is fully informed and the ethics committee approves it.

1. Study title
2. Invitation paragraph
3. What is the purpose of the study?
4. Why have I been chosen?
5. Do I have to take part?
6. What will happen to me if I take part?
7. What do I have to do?
8. What is the drug or procedure that is being tested?
9. What are the alternatives for diagnosis or intervention?
10. What are the side effects of taking part?
11. What are the possible disadvantages and risks of taking part?
12. What are the possible benefits of taking part?
13. What if new information becomes available?
14. What happens when the research study stops?
15. What if something goes wrong?
16. Will my taking part in this study be kept confidential?
17. What will happen to the results of the research study?
18. Who is organising and funding the research?
19. Who has reviewed the study?
20. Contact for more information

For more information: http://www.corec.org.uk

ICH GCP 4.8.10: http://www.emea.eu.int/pdfs/human/ich/013595en.pdf

INFORMED CONSENT PROCEDURES

Informed consent procedures have recently been reviewed by COREC (Central Office for Research Ethics Committees) in light of the EU Clinical Trials Directive and UK Regulations of Medicines for Human Use (Clinical Trials).

UK Regulations of Medicines for Human Use (Clinical Trials) definition of informed consent is:

A person gives informed consent to take part in a clinical trial only if the decision:

- is given freely after that person is informed of the nature, significance, implications and risks of the trial; and

either

- is evidenced in writing, dated and signed, or otherwise marked, by that person so as to indicate his consent,

or

- if the person is unable to sign or to mark a document so as to indicate his consent is given orally in the presence of at least one witness and recorded in writing.

Adults: procedures to be followed

- Information provided in advance, where possible, and reasonable time allowed for consideration
- The person has had an interview with the investigator, or another member of the investigating team, in which he has been given the opportunity to understand the objectives, potential benefits and risks and inconveniences of the trial and the conditions under which it is to be conducted.
- The person has been informed of his right to withdraw from the trial at any time.
- The person has given informed consent to taking part in the trial.
- The person has been provided with a contact point where he may obtain further information about the trial.
- The person may, without being subject to any resulting detriment, withdraw from the clinical trial at any time by revoking the informed consent.

COREC have provided details of informed consent procedures for minors and incapacitated adults (see below).

NOTE: Procedures for incapacitated adults are different in Scotland. Always refer to the applicable regulations.

Table 1: INFORMED CONSENT FOR A MINOR DEFINED AS < 16 YEARS OF AGE

	Person who may gi consent	Definition	Commentary
1.	Parent	A parent or person with parental responsibility.	Should always be approached if available.
2.	Personal legal representative	A person not connected with the conc of the trial who is: (a) suitable to act as the legal representative by virtue of their relationship with the minor, **and** (b) available and willing to do so.	May be approached if no person with parental responsibility can be contact prior to the proposed inclusion of the minor, by reason of the emergency nature of the intervention provided as part of the trial.
3.	Professional legal representative	A person nominated by the relevant health care provider (e.g. an acute NI Trust or Health Board) who is not connected with the conduct of the tria	May be approached if no person suita to act as a personal legal representat is available.

Table 2: INFORMED CONSENT FOR AN INCAPACITATED ADULT

England, Wales and Northern Ireland	Scotland
1. Personal legal representative A person not connected with the conduct of the trial w is: (a) suitable to act as the legal representative by virtue of their relationship with the adult, **and** (b) available and willing to do so.	**1. Personal legal representative** 1A. Any guardian or welfare attorney who has powe (in law) to consent to the adult's participation in research. 1B. If there is no such person, the adult's nearest relative as defined in section 87(1) of the Adults with Incapacity (Scotland) Act 2000.
2. Professional legal representative A person not connected with the conduct of the trial w is: (a) the doctor primarily responsible for the adult's medical care, **or** (b) a person nominated by the relevant health care provider (e.g. an acute NHS Trust) A professional legal representative may be approach no suitable personal legal representative is available.	**2. Professional legal representative** A person not connected with the conduct of the trial who is: (a) the doctor primarily responsible for the adult's medical care, **or** (b) a person nominated by the relevant health care provider. A professional legal representative may be approac if it is not reasonably practicable to contact either 1A 1B before the decision to enter the adult into the tria made.

NOTE: Procedures for incapacitated adults are different in Scotland. Always refer to the applicable regulations.

For more information*:* http://www.corec.org.uk

PATIENT INFORMATION ADVISORY GROUP (PIAG)

The government has stated, in the NHS Plan [and elsewhere] that the fundamental principle governing the use of information which individuals provide, in confidence, to the NHS is that of informed consent.

Section 60 of the Health and Social Care Act 2001 was introduced to provide a legal framework to permit essential clinical and epidemiological research to continue until measures were in place to anonymise patient data or informed consent for the use of those data could be obtained. The Patient Information Advisory Group (PIAG) was established in 2001 as an independent statutory body under the Health and Social Care Act to provide reassurance to the Secretary of State, through monitoring and oversight, that the use of information, where consent was not obtained, was appropriate. Section 60 does not apply in Scotland.

If a project is intending to use identifiable patient data without consent (because it is scientifically justifiable and/or it is impractical to obtain consent) approval must be obtained from a Research Ethics Committee and then from PIAG.

PIAG is not relevant to clinical trials where informed consent is usually obtained before a participant is recruited.

For more information: http:// www.advisorybodies.doh.gov.uk/piag

INFORMATION COMMISSION - DATA PROTECTION

The Data Protection Act

The Data Protection Act provides a legal framework for protecting personal rights and, in the case of clinical trials, protecting the participant and the researcher.

The Data Protection Act (1984) stipulated eight principles which researchers should adhere to when handling personal data. These principles only apply to paper records.

The eight principles of data handling are:

1. fair and lawful
2. processed for limited purposes
3. adequate, relevant and fit for purpose
4. accurate
5. not kept for longer than necessary
6. processed in line with the data subject's rights
7. stored securely
8. not transferred to countries without adequate data protection

The Data Protection Act (1998) came into force in March 2000. There are six important differences between the two Acts and four important dates.

The six differences are:

1. applies to both computer and paper records
2. includes obtaining, storing, organising, using and disclosure of data
3. applies to correspondence and publications using the data obtained
4. applies to sensitive personal data which includes: race, ethnicity, politics, religion, trade union membership, physical or mental health, sexual orientation or behaviour or criminal record
5. covers the rights of individuals: right of access, notification of use, notification of disclosure
6. prevents identifiable data being transferred outside the EU without appropriate waiver (individual or country)

Important dates

- **All** data being processed for the first time after **24 October 1998** came under the 1998 Act on **1 March 2000.**
- **Computer records** that were being processed on or before **24 October 1998** became subject to the 1998 Act on **24 October 2001.**
- **Paper records** that were being processed on or before **24 October 1998** become subject to the 1998 Act on **24 October 2007.**

See **Section 4** for trial management implications of the Data Protection Act.

For more information
http://www.informationcommissioner.gov.uk/eventual.aspx?id=34

FREEDOM OF INFORMATION ACT

The **Freedom of Information Act 2000 (FOI)** gives individuals a general right of access to information held by or on behalf of public authorities. It is intended to promote a culture of openness and accountability amongst public sector bodies, and therefore to facilitate better public understanding of how public authorities carry out their duties, why they make the decisions they do, and how they spend public money.

From the 1st January 2005, any person who makes a written request to a public authority for information must be informed whether the public authority holds that information, and, subject to exemptions, be supplied with that information. The public authority must reply promptly, not later than the 20th working day following receipt of the request for information, and in the format requested.

Exemptions

There are 23 exemptions from the general rights of access e.g. information relating to national security, information that would prejudice international relations, commercially sensitive information and confidential information.

For more information:
http://www.informationcommissioner.gov.uk/eventual.aspx?id=33

NHS RESEARCH GOVERNANCE FRAMEWORK

This document sets out a framework for the governance of research in health and social care in the UK. The standards in this framework apply to all research which relates to the responsibilities of the Secretary of State for Health - that is research concerned with the protection and promotion of public health, research undertaken in or by the Departments of Health, non-Departmental Public Bodies and the NHS, and research undertaken by or within social care services that might have an impact on the quality of those services. This includes clinical and non-clinical research, research undertaken by NHS staff using NHS resources, and research undertaken by industry, charities, research councils and universities within the health and social care systems.

Research Governance

- sets standards
- defines mechanisms to deliver standards
- describes monitoring and assessment arrangements

Aims to improve research quality and safeguard the public by:

- enhancing ethical and scientific quality
- promoting good practice
- reducing adverse incidents and ensuring lessons are learned
- preventing poor performance and misconduct

Applies to everyone who:

- participates in research
- hosts research in their organisation
- funds research proposals or infrastructure
- manages research
- undertakes research

Research Governance is for researchers, managers and staff, in all professional groups, no matter how senior or junior.

For more information:
http://www.dh.gov.uk/PolicyAndGuidance/ResearchAndDevelopment/ResearchAndDevelopmentAZ/ResearchGovernance/fs/en

NHS RESEARCH AND DEVELOPMENT (R&D) APPROVAL

All projects which involve NHS staff, patients, patient samples, patient records or facilities should be registered with the R&D Office and require approval from the R&D directorate. A project should be registered with R&D departments as early as possible in the development phase, particularly if that NHS Trust is proposed as sponsor.

Anyone proposing to undertake a research project must gain approval from the relevant head of department for the facilities they intend to use e.g. Head of Academic Unit, Clinical Director, and Business Manager. Any NHS support service requirements will be costed and reviewed as necessary.

The R&D standard application form can be found on the joint COREC / R&D website. It is possible to complete applications for both ethics approval and R&D permission simultaneously by using the on-line application process.

For more information:
http://www.dh.gov.uk/PolicyAndGuidance/ResearchAndDevelopment/ResearchAndDevelopmentAZ/ResearchGovernance/fs/en
http://www.corec.org.uk/

GOOD CLINICAL PRACTICE (GCP) IN CLINICAL TRIALS OF MEDICINAL PRODUCTS (as described in the UK Regulations of Medicines for Human Use (Clinical Trials))

The Principles of GCP as applied to trials of investigational medicinal products (IMPs)

1. Clinical trials shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with good clinical practice and the requirements of the UK Regulations of Medicines for Human Use (Clinical Trials).

2. Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial participant and other present and future patients. A trial should be initiated and continued only if the anticipated benefits justify the risks.

3. The rights, safety, and well being of the trial subjects are the most important considerations and shall prevail over interests of science and society.

4. The available non-clinical and clinical information on an investigational medicinal product (IMP) shall be adequate to support the clinical trial.

5. Clinical trials shall be scientifically sound, and described in a clear, detailed protocol.

6. A trial shall be conducted in compliance with the protocol that has a favourable opinion from an ethics committee.

7. The medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified dentist.

8. Each individual involved in conducting a trial shall be qualified by education, training, and experience to perform his or her respective task(s).

9. Subject to the other provisions relating to consent, freely given informed consent shall be obtained from every subject prior to clinical trial participation.

10. All clinical trial information shall be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

11. The confidentiality of records that could identify subjects shall be protected, respecting the privacy and confidentiality rules in accordance with the requirements of the Data Protection Act 1998 and the law relating to confidentiality.

12. Investigational medicinal products (IMPs) used in the trial shall be -

    a. manufactured or imported, and handled and stored, in accordance with the principles and guidelines of good manufacturing practice, **and**

b. used in accordance with the approved protocol.

13. Systems with procedures that assure the quality of every aspect of the trial shall be implemented.

14. A trial shall be initiated only if an ethics committee and the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.

15. The rights of each subject to physical and mental integrity, to privacy and to the protection of the data concerning him or her in accordance with the Data Protection Act 1998 are safeguarded.

16. Provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor that may arise in relation to the clinical trial.

Most of the above principles also apply in trials not assessing a medicinal product.

For more information:
http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=722
http://pharmacos.eudra.org/F2/eudralex/vol1/DIR_2005_28/DIR_2005_28_EN.pdf
http://www.mrc.ac.uk/pdf-ctg.pdf

See Trial Management section for day-to-day implementation of GCP.

It is also good clinical practice to register all trials. One such register is the International Standard Randomised Controlled Trial Number (ISRCTN) Register.

For more information: http://www.controlled-trials.com/isrctn/
http://www.icmje.org/clin_trialup.htm

PHARMACOVIGILANCE IN TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS (IMPS)

To comply with the UK Regulations of Medicines for Human Use (Clinical Trials), organisations taking on pharmacovigilance responsibilities need to make arrangements to record, notify, assess, report, analyse and manage adverse events in those trials.

The regulations distinguish between adverse events, Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs). The trial sponsor, or the delegated individual or organisation, must be notified of SAEs, SARs and SUSARS within the time specified in the protocol and have systems in place to ensure that they are assessed for

- causality (is it a reaction to a trial medicine or not?) and
- expectedness (is the reaction a recognised adverse effect of the medication or is it unexpected?)

The regulations allow the Sponsor/Chief Investigator to specify in the protocol SAEs that do not need to be notified immediately, for example if the event is one of the main outcomes in the trial.

Example 1: A mortality trial by definition expects deaths attributed to the disease being studied but unexpected deaths i.e. suicide, homicide or death from a road accident would be considered a SAE (but unlikely to be a SAR).

Example 2: A trial evaluating a medicine or procedure for stroke by definition would expect participants to suffer from strokes and consequent hospitalisation but hospitalisation due to unrelated surgery would be considered a SAE (but unlikely to be a SAR).

Sponsors have to make sure that SUSARS are reported promptly to both the regulatory authorities and the relevant Ethics Committee. The Regulations set time limits.

- Fatal or life threatening SUSARS:
  not later than **7 days** after the person responsible for pharmacovigilance received information that the case fulfilled the criteria for a fatal or life threatening SUSAR, and any follow-up information within a further 8 days.
- All other SUSARs:
  not later than **15 days** after the sponsor for pharmacovigilance had information that the case fulfilled the criteria for a SUSAR.

An annual safety report must be sent to the regulatory authorities and relevant Ethics Committee. The report should include adverse events (AE) explicitly detailed in the protocol; all reported Serious Adverse Events, Serious Adverse Reactions and SUSARs (see more information below).

The latest guidance from the MRC/DH Joint Project working group on Pharmacovigilance can be found at www.ct-toolkit.ac.uk

For more information:

- http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=101
- http://CIOMS.ch/cioms.pdf
- http://www.corec.org.uk/applicants/apply/safety.htm

PERMISSIONS FOR PARTICIPANT FOLLOW-UP

Both services described below are extremely useful if you are attempting to follow-up trial participants, and intend to use information from routine datasets such as national death and/or cancer registries. You will need approval from these agencies in addition to Ethics Committee approval and a Clinical Trial Authorisation (if appropriate). Details should also be included in the patient information leaflet and consent form if you plan to use either of these services.

OFFICE FOR NATIONAL STATISTICS (ONS)

The Office for National Statistics manages the National Health Service Central Register (NHSCR) that holds a record of all residents in England and Wales. The unique nature of the NHSCR can provide immensely helpful information for trials. Study participants can be 'flagged' as being in a study. Details such as date and cause of death, if a participant has left the country, and which Health Authority they are currently registered with, can be reported to researchers. A study that plans to use the facilities of the NHSCR must seek approval from the Chief Medical Statistician via the Office for National Statistics. There is a charge made for every participant flagged with the NHSCR.

Scotland and Northern Ireland have independent registries that offer the same service.

For more information : http://www.statistics/gov.uk/services/medical research

NHS STRATEGIC TRACING SERVICE (NSTS)

The NHS Strategic Tracing Service (NSTS) came into existence in 2002 and holds the database of people, places and organisations at the heart of the modern health care agenda. The database holds information including NHS number, name, date of birth, sex, date of death (if applicable), current address of all GP registered participants, GP details and practice addresses. The NSTS does not hold clinical data. The NSTS is probably more appropriate than the NHSCR if checking the whereabouts of a participant or if they have died and the date of death rather than cause of death.

The information is obtained from two key sources, General Practice (via the local Primary Health Care Trusts) and the Register of Births and Deaths (via the Office for National Statistics). It is comprehensive and covers all people in the NHS in England and Wales.

Researchers can apply to have access to this information but will also need to have access to the NHS intranet. Information can be obtained through NSTS by post if there is no access to the NHS intranet.

For more information: http//www.connectingforhealth.nhs.uk

A NATIONAL INFRASTRUCTURE – UK Clinical Research Collaboration (UKCRC)

Why was it set up?

In recent years there has been a growing realisation that the UK has not been realising the clinical research potential offered by the NHS. In response to these concerns the UKCRC was established to strengthen clinical research.

The UKCRC brings together the major stakeholders that influence clinical research in the UK and particularly in the NHS. The Collaboration includes representatives from: the main funding bodies for clinical research in the UK; the Departments of Health, the NHS; regulatory bodies; representatives from industry, charities, government and consumers.

The ultimate goal underpinning this initiative is to create a clinical research environment that will benefit participants and the public by improving national health, increasing national wealth, and enriching world knowledge.

For further information: http://www.ukcrc.org/

UKCRN

The UK Clinical Research Network (UKCRN) was established in February 2005 with funding from the Department of Health in England to provide a world-class health service infrastructure to support clinical research in the UK. It consists of a managed set of Clinical Research Networks, initially covering six priority topic areas – cancer, mental health, medicines for children, diabetes, stroke and dementias and neurodegenerative diseases. A Primary Care Research Network is also being established. The NHS R&D Strategy, Best Research for Best Health, launched in January 2006 introduces plans to extend the networks to other disease areas, enabling research to be conducted across the full spectrum of disease and clinical need. This will be known as the Comprehensive NHS Research Network for England (CRN).

Clinical Research Networks

- National Cancer Research Network (NCRN)
- Dementias and Neurodegenerative Diseases Research Network (DeNDRoN)
- Diabetes Research Network (DRN)
- Medicines for Children Research Network (MCRN)
- Mental Health Research Network (MHRN)
- Primary Care Research Network (PCRN)
- Stroke Research Network (SRN)

UKCRN aims to facilitate the conduct of randomised trials of interventions (including prevention, diagnosis, treatment, and care) and other well-designed studies in the broad area of clinical research through the creation of Clinical Research Networks and supporting related activities. Research funded by both commercial and non-commercial organisations will be supported.

How is UKCRN supporting the development and management of clinical research?

Expertise in the design, conduct and analysis of clinical trials and other well-designed studies is vital in order to ensure high quality, timely trial conduct and to meet regulatory and governance requirements. Links with those responsible for UKCRN studies is therefore key to the development of research activity within UKCRN. It is recognised that clinical trials management expertise can be provided in a number of ways, from specialised Clinical Trials Units (CTUs) set up with a specific remit to design, conduct and analyse multicentre clinical trials, to smaller teams established to work on indivudal studies.

It is important that those running UKCRN studies have the necessary specialist statistical, epidemiological and other methodological expertise required to undertake successful clinical trials. UKCRN is keen to ensure that those organisations responsible for co-ordinating UKCRN studies are supported and integrated with UKCRN and its activities.

In particular, it is important to ensure that those organisations co-ordinating UKCRN multicentre clinical trials are adequately resourced, in terms of access to expert staff and experience of co-ordinating such trials to high standards. It is also important to ensure that the research community has access to sufficient high quality clinical research management expertise, i.e. that there is sufficient national capacity to develop and manage the increasing numbers of trials that will result from the activities of UKCRC and UKCRN.

UKCRN will be undertaking work, together with the UKCRC partners, to document available expertise and to link those responsible for running UKCRN studies to the activities of UKCRN and its Research Networks.

Regulatory and governance advice

The regulatory and governance environment for clinical research in general, and clinical trials in particular, is complex. Researchers need to understand and comply with a wide range of legal requirements, most importantly the EU Clinical Trials Directive as translated into UK law, but also the NHS Research Governance Framework, the Data Protection Act and associated confidentiality requirements.

A UKCRN Regulatory and Governance team has been established to provide support and guidance in regulatory and governance issues to staff working on UKCRN studies, to help facilitate high quality clinical research. The team works closely with the UKCRC to promote a streamlined regulatory and governance environment, whilst protecting the rights, dignity and safety of participants.

The UKCRN Regulatory and Governance team aims to:

- develop clear national approaches to the implementation of regulatory and governance requirements
- act as a central source for advice, support and guidance
- promote models and examples of best practice, to streamline the clinical research process while ensuring the rights, dignity and safety of participants are protected.

For more information: http://www.ukcrn.org.uk/index.html

SECTION 3: GETTING STARTED

Assessing risk

It is recommended that researchers develop procedures and systems for trial management that meet the principles of GCP, and that these are clearly documented so that adherence is readily demonstrated.

For each clinical trial a risk assessment should generally be undertaken at the protocol development stage. This may be used to plan the details of trial management and the approach to, and extent of, monitoring in the trial. These plans should be documented, together with the risk assessment, so that the management strategy is both transparent and justified. This documentation is intended not only to facilitate the management of the trial but also to help prepare for internal audit and external inspection if the trial is evaluating an investigational medicinal product (IMP).

Thus, for each trial there would be:

- a clinical trial risk assessment
- a summary of trial management systems
- procedures for monitoring (centrally or at site)

These would not necessarily be separate documents and may be included in the protocol or in standard or trial-specific operating procedures.

For more information: http://www.ct-toolkit.ac.uk/

TRIAL OVERSIGHT

Trial oversight

Many trials supported by non-commercial funding bodies are overseen by three committees: a Trial Management Group (TMG), a Trial Steering Committee (TSC) and a Data Monitoring Committee (DMC)

Trial Management Group (TMG)

The Chief Investigator(s) (CI(s)) should form a small management group consisting of at least the CI(s), Trial Manager, programmer and statistician to consider day-to-day management issues and the overall progress of the trial. It may be beneficial to include a consumer, independent trialist or person with relevant expertise who can comment on the trial's progress from a different perspective. This group would meet frequently initially and then at least quarterly.

Trial Steering Committee (TSC)

Some sponsors recommend that there should be an independent Chairman, and at least two other independent members, a representative from a consumer group, plus the Chief Investigator(s), the Trial Manager, statistician and other relevant expertise e.g. health economist, psychologist etc. The Medical Research Council recommends that a TSC should meet once ethics approval has been given and before the trial begins recruitment, to agree Terms of Reference for the TSC and the final protocol. Once the trial has started the TSC should meet at least annually to monitor the progress of the trial. Meetings of the TSC may be called more frequently if the Chairman or the CI(s) think it is necessary. The TSC should provide oversight of the progress of the trial and ensure the trial is conducted in accordance with the principles of GCP.

Data Monitoring Committee (DMC)

Usually the Data Monitoring Committee is the only group to see the accumulating data by randomised group during the trial. All members of the Data Monitoring Committee should be totally independent of the trial. The trial statistician usually attends the meetings and presents the data. The DMC terms of reference, or Charter, should be agreed before the start of the trial at their first meeting and will outline any stopping rules and the frequency of interim data analyses during the recruitment phase of the trial. The DMC Chairman will report their recommendations to the Chairman of the Trial Steering Committee. During the course of the trial the DMC will also consider safety issues.

Whereas the default position is that a trial will have a DMC, for relatively small and/or low risk studies, the TSC may also assume the role of DMC. The TSC or the funder and/or sponsor may decide this.

Recommendations for the content of a DMC Charter can be found at www.abdn.ac.uk/hsru/documents/damocles2.doc

SUMMARY OF RESPONSIBILITIES OF SPONSORS FOR TRIALS INVOLVING MEDICINAL PRODUCTS

Sponsors are defined as the persons named as responsible for GCP in a clinical trial under the UK Regulations implementing EU Directive 2001/20/EC and the NHS Research Governance Framework.

Key points

Directive 2001/20/EC defines a sponsor as an *individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial*.

SPONSORSHIP OPTIONS IN THE UK

a) A group could take on the roles and responsibilities of sponsorship **OR**

b) The parties to a group could agree in writing to allocate roles and responsibilities to particular persons and organisations; and each party would then be responsible for the roles and responsibilities it takes on **OR**

c) Sponsors could delegate responsibilities for which they remain ultimately responsible.

Before initiating a trial, the sponsor(s) should define, establish and allocate all trial-related duties and functions. The trial protocol would include a scheme of allocation and delegation.

UK regulations enable allocation/delegation of sponsorship responsibilities

Sponsorship responsibilities could be allocated in three sets: authorisation; GCP and conduct; and pharmacovigilance.	Clinical Trial Authorisations (CTA) could name persons (other than sponsors) responsible **for duties** relating to GCP and conduct of the trial.	These **investigator responsibilities** correspond to the sets of sponsorship responsibilities.
Authorisation Request CTA Allow inspection Notify CTA amendments Notify protocol amendments Notify end of trial		Request ethical review of the protocol
GCP and conduct GCP arrangements IMPs free of charge Urgent safety measures	*Sponsor or named persons*	Obtain consent Urgent safety measures
Pharmacovigilance Record adverse events Record/report SUSARS Tell investigators of SUSARs Enter SUSARs on EMEA database Annual list, safety report		Report SUSARs to sponsor Report other adverse events according to protocol Supply information on deaths

For more information: http://www.ct-toolkit.ac.uk

CLEAR WRITING

To ensure people will understand clearly what the study is about and what it entails, trial protocol, materials and particularly the participant information leaflet (sheet) should be written in a clear unambiguous way. Scientific terms are unlikely to be understood by participants. A clear summary protocol is also a useful tool for busy investigators.

Words are the most powerful tools we will ever use.

Tips:

- Make sure you think about your reader as a person – use 'you'
- Be reader-centric
- Use plain language
- KISS – Keep It Short and Simple
- Cut unnecessary words and phrases
- Change big words to smaller words
- Change long phrases to shorter phrases
- Pilot your information on the people it is planned for
- Involve consumers in the writing of the Participant Information Leaflet

Think about relevance to the audience

- Short versions for emergency situations e.g. stroke, heart attack, labour
- Large print for elderly participants
- Simple language and pictures for young children
- Ethnic diversity

Example 1 Original abstract

It has been estimated that up to 1 in 5 people with diabetes are affected by foot ulcers. The burden of these ulcers on people is considerable as they often take months to heal. During this time the patient has to restrict their movement (so avoid putting pressure on the foot) and they are also at risk of foot infections. Indeed, in extreme circumstances, foot ulcers can result in amputation.

Example 2 Edited abstract using 'clear writing' techniques

One in five people with diabetes get foot ulcers, which can take many months to heal. During this time the patient must avoid putting pressure on the foot, and the ulcer may get infected. In extreme cases, foot ulcers can lead to loss of the foot by amputation.

Reference: Martin Rosser, Transference Ltd.

CONSUMER INVOLVEMENT

Defining involvement

'The *active* involvement of consumers in the research process rather than the use of consumers as the "subjects" of research'

Hanley B, *Involvement Works*, DOH 1999

Various forms of involvement

INVOLVE* defines three levels of involvement:

- Consultation: Using consumer views to inform decision-making;
- Collaboration: active ongoing partnership in the research process, e.g. Steering Committee membership or working with researchers to design, conduct and/or disseminate results of a research project;
- User control: professionals involved only at the invitation of consumers

Consumer involvement can:

- define what research is needed
- be useful during the trial development phase
- help to develop patient-centred outcomes
- optimise chance of funding / MREC approval
- develop information leaflets that participants understand
- maximise recruitment
- include membership on a Trial Steering Committee
- disseminate results effectively and in a clear, understandable way
- influence medical practice

Potential problems

- Can be difficult to identify relevant consumers e.g. stroke patients
- What is a "real" consumer
    - general public
    - member of an organisation (broad and specific)
- Potential conflict between participants and researchers. Need to accommodate different perspectives.
- Training needs and costs involved (both money and time)

Requires flexibility and commitment from both researchers and consumers.

Qualitative research led by an experienced researcher (e.g. focus groups) can be used to elicit valuable information (sometimes identifying misconceptions) and attitudes and can help in the presentation (both oral and written) of the trial

*INVOLVE is a national advisory group, funded by the Department of Health, which aims to promote active public involvement in NHS, public health and social care research.

For more information: http://www.invo.org.uk

TRIAL CO-ORDINATING CENTRE

What is a Trial Co-ordinating Centre?

The Trial Co-ordinating Centre is the heart of the trial whether it is a single site or multi-national trial. The Trial Co-ordinating Centre can be referred to by a variety of names and can be set in many different environments. It can be:

- part of a dedicated Clinical Trials Unit
- an office/desk in a clinical department in a hospital
- an office/desk in a GP practice
- an office/desk in an academic department in a University

The Co-ordinating Centre will need

- Agreements with the funder and sponsor to determine delegated tasks
- Space
- Staff
- Equipment
- Systems for data management, administration, finance, personnel etc.

Space

- The contract with the host institution (who may be the sponsor as well) should provide adequate accommodation
- Remember the project will grow – data require a lot of space, the trial may require additional staff as the trial progresses

Staff

The Chief Investigator and Trial Manager should review

- the funds awarded for staff salaries
- the staffing needs of the project

Funds can usually be redirected (vired) between budget headings, if necessary

A typical trial team consists of:

Chief Investigator(s)
Trial Manager
Programmer/IT support (may be from host institution)
Database manager and/or data clerks
Trial statistician (or consultancy)
Trial secretary

Customise the trial team to meet the needs of the trial, which may change over time. You may need more of one skill and less of another, e.g. two data clerks and 50% programmer

- Begin to draw up a blueprint of how the team will function, what the members' responsibilities will be, and anticipate workload hot spots.

Employing staff

- This is usually done through the host institution
- Draw up job descriptions and advertisements – check with the UK Trial Managers' Network for generic documents

- Never employ the whole team on day one (there will not be enough work)
- Talk to people who have hired staff on similar projects.

Remember: the posts are usually on short-term contracts – so make the job description interesting, exciting and realistic. There must be a probationary period after every appointment – time for both parties to learn and reflect.

Equipment

Get advice on hardware and software before making purchases – talk to the experts – talk to other trial teams.

Remember: technology changes rapidly – has the budget got sufficient funds for upgrades during the life of a project?

- Look at the equipment budget in the grant and review what equipment the project will actually need.
- You may need a full range of equipment such as computers, network server, printers, fax machines, answer phones, lap-top computers, mobile phones, pagers, scanners, dedicated internal computer network and laboratory equipment (if appropriate).
- The host institution should provide the basics - desks, chairs, lighting, telephones - but you may not need everything outlined in the budget at the beginning - always check that the host institution is aware of your total needs. The basic infrastructure should be provided by the overheads paid to the institution from the trial funding.

Systems

- General office systems – date stamping, filing, messages
- Communication systems – phone, fax, email, website
- Information systems – contact details of investigators, hospitals, etc.
- Randomisation system
- Data management systems
- Drug pack (intervention) management systems (if needed)

There should be a written description of all trial management systems and conventions. This documentation forms the operating procedures, often referred to as Standard Operating Procedures (SOPs). These are usually generic to the Trials Unit or Institution. A trial specific operating procedure **must** be developed for each trial. These may be called MOPs (Manual of Operations, Modified Operating Procedures) or TSOPs (Trial Specific Operating Procedures).

THE TRIAL TEAM

Chief Investigator(s) (CI)

The Chief Investigator is the person who has initiated the trial, developed the trial design and methodology, and applied for funding through a grant application that has been peer reviewed. The CI is an expert in the field who commands respect of fellow investigators and the trial team. The CI should be committed, supportive and value the trial team. A good relationship between the CI and Trial Manager is vital. These two people usually take overall responsibility for the management of the trial. While the CI takes overall responsibility for the whole trial, the CI does not have to be involved in the day-to-day management of the trial. If the trial is multicentre, each trial site will have a Principal Investigator (PI) who takes the lead for trial activities at their trial site.

The CI and PI (s) should:

- be leaders
- be well respected
- be committed
- be available

Trial Manager

One of the keys to success is trial management; the Trial Manager therefore, holds a pivotal position. Successful Trial Managers need to be multi-talented, hard working, well organised, capable of forward planning, and excellent communicators. He or she should never under estimate the importance of common sense and obsessional attention to detail in trial management.

Strengths should include:

- ability to work within a team and organise it
- management skills
- strategic planning
- ability to prioritise
- motivator/listening skills
- focused, but flexible approach
- perseverance
- knowledge/experience of all relevant guidance/regulations

Programmer

Programmers with specific experience in trials are rare. The ability to work with the Trial Manager and understand the requirements of the trial is essential. The programmer will need knowledge of RCTs and an in-depth knowledge of the specific trial being conducted. He/she should be able to use their knowledge in an innovative way and a willingness to learn is essential. A programmer will be needed throughout the trial to develop, establish and maintain the programs. This position is not necessarily a full-time post. Programming not only includes programs for data management and analyses but general monitoring systems for all aspects of the trial. If commercial clinical trial software (e.g. CLINFORM or MACRO) less programming/IT may be required.

A programmer should:

- have a global view of the trial
- have analytical skills
- be pro-active and involved
- be a team player

Database Manager

The Database Manager will have an intimate knowledge of the trial's data collection and management systems.

Desirable characteristics should include:

- attention to detail
- accuracy
- persistence
- flexibility
- being a team player

Data Assistants

The Data Assistant's role combines data processing and many other office duties, e.g. filing and mail-shots. This is a crucial role - accurate and complete data are essential.

The Data Assistant should be:

- methodical
- accurate
- reliable
- a team player

Statistician

A trial will rarely need full-time statistical support. Input is concentrated around the planning phase, monitoring the quality of the data, interim and final analyses. This aspect of a trial could be provided by someone outside the co-ordinating centre, for example in an expert unit. It is essential that a statistician is committed and involved from the start of the trial to ensure the systems will produce the data required. However, a statistician, working closely with a clinical co-ordinator, will lead some trials.

A statistician should be:

- experienced in trials
- open minded
- committed
- a team player

Trial Secretary

The Trial Secretary at the co-ordinating centre will often be the first point of contact with the outside world and, therefore, should be personable, reliable and interested. Secretarial support is expensive and many trials cannot afford to have one, or justify one. However, whether or not a trial needs a dedicated Trial Secretary should be considered early in the planning stages and included in the budget if appropriate.

The Trial Secretary needs to be:

- organised
- adaptable
- committed
- a team player

Remember - not all trials will need a team as described above. Roles may be combined or part time or seconded from the host institution or department. A very large trial may need a bigger team.

A generic job description for a Trial Manager is available on the UKTMN website. http://www.tmn.ac.uk

GETTING STARTED CHECKLIST

Are you ready to start?

Before you start recruitment, ensure that all trial sites, if a multi-site trial, have all the information they require and that written guidance is provided.

- Inform all sites that approval has or has not been given for their site
- Ensure all sites have correct version of documentation
- Inform sites, through a written agreement, who the Sponsor(s) are, and of any allocated or delegated responsibilities
- Confirm any monetary agreements in writing
- Ensure all sites know how to report Adverse Events, in particular SAEs and SUSARs
- Inform sites they can begin recruiting
- Circulate approved site list to all sites

Next step

Promoting and marketing the trial are vital tasks to getting a trial started.

This will be helped by:

- A relevant question that investigators are interested in answering
- A clear 'identity for the trial' – a professional image
- Minimal work for investigators and participants

For more information see: http://www.ct-toolkit.ac.uk

SECTION 4: TRIAL MANAGEMENT

TRIAL ETHOS

- The trial does not belong to any one individual – so encourage the investigators (this usually means the investigators responsible for the care of trial participants) to be involved in as many aspects of the trial as is practically possible, from protocol development to publication of the results.
- The investigators are important so respond quickly, efficiently and appropriately to their requests
- If you don't know, refer to the appropriate person who will know the answer. Never say 'I don't know', always say 'I will find out for you' and get back to them
- Listen to problems, suggestions that investigators may have and respond accordingly
- Always do what you say you will do

REMEMBER – a primary part of the co-ordinating centre's role is to provide a support service to the investigators.

MARKETING THE TRIAL IDENTITY

Why is identity important? The trial is like any other venture and should be promoted to ensure that it is at the forefront of the minds of the investigators and participants. This is the only way the trial will successfully recruit sufficient numbers of participants in the timeframe agreed and within budget. There may not be an identifiable budget for promotion! Be inventive.

Consider the following:

- Aim to give the trial an individual identity
- The name, acronym and logo should make it recognisable and memorable
- Don't waste your time – consult the experts such as medical illustration, departmental reprographics
- Promote the trial identity – make it known – always use it, publicise it
- Use the trial identity on all customised stationery, data forms, mugs, pens and other promotional material
- Set up dedicated telephone lines, answering machines, fax machines, email addresses and website addresses

THINK

CLINICAL TRIALS AS BUSINESSES

Consider business-marketing techniques such as:

Brand values are the 'meanings' that potential trial participants ascribe to the trial. Without clear and explicit brand values it is difficult for a coherent perception of a trial to be communicated.

Legitimacy The trial is perceived to be ethical and supported by the medical establishment.

Prestige means that the trial is tagged with meanings of honour and respect. Legitimate and prestigious trials are more likely to acquire buy in.

Signalling The emphasis is on the efficiency and effectiveness of *signalling* – effectively conveying the worthwhileness of the project. Without the target market realising the importance of the trial, there will not be the preconditions for buy-in.

Processes are sequences of interdependent actions that, collectively, achieve a beneficial outcome. Without simplicity and complete processes, buy-in will not be achieved or dropouts will occur.

Resistance refers to the factors that cause potential investigators to reject the trial or undertake it with less than full commitment. Buy-in occurs when resisting factors are diminished or eliminated.

An Explicit Marketing Plan is usually a written plan and adopts a standardised format (to a large extent). Without a written marketing plan Trial Managers lack knowledge of 'the market' and their plan for winning in it.

Advocates Trial Managers need a network of supporters to 'spread the message' and get people involved.

Multi-audience are the different interest groups involved. ***Multi-level*** means aiming at both the heart and the head.

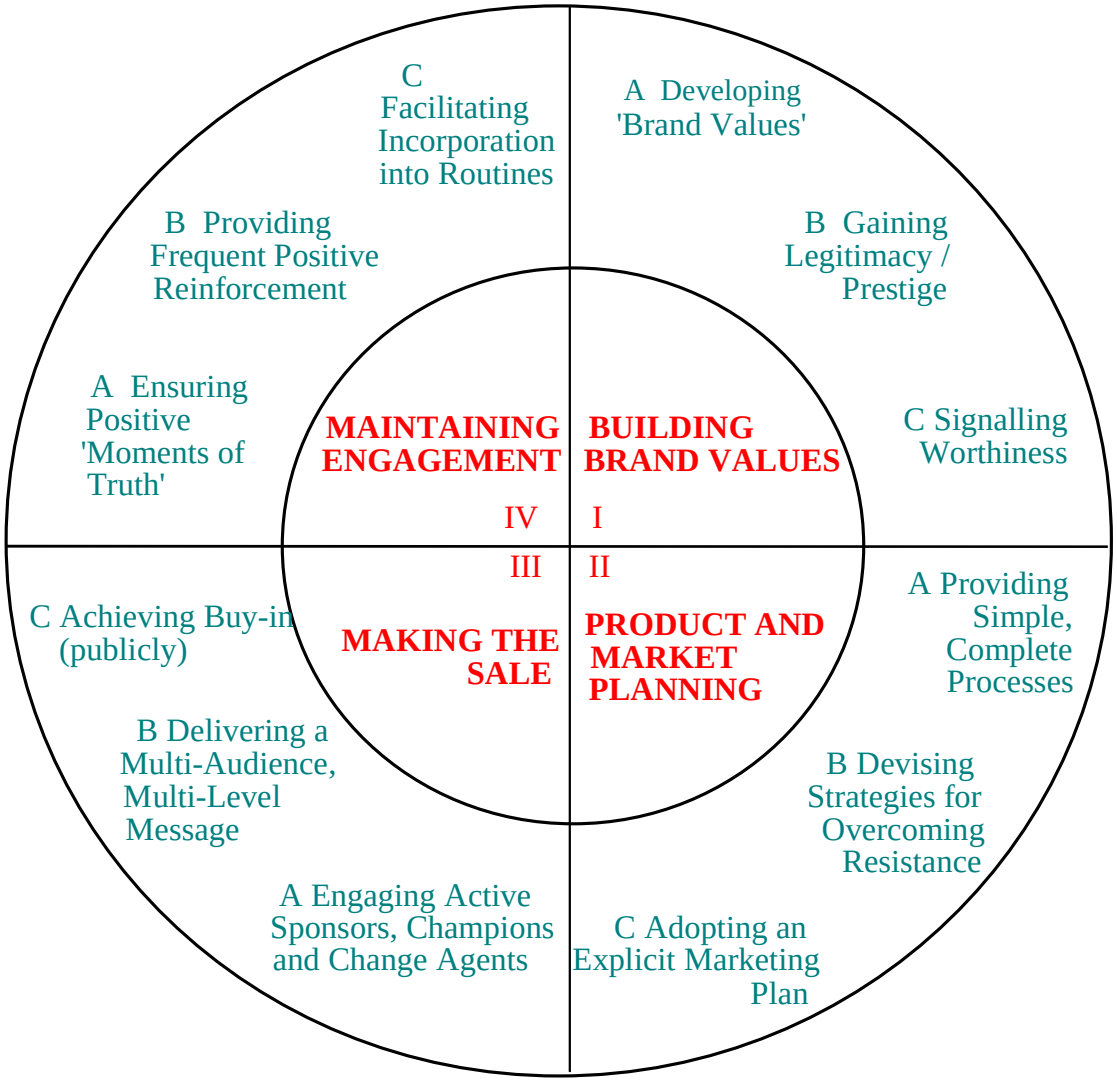
Public Buy-In is the announcement, in public, of an intention and commitment to being part of the trial. Once someone states in public that they are willing to undertake an action, they are much more likely to actually do it.

Moments of truth refer to those instances when you really find out what an organisation is like. People judge organisations on the basis of their experience at critical moments (for example, when something goes wrong). If an organisation behaves well in a moment of truth then loyalty grows; if not, loyalty diminishes.

Positive reinforcement is rewarding appropriate behaviour. Without reinforcement behaviour will not persist (Maslow 1954). Reinforcement is perceived to provide an effective response to queries (Stephens and Eden 1995). If Trial Managers consider both extrinsic and intrinsic motivation of investigators they can list these and provide a point-by-point motivation plan (Yavas and Riecken 1997). Providing opportunities for networking, social interaction and sharing of experiences (Bessant and Tsekouras 2001) will reinforce positive behaviour. Investigators' meetings need to be held to summarise findings, bring investigators up to date, discuss problems, encourage, discuss ideas for

development, coordinate with other groups and inform investigators. They also provide an opportunity for social activities (Girling 2000).

Routines are 'the way that we do things around here'. The procedures that are needed for a trial need to be incorporated into the ordinary procedures of the units undertaking the work – in other words they need to become 'routines'.



For more information and full references: Clinical Trials as Businesses: Strategies for Trials Enrolment and Participation Study. Clinical Trials 2005 (2): 579-580.

BUDGET CONTROL
Most external grants

- include full economic costs (FEC)
- are activated as soon as staff are appointed
- are cash limited
- are also time limited
- allow funds to be vired between spending headings

For trials funded on a grant, the Chief Investigator is likely to be the grant holder.

If the trial involves a commercial sponsor or partner(s) they must be involved from the beginning of negotiations and a contract agreed at an early stage.

Strategies for getting the best value for money

- The finance department of the host institution is charged with administering the grant award. Seek advice, explanations and training in budget management from them
- Meet the person who will manage the grant on day one and tell them about the project
- Cultivate a positive relationship with an identified person
- Always keep them updated and talk to them about how you want to manage the budget
- Ensure that statements from the finance office are sent to the Co-ordinating Centre at intervals mutually agreed
- Prepare a spreadsheet of each funding stream: start dates, milestones and end dates
- Monitor spending, check invoices (if possible), plan ahead
- Put aside a regular time to deal with financial matters each week / month
- Always take a global view of the funding – don't get obsessed with balance sheet accounts
- Prepare regular financial reports
- Use funds creatively (but within the law)
- Always be aware of the possibility of new or additional funding streams
- Attention to detail is extremely important

REMEMBER the trial must deliver on time and within budget.

Funding supplements are hard to justify and should not be expected

Time only extensions can be requested but must be fully justified and requested in plenty of time.

Trial Master File (trials of IMPS)

A Trial Master File should be set up at the beginning of a trial. The Trial Master File should be held at the principal site (Chief Investigator's office or Co-ordinating Centre) and copies of relevant documents should be kept at participating sites in the Investigator's Site File. The essential documents that make up the file should be kept in a secure but accessible manner and the purpose of each document should be clearly described. Essential documents serve a number of important purposes; they can help with efficient trial management, independent audit, closeout and archiving. All essential documents should be legible and accurate.

Essential documents are those 'documents which *individually and collectively* permit evaluation of the conduct of a trial and the quality of the data produced' i.e.:

- Documents that help you to understand a project's purpose and methodology and, if appropriate, management structure (e.g. trial protocol).
- Documents that record relevant approvals and any related conditions (e.g. financial approval, scientific approval, ethics approval, MHRA approval, sponsorship authorisation) and evidence that all trial staff are qualified and authorised to work on a trial (e.g. curriculum vitas, honorary contracts).
- Documents that record substantial amendments to approvals and documents that authorise the substantial amendments.
- Documents relating to participants in a trial (e.g. recruitment procedure, consent form(s) used, information sheet(s) used).
- Documents that demonstrate where adverse events and/or health and safety incidents have taken place, that the events/incidents have been properly recorded, reported and acted upon to prevent them from recurring.
- Documents that record the trial's findings (e.g. final report) and which demonstrate dissemination and archiving arrangements.

Filing essential documents in a clear and timely manner can greatly assist the Chief (or Principal) Investigator and Trial Manager in the successful management of a trial, the trial's sponsor in auditing a trial and (for trials covered by the UK Regulations) the Medicines Healthcare Regulatory Authority (MHRA) in inspecting a trial.

'*Trial-related' documents*, such as invoices, do not need to be included in the Trial Master File, but the document list should clearly describe any trial-related documents and should specify where they are located**.**

Investigator's Site File

This file contains all essential documents as described above and any specific local documentation, approvals and permissions that relate to the conduct of the trial at that site.

Standard Operating Procedures
Standard Operating Procedures (SOP), Manual of Operations or Trial Specific SOPs, should be developed for all aspects of trial conduct and management.

For a guide to SOP development see the MRC Clinical Trials Unit website:
http://www.ctu.mrc.ac.uk/sops.htm

Data monitoring
According to Good Clinical Practice (GCP) data should be monitored appropriately as set out in ICH-GCP.

Monitoring plan
The monitoring plan to be adopted should be proportionate to the risks of the trial and clearly documented in the protocol and data monitoring SOPs. Monitoring plans can include a combination of on-site source document verification (SDV) and on-site system review, central monitoring and DMC surveillance.

ICH-GCP Extent and Nature of Monitoring (quoted from ICH-GCP 5.18.3)
"The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified."

Source Document Verification
The trial Risk Assessment will dictate whether Source Document Verification (SDV), 'appropriate and proportionate to the trial risk', forms part of the data monitoring procedures. SDV means going back to source documents (usually hospital notes) to validate key items of data. This usually requires a member of the trial team to visit the participating hospital or clinic to compare the content of the data collection form with the hospital or clinic notes.

Central monitoring
An appropriate plan for central monitoring and/or statistical monitoring should be determined by the Risk Assessment carried out at the planning stage of the trial.

For more information: http://www.fda.gov/cder/guidance/959fnl.pdf
http://www.ct-toolkit.ac.uk

TRIAL RECRUITMENT

LOGISTICS

Make recruitment easy to do, with clear instructions. Think about what will work. It is no good planning telephone randomisation where phones are not easy to access. It is crucial that whatever recruitment plan is adopted that concealment of random allocation can always be maintained.

Consider

- Where participants are recruited
- Who will recruit them
- When this will take place

If possible visit the place where recruitment will take place and talk to the people who will be recruiting participants.

- Develop the most appropriate randomisation systems (consider options below)
- Participant details must be recorded prior to intervention allocation
- Make sure neither the investigator nor the trial staff are able to find out (or predict) the next intervention allocation (adequate concealment)

Options for randomisation

External systems – central telephone randomisation service, web-based system, email or fax (where the Form is either emailed or faxed to the Co-ordinating Centre), automated electronic system with voicemail recognition.

A central telephone randomisation service or an automated electronic system with voicemail recognition is considered to be the optimal method of randomisation as it is carried out by independent operators, captures the baseline details as soon as the patient is entered into the trial and the patient can therefore be tracked for outcome data. The treatment allocation is held electronically and is secure.

Internal systems – allocation codes held by pharmacy, randomisation envelops, sequentially numbered intervention packs. These systems are less secure as the allocation can be subverted if an investigator does not like or want the next allocation and there is no central record that the allocation (code, envelope or pack) has been taken and abandoned without the site being monitored regularly.

Golden rules to ensure optimal recruitment

- Keep trial work for investigators simple and minimal
- Plan and target marketing strategies and site visits effectively
- Review the impact of these strategies
- Do what you say you will do and always be polite
- Use all methods of communication as appropriate
    - Telephone
    - Email
    - Publication and letters
    - Website
    - Personal contact

Ideas you might consider using to ensure optimal recruitment of participants

- Membership lists of relevant colleges or other professional organisations

- Flyers in journals for interested investigators to contact you
- Attend relevant conferences to lobby opinion leaders and set up satellite meetings to promote interest
- Produce a 'starter pack' for investigators and nurses to launch recruitment
- Visit centres that have little research experience

End of the recruitment period

Recruitment of a trial will close:

- when the target, as defined in the protocol, has been reached, **or**
- if the DMC recommends that the trial should close and the Trial Steering Committee endorses this decision, **or**
- if, in the absence of a DMC, the Trial Steering Committee decides to close recruitment to the trial.

The investigators, MREC, LRECs, the Sponsor, and in the case of a trial of a medicinal product the MHRA, must be informed of the date recruitment closes. If participants are to be notified, the content of the letter to participants should be agreed by the Trial Steering Committee and then forwarded to the MREC for approval prior to being distributed.

Informing investigators

Unless recruitment to the trial is stopped early the investigators should be given plenty of warning that the recruitment phase is drawing to an end, to enable them to ensure that all patients who may have been approached for the trial can be randomised before recruitment closes. When recruitment closes all investigators should be sent a letter outlining their ongoing obligations to the trial. The letter should:

- thank the investigator for their participation
- summarise overall recruitment
- outline follow-up plans/duration of follow-up
- remind the investigator of the continuing trial obligations
    - complete data on all participants,
    - complete details of any further follow-up
    - SAE / SUSAR reporting (if applicable)
    - monitoring/SDV (if applicable)
    - possibility of audit (if applicable)
- arrange for the return or destruction of trial supplies and/or drug supplies (if applicable)

Financial requirements

When the trial closes to recruitment, the Trial Manager should ensure that all recruitment payments to centres (investigators, pathologists etc.) have been made.

MONITORING RECRUITMENT TARGETS

You will need to:

- Set realistic targets for both numbers of participants and centres – review regularly
- Use computer systems to monitor recruitment
- Change activities if necessary – monitor their impact and change things that do not work
- Be open minded – think laterally
- Keep the trial exciting to maintain interest
- Plan ahead

And think about:

- Regular changes in hospital staff
- Communication strategies
- Regular newsletters to all investigators
- Individual feedback to centres
- Branding – relevant incentives, mugs, post-its, pens, mouse mats, key-rings, trial specific items
- Attendance at conferences with trial specific literature – take an exhibition stand

Encourage ownership by investigators

- Publish regularly as a group to keep trial interest high
- Attend conferences and plan who you want to speak to
- Visit centres that are recruiting well and not well so you can learn what works and what doesn't
- Arrange meetings for investigators which may be
    - Local
    - Regional
    - Satellite meetings at conferences
    - Investigators' meetings

If recruitment is not going well consider

- Is the question still relevant?
- Are investigators still interested?
- Are participants prepared to join?
- Are procedures appropriate and flexible?

If you have exhausted all suggestions and recruitment is not going well, contact UKTMN for support.

RETENTION AND FOLLOW-UP

Participant follow-up needs to consider the aims of the particular study, the population under investigation and the resources available.

- Make sure you have all the necessary permissions (Ethics, ONS, PIAG, NSTS)
- Make sure you have the necessary consent and relevant contact details (addresses etc.) so you can follow up the participants
- Make sure participants know what follow-up entails by including details in the participant information leaflet
- Start to organise systems and plan when the next contact with the trial participant should be made

Think about:

- Warning the participant by letter when contact is due
- Re-arranging the contact if the participant does not respond or attend clinic
- Using birthday cards, anniversary cards/Christmas cards/change of address cards
- Using participant newsletters
- Other methods of communication:
    - phone
    - mobile phones and text messages
    - email
    - letter

If you do not get a response think about another way you could get the data (especially the primary outcome data). This may require amendments to permissions and approvals.

- Questionnaire to the participant's GP
- ONS death details
- A shortened questionnaire including just the primary outcome data for participants reluctant to complete a full length questionnaire

Participant's questionnaire response rates

Good quality evidence from two systematic reviews of studies mainly conducted in commercial setting suggests there are many ways the response rate to a postal questionnaire can be improved. This evidence should be applied to your particular trial as appropriate. Main messages from the systematic reviews are:

- Participants should be sent an [introduction] letter to tell them to expect a questionnaire
- Questionnaires should be sent by first class post or recorded delivery
- Provide a pre-paid return envelope
- Incentives should be offered (preferably a small amount of money) – if available
- One or more reminders should be sent with a copy of the questionnaire

DATA COLLECTION AND MANAGEMENT

Data collection should always

- provide essential data on the primary and secondary outcomes
- ensure the data you want are routinely recorded and readily available
- be recorded using a black or blue pen to ensure clear photocopying where necessary

Make data collection forms attractive and as easy as possible to complete

- Use trial logos, colours, consult the experts
- Use simple yes/no questions and tick boxes where possible
- Minimise free text fields and photocopying (use NCR paper)

Data Management

- Work with the programmer on the data collection forms to develop the specification for logic, range and consistency checks.

Develop and validate computer programmes to support

- Logic checks (sensible dates e.g. not dead before enrolled)
- Range checks – consult experts
- Consistency checks
- Coding of free text data

Data entry

- Develop a housekeeping system to keep track of data in the office, including date stamping all documents on receipt
- Immediately enter all data on to the trial database
- Don't rely totally on the computer – systematically deal with the data forms – action trays, pending trays, filing system etc.
- If an optical form reader will be used, do extensive style checking before printing to ensure forms are readable by the optical reader

Checking data accuracy - Double data entry

- Data are entered twice by two different people
- Double entry can be done in house or sent out to specialist companies
- Comparison of the two data entry sets is made to detect inconsistencies and identify queries
- These may be resolved in house but more often need to be sent back to the investigator for resolution
- This is a gold standard. It may be sufficient to agree a sample (say 20% or, if simple, key variables) of the data to be double entered. The percentage can be lowered if the data is accurate and raised if the error rate is unacceptable

Missing and inconsistent data

- Develop a system of computer-generated reports to monitor missing or inconsistent data and act upon them
- Many queries will need to be resolved by the investigator and these queries should be sent out as soon as possible with a clear request
- All query resolutions should go through the same checking process as the original data

- To comply with Good Clinical Practice (GCP) guidelines, all changes to the data forms should be clearly altered using a coloured pen by striking out (not obliterating) the original data, inserting the correct data, initialling and dating the amendment. The source of the change should be filed with the original data form completing the data trail
- Once all outstanding queries are resolved the data can be incorporated in the dataset
- If missing or inconsistent data are repeatedly ignored by the investigator, change strategy – send a letter, phone, email or visit
- Identify recurring errors or omissions quickly and bring them to the attention of the investigator

Follow-up data - never give up on data collection

- Once a participant has agreed to join the trial it is the Co-ordinating Centre's responsibility to collect data and the investigator's to provide it
- Get to know the way the collaborating hospitals work
- Develop effective relationships with investigators and the associated disciplines e.g. nurses, GPs – remember they are all important to the trial
- If needed send them regular reminders of outstanding data forms required
- Acknowledge the investigator's and/or nurses' part in the trial, for example by including them in newsletter mail shots, meetings and publications
- Use National Health Service Central Register (NHSCR) to collect death data or trace participants – they are the experts
- In international trials it may be necessary to contact similar registries in other countries
- Think laterally – is there anywhere else the data needed may be stored?

Data backup and storage (See section on Data Protection)

- Backup - computers should be backed up regularly. The frequency of backup needs to be governed by the importance of loss that would be incurred. There are many ways of doing this, such as tapes, CD ROM and a network server
- Whenever possible backup data should be stored securely off site e.g. on a remote network server
- Storage & archiving – develop systems for storing processed participant data, data records that are still in process, and for archiving the data for the whole trial, both electronic and paper data, for the stipulated length of time. (see Archiving and storage)

NO DATA – NO TRIAL – IT IS THAT IMPORTANT

DATA PROTECTION - THE PRACTICALITIES

Data protection framework

- Register under the Data Protection Act with your host institution
- Consider if waivers are required for collaboration outside the EU
- Consult with Information Commissioner if there is any uncertainty about process

Implications for staff

- Ensure confidentiality clause in staff contracts
- Develop procedures for breaches of confidentiality
- Ensure staff are aware of data protection protocols within the Co-ordinating Centre
- Identify lead person for Data Protection issues

Implications for participants

- Must give consent to process all personal information
- Must be given accurate information regarding the use of data/samples collected both now and in the future
- Access to all personal information held, via a process developed by the Co-ordinating Centre. The process will ensure correct participant identification. Use NHS systems where possible

Day to day management

- Only collect data fit for purpose and approved by ethics committee and registered under the Data Protection Act
- Ensure adequate security and restricted access to paper records by use of lockable cabinets and a password protected computer network
- Ensure information held on participants is anonymised/unlinked as soon as practically possible, depending on the trial design. That may be when an individual's data collection is completed, and it is considered that the risk of emergency unblinding is minimal
- Document the reason for the timing of anonymisation of data

Simple solutions - paper

- Store securely, ideally in locked fire proof filing cabinets
- Never leave data out on a desk overnight (or take out of the office)
- Plan access and archiving procedures (kept for up to 20 years) with your host institution or sponsor

Simple solutions - electronic

- Password protected systems and
- Password protected email addresses
- Daily back up - stored off site
- Consider encryption, coded identifiers

For more information: *http://www.dataprotection.gov.uk*

DRUG PACK MANAGEMENT SYSTEMS

- If the drug / intervention is being provided by the Co-ordinating Centre (e.g. drug or device), a distribution management system is essential. If clinical centres have no stock of trial intervention or trial documentation they cannot recruit into the trial.
- Effective trial pack management is particularly important in a multicentre trial. (Remember the trial documentation and instructions may need to be in more than one language.)
- A system for independently testing a random sample of packs prior to distribution, especially if the trial is placebo controlled, should be developed to ensure the contents of numbered intervention packs match the allocation code.
- A system for the destruction of unused trial drug, during and at the close of the trial, will need to be developed early in the planning stages.
- Distribution methods need to be reliable, economical and budgeted for, e.g. Courier service, Data Post, Hospital delivery services.
- All trial packs distributed will need to be destroyed and accounted for at the close of the trial.

N.B. If the trial involves a drug and the Co-ordinating Centre is providing specialised labelling for the trial intervention, **ALWAYS** consult a Clinical Trial Pharmacist in the host institution, or the UK Medicines and Healthcare products Regulatory Agency (MHRA). See Pharmacy Issues.

Unblinding (also known as unmasking)
It is essential that there are systems in place to ensure that only essential unblinding is carried out.

Unblinding the trial allocation in an individual patient/participant (disclosing which drug/intervention has been allocated)

- In general this should only be done if further clinical management depends on knowledge of which intervention was allocated (e.g. an anaphylactic reaction). This is to protect the integrity of the trial – doctors and trial team are not influenced by knowledge of the intervention. If there are concerns about side effects but there is no clinical need for knowledge of the trial intervention for future management, it can be stopped or interrupted temporarily or permanently without unblinding.
- Ideally, the randomisation codes should be held centrally by an independent unit/person e.g. randomisation service, 24-hour pharmacy. Unblinding should be available 24 hours a day, 7 days a week, although this can be expensive.
- All unblinding requests should be controlled by the use of a gate keeping process e.g. criteria for unblinding, refer-on process. Ultimately the CI is responsible for ensuing the trial blinding and integrity is maintained.
- Records of ALL participants unblinded and the reason for unblinding should be kept on a central system. The trial team should not have access to these data.
- In some circumstances it is ethical to unblind at a participant's request for example, in a trial of a common intervention such as antibiotics a participant may have side effects that are sufficiently serious that they do not want to be prescribed the drug again.

PHARMACY ISSUES (for trials of IMPs)

For trials evaluating a medicine that fall within the scope of the UK Regulations and the EU Clinical Trials Directive, there is a need for effective and sustained input from pharmacy to the design, conduct and troubleshooting of trials. The manufacture, packaging, labelling, distribution, prescription, storage and accountability of randomised study medication are all issues that, whilst the ultimate responsibility of the sponsor, the study pharmacist and the Trial Manager will need to be familiar with. In publicly funded trials the study medications may be supplied from one or more central locations, and distributed to local (perhaps hospital) pharmacies. It is the local pharmacy that then ensures the correct medication for the allocated randomised group is given, which means the pharmacy often needs to know the randomised allocation. This type of communication needs careful oversight, and it may be that the task of putting in place systems to ensure this oversight falls to the Trial Manager.

For anything but the simplest trials, it is now becoming common for a pharmacist to be a grant-holder and a member of the Trial Management Group. The Trial Manager would then work closely with this Chief Trials pharmacist in developing and documenting the trial procedures relating to pharmacy. Typical documents that are produced are the dispensing procedure, a drug accountability log, prescription sheet, labels and a process for drug destruction.

The Trial Manager may well be the natural point of contact during the conduct of the trial for all pharmacies as they raise issues, or simply in the routine transmission of information on drug stocks and supplies used to facilitate efficient stock control and re-supply. When undertaking site visits, pharmacy staff should always be included in any meetings.

The Trial Manager would be centrally involved in reviewing any suspected deviations from the protocol (from issues such as suspected overdoses through to misallocation of intended randomised medication). A description of the responsibilities of the trial pharmacists should be included in the trial protocol and Standard Operating Procedures (SOPs). In addition, the pharmacy study file should contain all relevant information specific to a trial, including code-breaking procedures (unblinding), see page 52.

For more information:
http://archive.instituteofclinicalresearch.org/Pharmacists/PGMay05.pdf

WEB BASED TRIALS

The delivery of multicentre randomised controlled trials has become increasingly dependent on information technology in the last few years, a trend that is likely to continue and probably accelerate in the coming years. Although the essential processes that make up a successful trial have not changed, the increased role of IT has changed the mix of a Trial Manager's responsibilities and priorities. Many publicly funded trials now have a study web portal, accessed over the Internet, on which a wide variety of study information is held. This information usually includes:

- the protocol, protocol summary for consumers
- contact details of the study personnel
- study materials such as Case Report Forms, Participant Information Leaflets, Consent Forms etc.

It might include an electronic, downloadable version of each participating centre's Site File. It can contain guidance on how to complete study authorisations for a site (e.g. ethical approval).

Up to date information can be found on study progress, including recruitment. There may be a participant area which people interested in taking part in the study can browse, accessing often dynamic and interactive material describing the study (e.g. video clips, audio streams). There may be a study personnel area in which, for example, recruiting staff can share experiences via a bulletin board, allowing standardised responses across centres to be developed for emerging issues.

The study web portal has therefore given the opportunity for dramatically improved communication both between the study team and potential and actual participants, and within members of the study team itself. Although this can prove a very useful resource for the Trial Manager, and an effective tool in managing the trial, it does however come at a price to the Trial Manager.

The study web portal

The Trial Manager is usually involved in the design and building of the website, in collaboration with the programming team. Study websites are only useful if they are done to a professional standard and are maintained and kept up to date - a poorly designed, out of date website can be detrimental to a trial's progress. It quite often falls to the Trial Manager to ensure that trial materials on the website are correct and up to date, which can be time consuming.

In addition, study web portals can be used for data entry. This has profound implications for how a trial is run. The usual paradigm for a paper-based trial is that the data are recorded on paper CRF at the local site, and make their way to the Study Data Centre by post or fax. Experienced clerical staff, perhaps using entry and verification, or perhaps using double entry, then enter the data. Range checks and consistency checks are then run, queries issued on suspect data items, and sent back to the centre for investigation and resolution. The queries are then returned and entered at the Data Centre and usually some are then reissued as not having been satisfactorily resolved.

Data entry using a web portal

Data entry using a web portal offers a completely different paradigm. Instead of delayed entry by clerical staff at a central Data Centre, data are entered on-line by local staff (usually the study nurse or investigator) with built in queries at the point of data entry. Not only are the data being uploaded to the central study database much more quickly, the quality of the data is being updated in real time. Missing data reports can be generated and circulated regularly. However, whilst there are undoubted benefits to this route for data entry, it does create different challenges for the Trial Manager.

Experience has shown that the successful operation of these systems relies very heavily on up front training for the users at the local sites, and continuing support whilst the study progresses. More site visits may be required to enable data checking against source documents.

An example of a study web portal

To see an example of a study web portal

1. Log on to www.charttrials.abdn.ac.uk/example
2. Click on 'Study Personnel' and
3. Use the logon id 'GuestTMN' and the password ‘TMN’.

Although this is the website of a real trial, you are only seeing a Test Centre with fictitious data.

TRIAL CLOSURE

Early termination or temporary suspension of the trial

If the trial is terminated early, or is temporary suspended, the MREC and the MHRA, if the trial involves an investigational medicinal product (IMP), should be notified using the End of Trial Form within 15 days of closure.

The following information will be required:

- justification of the premature ending of a trial
- number of participants still receiving treatment
- proposed management of participants still receiving treatment

The sponsor should be notified immediately by letter or fax.

All investigators must be informed using expedited means of communication. The reasons for early termination (or temporary suspension) should be explicit.

Planned closure

The end of the trial date should be specified in the protocol.

Informing investigators

Investigators should be informed of trial closure via a letter from the Trial Manager or the Chief Investigator. The letter should:

- thank the investigator for their participation
- summarise patient status – number of withdrawals, deaths, SUSARs, SAEs etc
- remind the investigator of any continuing trial obligations, e.g. archiving
- availability for queries arising after trial closure
- arrange for the return of trial supplies and/or drug supplies, if applicable
- advise of the possibility of audit or inspection if applicable
- outline the results of the trial **or** provide a copy of the trial report
- inform the investigators, if possible, of the expected timing of publication.

The investigators are responsible for informing local personnel at their centres that the trial has closed.

Informing participants

Where possible, participants should be informed of the trial closure. The need for this should be discussed and agreed by the Trial Steering Committee.

Informing the Sponsor

The Trial Manager should ensure that the Sponsor has been informed that the trial has reached its defined end date.

Final analyses

When the final analyses have been undertaken the trial is completely closed. The following sections detail the procedures that must be carried out.

Processes for end of trial notification, including safety reports:
The Trial Manager should, on behalf of the Chief Investigator, inform the MREC that a trial has reached its defined end date using the End of Trial Form.

- Notify the MREC using the End of Trial Form
- A minimum set of documents should be archived as outlined in ICH-GCP. See Storage and Archiving

For trials involving an IMP

- Notification within 90 days to the MHRA (Competent Authority)
- For trials conducted within the EU the Competent Authority in each Member State should be informed of the end of the trial
- A form should be completed on EudraCT (European database for clinical trials of a medicinal product) that lists:

  Number of participants recruited, withdrawn, completed and drop-outs
  - Serious Unexpected Adverse Reactions (SUSARs), including a critical appraisal of these reactions.
  - Anticipated date of final data analysis and of final study report availability.

Preparation of final reports and publication
When the final analyses have been conducted, the final reports should be prepared. This will involve the preparation of publication(s) and the final report for the sponsor. The project team should be involved in the preparation of the publication, which is usually led by the Chief Investigator. The exact requirements for final reports vary and the guidance given by the Sponsor should be followed. It is important to clarify who will be responsible for each section; a plan should be discussed and agreed in advance of any deadlines, especially for final reports.

For trials involving an IMP: trial drug supplies
An agreement should be made as to where and how study medication should be handled. Trial supplies will usually either be returned to the co-ordinating centre or destroyed on site. The Trial Manager should ensure that centres/pharmacies are aware of the requirements for the end of trial and that proof of destruction is received by the co-ordinating centre in a timely manner.

For more information see:
http://www.corec.org.uk
http://www/mhra.gov.uk
http://www.doh.gov.uk/research/
http://www.pharmacos.eudra.org/F2/pharmacos/docs.htm#news
http://www.dataprotection.gov.uk/
http://www.mrc.ac.uk/

PUBLICATION AND DISSEMINATION

Results
The results of a trial must be published, whether or not they show a difference in outcome between the groups compared. It is scientific misconduct not to aim to publish the trial results. In order to publish the results of a trial in most medical journals you will need to register the trial on an approved registry before the first patient is recruited.

Confidentiality
Information which may identify individual participants should not be published in written descriptions or photographs, unless the information is essential for scientific purposes and the participant (or parent or guardian) gives consent for publication. In such cases the person involved is shown the draft manuscript.

Publication policy
The trial protocol can be reviewed and 'published' by the Lancet and if approved the journal guarantees that the trial report will be sent for peer reviewing.

The policy for publication of both interim and final papers should be clarified and documented at the start of the trial – it may already be in the trial protocol. No other publications, either in writing or orally, should be made before the definitive manuscript has been agreed and accepted for publication, without the prior approval of the Trial Steering Committee.

It is common practice to set up a sub-group of the Trial Management Group as a 'Writing Committee'. Both interim and final reports are then reviewed / approved by the Trial Management Group and Trial Steering Committee.

Authorship
Arrangements for authorship should be agreed early and described in the protocol. Many large trials have group authorship with a list of contributors at the end of the paper, giving details of who did what in the stages of the trial, e.g. the Trial Steering Committee, the Trial Management Group, collaborating investigators etc. and not forgetting the participants.

The CONSORT Statement
A common format for reporting randomised trials has now been widely adopted. This is known as the CONSORT statement (ref JAMA (2001)) and provides a checklist consisting of 21 items that appertain mainly to the methods, results and discussion of an RCT report and includes key pieces of information necessary to evaluate the internal and external validity of the trial. A flow diagram provides information about the progress of participants throughout the trial. Diagram extensions for particular trial designs are also available (Campbell et al 2004 for cluster trials, and Piaggio 2006 for non-inferiority trials).

Dissemination of trial results
It is good practice, wherever possible, to prepare a lay summary of the trial results to be sent to each participant and made available on a website. Whenever possible the results should be shared with all investigators and participants, before public release, either orally or in writing.

For more information:
http://www.consort_statement.org
htttp://www.controlledtrials.com
http://www.clinicaltrials.gov

STORAGE AND ARCHIVING

Introduction

The documents that individually and collectively permit evaluation of the conduct of a clinical trial and the quality of the data produced, are defined as essential documents.

These documents should be filed in an organised way that will facilitate management of the clinical trial, audit and inspection (Trial Master File).

The Trial Master File should be set up at the beginning of a trial and maintained throughout the trial. Archiving applies to both the investigator sites and the central trial co-ordinating office.

For trials involving an IMP

Essential documents must be retained (archived) for sufficient periods to allow for audit and inspection by regulatory authorities and should be readily available upon request.

Storage

Essential records should be maintained in a legible condition. Prompt retrieval should be possible. Plans for archiving trial documents should be made in the design phase of a trial and costs of storage should be considered. Adequate and suitable space should be provided for the secure storage of all essential records upon trial completion. The facilities should be secure, with appropriate environmental controls and adequate protection from fire, flood and unauthorised access. The storage of the Sponsor's documentation may be transferred to a sub-contractor (e.g. a commercial archive) but the ultimate responsibility for the quality, integrity, confidentiality and retrievability of the documents resides with the Sponsor, or delegated person. This means that the Sponsor, or delegated person, should audit the site and be satisfied, and document, that the storage is appropriate.

An archive index/log should be maintained to record all essential documents that have been entered into the archive, and to track and retrieve documents on loan from the archive.

The investigator should make the Sponsor/trial organisers aware of the arrangements for the documents to be stored at investigator sites. If the investigator becomes unable to store their essential documents, the Sponsor/trial organisers should be notified in writing so that alternative storage arrangements can be agreed. If the investigator is no longer able to maintain custody of their essential documents, the Sponsor/trial organisers should be notified in writing and the investigator/institution see to it that appropriate arrangements can be made.

Storage of personal data is subject to applicable elements of EU Directive 95/46/EC and the Data Protection Act 1998.

For trials involving an IMP

Access to archives should be restricted to authorised personnel. Any change in the ownership and location of the documentation should be documented in order to allow tracking of the stored records.

Duration of archiving

The Sponsor, or delegated person, should consider whether the results of a trial will or may be included in a marketing authorisation application and should take the necessary steps to ensure appropriate retention of the essential documents (see Trial Master File).

Consideration of site-specific archiving requirements, as detailed by each R&D Department, is essential as these may differ from those outlined below:

a. Trials, which are not to be used in regulatory submissions
Essential documents of the Sponsor/trial organisers and investigators, from trials that are not to be used in regulatory submissions, should be retained for at least five years after completion of the trial. These documents should be retained for a longer period if required by the applicable regulatory requirement(s), the Sponsor or the funder of the trial.

b. Trials to be included in regulatory submissions

- *Sponsor's responsibilities*

The Sponsor, or delegated person, should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the Sponsor intends to apply for approval(s).

The Sponsor-specific essential documents should be retained until at least two years after the last approval of a marketing application in the EU. These documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

- *Investigator responsibilities*

Essential documents should be retained until at least two years after the last approval of a marketing application in the EU. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by agreement with the Sponsor. It is the responsibility of the Sponsor, or delegated person, to inform the investigator/institution as to when these documents no longer need to be retained.

Destruction of essential documents
The reasons for destruction of essential documents should be documented and signed by a person with appropriate authority. This record should be retained for a further five years from the date that the essential documents were destroyed. The Sponsor, or delegated person, should notify investigators in writing when their trial records can be destroyed.

The Medical Research Council is “in partnership with other research groups” investigating procedures that will enable Data Sharing and Preservation for the public good (2006).

For more information: http://www.mrc.ac.uk/index/strategy-strategy/strategy-science_strategy/strategy-strategy_implementation/strategy-other_initiatives/strategy-data_sharing/strategy-data_sharing_policy.htm

GLOSSARY

CA	Competent Authority
CI	Chief Investigator
Collaborative Group	Group of investigators collaborating in a trial
COREC	Central Office for Research Ethics Committees
CHMP	Committee for Medicinal Products for Human Use
CRF	Clinical Record Form/Case Report Form
CRO	Clinical Research Organisation
CTD	Clinical Trial Directive
CTD	Common Technical Document
CTA	Clinical Trial Authorisation
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DMC	Data Monitoring Committee
EC	European Commission
EMEA	European Agency for the Evaluation of Medicinal Products
EU	European Union
EU CTD	European Union Clinical Trial Directive
EudraCT	European Clinical Trial Database
EudraVIGILANCE	European Database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
Investigator	Investigator collaborating in a clinical trial
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MS	Member State
MREC	Multicentre Research Ethics Committee
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
NSTS	NHS Strategic Tracing Service
ONS	Office for National Statistics
Participant	Person participating in a clinical trial
PI	Principal Investigator at a trial site
PIAG	Patient Information Advisory Group
PIL	Participant Information Leaflets
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person responsible for final despatch of trial drug
RCT	Randomised Controlled Trial
R&D	Research & Development

REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SD	Standard deviation
SDV	Source document/data verification
SOPs	Standard Operating Procedures
Sponsor	Individual/organisation responsible for the initiation, management/financing of a clinical trial
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUE	Serious Unexpected Event
SUSAR	Serious Unexpected Suspected Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRC	United Kingdom Clinical Research Collaboration
UKCRN	United Kingdom Clinical Research Network
UKTMN	United Kingdom Trial Managers' Network

SUGGESTED READING (in no particular order)

1. Peto R, et al. Why we need large simple randomised trials. Stats in Med 1984; Vol 3, 409-420
2. Pocock S. Clinical Trials: A Practical Approach. Wiley 1983
3. Warlow C, et al. How to do it - organise a multicentre trial. BMJ 1990; Vol 300, 180-183
4. MRC GCP Guidelines. MRC Head Office 1998
5. MRC Ethics series. MRC Head Office 1991
6. International Conference on Harmonisation on Good Clinical Practice Guidelines (ICH-GCP). 1996
7. BACUP booklet. Understanding Clinical Trials
8. Raven A. Clinical Trials: An Introduction. Radcliffe Medical Press
9. Jadad A. Randomised Controlled Trials. BMJ Books 1998
10. Baum et al. Ethics of clinical research – lessons for the future. BMJ 1989; Vol 299, 251-253
11. Moher D et al. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285(15):1987-1991
12. Horton R, Smith R. Time to Register Randomised Trials. BMJ 1999, Vol 317, 865-866
13. Faulder C. Whose Body Is It? The Troubling Issue of Informed Consent. London: Virago 1985
14. Friedman LM, Furberg CS, Demets DL. Fundamentals of Clinical Trials. Boston 1981; John Wright/PSG Inc.
15. Flather M, Ashton A. Handbook of Clinical Trials. Remedica Publishing; 2001
16. Duley L, Farrell B (eds), Clinical Trials. BMJ Books, London, 2002
17. Wang D, Bakhari A (eds), Clinical Trials: A Practical Guide to Design, Analysis and Reporting. Remedica, 2005
18. Campbell MK, Elbourne DR, Altman DG for the CONSORT Group. CONSORT statement: extension to cluster randomised trials. BMJ 2004; 328**:**702-708.
19. Piaggio G**,** Elbourne DR, Altman DG, Pocock SJ, Evans SJ for the CONSORT Group. Reporting of Noninferiority and Equivalence Randomized Trials: An Extension of the CONSORT Statement. JAMA, March 8, 2006; 295: 1152-1160.

USEFUL WEBSITES (some are included in the document)

Bandolier: Evidence Based Medicine
British Medical Journal
Centre for Evidenced Based Medicine
Central Office for Research Ethics Committees
Clinical Trials Tool Kit
Cochrane Library
Current Controlled Trials
CONSORT Statement
Data Protection Act
Database of funding sources
Declaration of Helsinki
Health and Social Care Act
INVOLVE (Consumer involvement in clinical trials)
Institute of Clinical Research
ISCTN Register
Medicines and Healthcare products Regulatory Agency
Medical Research Council
MRC Consumer Liaison Group
National Electronic Library for Health
NHS Strategic Tracing Service
National Office of Statistics
NHS R&D Health Technology Assessment Programme (HTA)
Pharmaschool
PubMed Database
Register of Current Controlled Trials
Research Governance Framework
The Lancet
Worldwide Regulatory Authorities

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arc Arthritis Research Campaign

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Please read the questions below and comment. Suggestions are most welcome.

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