Society for Clinical Trials 32nd Annual Meeting

Workshop P5
Trial and Site Management for Multi-Center Trials

Part 2 of 3

Sunday, May 15, 2011
8:00 AM - 12:00 PM
Georgia B

Workshop 5

Trial and Site Management for Multi-Center Trials

Additional Information

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Information included

1. Committee Structure
2. Data Collection Options
3. Publication Arrangements
4. Study Record Keeping
5. Paperwork/Approvals

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Committee Structure

- Most trials have a variety of committees depending on the needs of the trial.
- Most of these will be coordinated through the central office.
- The names are sometimes different depending on country but the tasks they perform are the same.

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- Web site from the UK outlines the MRC guidelines on what the committees should do.

  http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002416.

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In general the committees need to:

- Monitor overall progress of the trial
- Approve the scientific agenda
- Establish polices and procedures for the trial
- Monitor adherence to the protocol
- Consider new information as it is available from other trials
- Ensure patient safety in general (ethics approvals and consent documents)

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- Ensure patient safety by reviewing adverse event reports and results of planned interim analyses
- Oversee the day-to-day activities of the trial

Very common committees are:

- Executive
- Steering
- Operations
- Data Safety & Monitoring (DSMC)

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Things to consider:

- The major funders in the UK expect that trials will have independent steering and data monitoring committees
- One format to consider is having a joint steering/data monitoring committee from the onset of the trial
- Patient representation on steering committees is very common in the UK.
- A good resource about lay involvement is www.lindalliance.org

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- Having experienced people on data monitoring committees is very important. Therefore consider carefully who to invite.
- It is becoming increasingly difficult to appoint statisticians to DSMCs, given their workload and lack of statisticians with relevant experience
- The composition of a DSMC has been the source of much debate over the past few years.
- The main issue is whether it should be totally independent or whether trial personnel (i.e. the PI) should be part of the committee.
- There continues to be 2 points of view on this issue.

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DAMOCLES project

- The aim of this UK project was to clarify the advantages and disadvantages of alternative approaches to the ways in which accumulating data are monitored and acted on in randomised controlled trials. It led to recommendations for the conduct of randomised trials within the NHS in the UK, including a charter for DMSC.
- Journal reference:

  The DAMOCLES Study Group. A proposed charter for clinical trial 2005 data monitoring committees: helping them do their job well. Lancet 2005; 365: 711-22.

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Data Collection Systems

There are 4 types of data collection systems -

1. Paper based data collection forms or case report forms (CRF)
2. Direct data collection into a computer based system
3. Direct data collection onto a web-based system
4. Combination system

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Paper Based System

- Data from a medical chart are abstracted and written on paper forms
- Study participants complete questionnaires on paper
- These completed paper forms are either sent to the Central Office by mail/fax or local study staff enter them on-site into a computer database

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- If mail is being used it is very important for the sites to keep backup copies in case of problems with the mail. These copies must be held securely.
- After being processed at the Central Office data queries are mailed or faxed back to clinical site for correction or verification
- Data changes are recorded and initialed on the original data forms

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Direct into a Computer Based System

- Data from a medical chart are abstracted and entered directly into a computer database
- Phone calls are made to study participants and data are collected over the phone and entered directly into a computer database
- The data entry is done at the local site and transmitted electronically to the Central Office. This transmission is usually done on a regular basis.

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- Data queries are returned electronically to the sites
- Data changes are done directly on the system and an audit trail is created of all changes
- Double data entry may be used to avoid keying mistakes. This is entry of some (or all) of the data twice, ideally by 2 individuals. A third person would resolve any discrepancies. The idea is that 2 people will not make the same random error.

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- Data collection can be done using handheld computing devices such as PDAs, or mobile (cell) phones
- Local backup may be required if a lot of data are entered between the regular transmissions to the Central Office. Otherwise backup is handled centrally by the Central Office.

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Direct into a Web Based System

- Data from a medical chart are abstracted and entered directly onto a secure web page
- Data are checked in real-time as data entry is done. The vast majority of corrections and verifications are done during data entry
- Data changes are done directly on the system and an audit trail is created of all changes
- Backup is handled centrally by the web provider.

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Combination System

- Some studies use a combination of the systems outlined above - e.g. clinical data are input at the sites and participant completed CRFs are entered centrally
- In some studies data are collected from sources other than the clinical site
  - Lab results directly from clinical laboratories
  - Direct data from hospital record systems – often done for economic analyses
  - Routine national databases (e.g. death registries, hospital episode databases)
  - Third party non-medical databases (e.g. insurance databases).

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Publication Arrangements

It is a good idea to include a publication policy as an appendix to study protocols.

This ensures that collaborators and others working on the study are aware of the policy at the outset, avoiding any disharmony when publications are being considered.

Two examples are included with your handouts.

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- Any authors of a publication must meet the requirements of the journal. Many journals use the International Committee of Medical Journal Editors guidelines http://www.icmje.org

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In general this means:

- Each author should have participated sufficiently in the work represented by the article to take public responsibility for the content.
- Participation must include three steps:
  - conception or design of the work represented by the article OR analysis and interpretation of the data OR both; AND
  - drafting the article or revising it for critically important content; AND
  - final approval of the version to be published

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- For multicentre trials often the authorship line includes "*[trial name]* Investigators or *[trial name]* Study Group with a listing in the Acknowledgment section at the end of the article of all the Centre Collaborators and Research Nurses.
- Funding sources, including grant numbers, need to be included as well.

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- Centre Collaborators are not usually primary authors of the publication of the main results of a trial.
- Often they are primary authors of secondary analyses that they propose themselves or work on as part of a group of Centre Collaborators

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Things to consider:

- The central office can encourage staff from the good recruiting sites to be part of secondary papers
- Set a timeline for secondary papers
- Have a policy of how to deal with members of the writing group that aren't proceeding as expected

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Study Record Keeping

Good record keeping is critically important to ensure complete data are collected on all cases and to meet legislative requirements.

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Things Clinical Sites Need to Do

- Study record keeping is required to keep track of patient contacts, patient payments (if applicable) and for data completion.
- Record keeping can be done in a variety of computer programs: Excel or Access or now more commonly database servers such as SQL Server with a visual front end .
- Having one source of contact information for participants is important so that any updates are only done in one place and current information is available for all study staff.

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- Having information available to correctly identified research team members, rather than only one person, ensures that data collection tasks can be continued during staff member vacations or absences.
- Information that links patient identifying information and study data should be stored separately to ensure confidentiality.
- Patient identifying information and data must be stored in secure locations. This means locked offices and filing cabinets for paper items and password protected computer access for computer files.

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- There may be special regulations for where the original consent form is stored. These regulations may be set by the study or by the clinical site.
- Accurate record keeping and storage of data is important so that it is easily available during any monitoring/audit/inspection visits that may occur.
- There may be national legislation as far as data storage is concerned (e.g. UK Data Protection Act, US – HIPAA regulations, Canada – Tri-Council Guidelines).

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- Retention of the data is required after the study is over.
- This could mean storage of paper forms and/or storage of electronic data.
- The length of storage will vary depending on the country, the study, the funder and the site.
- The Central Office may scan paper forms to allow for long term electronic storage.
- With all electronic storage it is important to consider that data systems/platforms become outdated and it may be necessary to migrate the data to an updated program.

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Paperwork/approvals

The paperwork required is usually dependent on the funding source for the trial. It will also vary depending on the country where the clinical site is located and the type of trial (eg investigational medicinal product (IMP), surgery intervention).

The following are always required in some form or another:

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IRB or ethics approval

- The ethics approval obtained by the Central Office will be considered sufficient at some sites.
- At most sites however a local IRB or ethics approval is also required.
- The process of getting IRB approval can be fairly cumbersome for centre collaborators that haven't done it before. Suggest to them that they find someone at their site who has experience/provide support from the central office.

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IRB or ethics approval

- In the UK if a clinical trial is being conducted in two or more geographical areas, multi-domain NHS Research Ethics Committee approval is required in addition to hospital (research and development) approval. The Integrated Research Application system (IRAS) https://www.myresearchproject.org.uk/
- Other approvals as necessary (eg approval from the regulatory authority for IMP trial)

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Contract with the Central Office

- This will vary in complexity depending again on the funder and the country.
- Sometimes it is a simple contract stating what the site will do and what the Central Office will do.
- At other times it is a complex sponsorship agreement.
- Details about requirements specific to NIH funded trials are in handouts.

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Agreement from management at the site that they will support the research effort

- This again will vary depending on the site and the country.
- It may be a formal application to management body at the institution (eg NHS Research & Development Offices in the UK); approval from a research committee at the site; or signatures from all department heads whose department will need to support the research effort.
- It is usually something handled by the local centre collaborator (but they will require support from the central office).

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