Society for Clinical Trials 33rd Annual Meeting

Workshop P2
Trial and Site Management for Multi-Center Trials

Part 2 of 2
Additional Resources

Sunday, May 20, 2012
8:00 AM - 12:00 Noon
Tuttle North

Workshop 2

Trial and Site Management for Multi-Center Trials

Additional Information

Additional slides

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

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

- 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

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)

- 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)
- Publication

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. Computerized system
3. Web-based system
4. Combined systems

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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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- Copies are kept at the site for reference. These copies must be held securely
- After being processed at the Central Office data queries are emailed, faxed or mailed back to clinical site for correction or verification
- All records of changes to the data, authorization and date of the changes are maintained

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Electronic Data Capture System

- Data abstracted from a medical chart or reported by the patient are collected in electronic format
- Data collection is done remotely (eg by entry into a computer or using handheld devices or mobile phones)
- Some valid value, range and logic checks are done by the system at the time of data entry

- These data are transmitted electronically to the Central Office usually on a regular basis
- Data queries are returned electronically
- Data changes are done directly on the system and an audit trail is created of all changes
- 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

Central Web Based System

- Data from a medical chart are abstracted and entered directly onto a secure web page and are received in real-time
- Some valid value, range and logic checks are done by the system at the time of 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

Combined Systems

- Often a combination of the systems is used (eg clinical data are input at the sites and participant competed questionnaires are entered centrally)
- In some studies data are also acquired from sources other than the clinical site
  - Lab results directly from clinical laboratories
  - Data from medical record systems (often used for economic analyses)
  - National databases (eg death registries, hospital episode databases)
  - Third party non-medical databases (eg insurance databases)

Publication Arrangements

Authorship requirements:

- 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

- 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

- 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

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

Study Record Keeping

There are specific GCP requirements for record keeping on clinical trials (5.5 Trial Management, Data Handling, and Record Keeping)

Good record keeping is also critical to the quality and efficiency of managing the study and the study data.

Things Clinical Sites Need to Do

- Study record keeping is required to keep track of study staff, patient contacts, patient payments (if applicable) and for protocol compliance and data collection
- Record keeping can be done in a variety of computer programs (eg Excel, Access)
- 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

- 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
- 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

- 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)

- Retention of the data is required after the study is over. This could include storage of designated essential documents and electronic records
- The length of storage will vary depending on the country, the study, the funder and the site.
- Storage systems must be validated (eg scanning, microfiche)
- 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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Society for Clinical Trials 2012

Trial and Site Management for Multi-Center Trials Workshop

Extra documents

1. Paperwork needed for NIH funded studies
2. Sample Publication Policy – US site
3. Sample Publication Policy – UK site
4. Example Co-sponsorship Agreement
5. Sample Agreement for US Central Office and Non-US site
6. List of Acronyms
7. Useful Resources, Web Links and Publications

Specific Paperwork for NIH funded studies

Each participating site requires the following:

1. **Assurance of compliance with United States Federal regulations for protection of human subjects in research:**

All institutions must assure that they will comply with the Common rule (for NIH, 45 CFR 46.103; for FDA 21CFR subpart 50, HIPPA).

In many cases an institution will have many NIH projects underway and will have received a Federal-Wide Assurance (FWA) number. Once an institution has this number the project is automatically covered and will need to be provided to the Data Coordinating Center (DDC).

If it is the first NIH project to be undertaken at a particular institution the DCC can cover it under their FWA. A special agreement will have to be signed for this to happen. If the institution is collaborating on multiple NIH studies it must apply for its own FWA number. The following web link has instructions about this. (http://ohrp.cit.nih.gov/efile/FwaStart.aspx) There are FWA's for International (Non-US) Institutions and Institutions within the US.

2. **Documentation of education on the protection of human subjects in research**

The site collaborator and all other research personnel must provide documentation of this education. The institution will stipulate what the education needs to be. Often, it's an on-line course which can be completed at one's own pace.

Some examples are:
Protection of Human Research Subjects: Computer-Based Training for Researchers - http://phrp.nihtraining.com/users/login.php This is an NIH-sponsored course.

Interagency Panel on Research Ethics - http://www.pre.ethics.gc.ca/english/tutorial. This is a Canadian course that covers the Canadian regulations.

3. **Contracts/Consortium Agreements**

The DDC must arrange contracts/consortium agreements with all participating clinical sites. These contracts have wording and specific clauses required by NIH. The DCC is accountable to the NIH for the overall performance of the project, appropriate expenditure of the grant funds by all parties, and all other NIH requirements. The contracts outline for the sites their responsibilities. Often these are standard contracts but negotiation on some things can be undertaken.

4. **Identification numbers required for anyone dealing with the US Federal Government.**

These are:
DUNS number (Data Universal Number System)
EIN number (Employer Identification Number)

CCR (Central Contractor Registration)
NATO Commercial and Governmental Entity (NCAGE) Code (required for foreign sites only)

A site may have some, or all, of these numbers already. One can search at https://www.bpn.gov/bincs/begin_search.asp for existing DUNS and CAGE numbers. If a site has received NIH funds at any time in the past they will have an EIN number.

If any of these four numbers are needed, the following website takes you through the process - http://era.nih.gov/ElectronicReceipt/preparing_grantsgov_reg.htm

5. Bayh-Dole Acknowledgement

This is a form that all trial employees need to sign regarding the process to be followed for any inventions arising from federally supported research.

SAMPLE POLICY FROM US SITE

[STUDY NAME]
Publication and Presentation Policy

A. GOALS

1. To encourage high quality publications and presentations in a timely fashion.
2. To encourage broad participation by *[STUDY]* investigators in publications and presentations.
3. To encourage multidisciplinary and creative use of the *[STUDY]* data and resources.
4. Ensure appropriate recognition of *[STUDY]* investigators.

B. SCOPE OF THE GUIDELINES

The policy covers papers, abstracts, and presentations that involve unpublished data collected as a part of the *[STUDY]* study. These policies will remain in force for the duration of data analysis by the *[STUDY]* Executive Committee.

C. *[STUDY]* PUBLICATION REVIEW

The Executive Committee will have overall responsibility for publications from *[STUDY]*.

D. TYPES OF REPORTS

These guidelines deal with 4 different types of reports.

- Main papers: Primary hypotheses and outcomes to be presented and published
- by whole *[STUDY]* Study Group
- Other study publications: May be undertaken by smaller groups for the *[STUDY]* Study Group with all participants at the end of the paper.
- Abstracts submitted to national or international meetings.
- Presentations made to national or international meetings.

E. AUTHORSHIP AND ACKNOWLEDGEMENTS

- Authors must participate in the writing of the paper in accordance with the International Committee of Medical Journal Editors guidelines (N Engl J Med 1991; 324:424-8). First authors are expected to delete names from the final list of authors if those individuals have not participated in the writing and/or analysis of the paper in accordance with those guidelines.

- All *[STUDY]* papers and abstracts should include either "*[STUDY]* Investigators" or "for the *[STUDY]* Study Group" in the authorship line.

- All *[STUDY]* papers should include an "Acknowledgements" section that lists the *[STUDY]* investigators and principle staff at the Coordinating Center, Statistical and Data Management Center, Imaging Center, and Clinical Sites. Also the NIH NINDS grant number should be cited (*[Grant Number]*).

  When the results from the genome scan are cited, acknowledge CIDR as: "Genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institute of Health, to Johns Hopkins University, contract #*[contract number]*.

- Authorship of main papers: Authorship of main papers may include investigators from the Coordinating Center, the Statistical and Data Management Center, Imaging Center, clinical sites, and NINDS Study Representative. In general, these authors should be those who have made the most substantial contribution to the study. The Executive Committee will recommend the composition of authorship for the main papers and may make exceptions to these guidelines.

- Authorship of other papers: Where feasible and appropriate, at least one investigator from the Coordinating Center or Data Management Center will work with the investigator proposing the analysis and publication in completion of the analysis and manuscript using *[STUDY]* data.

First authorship of *[STUDY]* papers

- First authors of main papers will be *[STUDY]* Study Investigators/Group. For other *[STUDY]* papers and abstracts, *[STUDY]* Investigators will also receive priority.

- In general, the investigator who first conceived of the project and submitted a plan for the manuscript to the Executive Committee should have the option of serving as first author, so long as they complete the paper within a reasonable amount of time.

1. Co-authorship

- The order of authorship on a paper should be proposed by the writing group to the *[STUDY]* Executive Committee for that project. In general, the authors will appear in order of contribution to the writing and analysis of the paper.

- When contributions to writing and analysis have been similar, priority should be given, in order of preference, to 1) *[STUDY]* investigators or staff 2) more junior authors, 3) those who have contributed to a greater degree to management and data collection for the study, and 4) *[STUDY]* investigators or staff who have had fewer opportunities to author *[STUDY]* papers.

2. Disclosures

- *[STUDY]* papers should include a paragraph describing the source of funding (NIHNINDS and CIDR) and their role in the analysis, writing and review of the paper.

- NIH funding (grant # *[Grant Number]*) should also be acknowledged.

F. ANALYSIS OF DATA

- The Statistical and Coordinating Center will finalize study-wide data and will perform analysis to support specific proposals upon priority and approval established by the Executive Committee.

- Analyses for the main papers will be performed collaboratively by the Statistical and Coordinating Center. Analyses done by other groups must be first approved by the Executive Committee.

G. ASSIGNMENT AND APPROVAL PROCESS FOR ANALYSIS PROPOSALS

1. Analysis plans

- The first step for all *[STUDY]* papers, abstracts, posters, and presentations of unpublished data is for an investigator to submit a plan to the Executive Committee. The plan should specify the content including the hypothesis, patient population (inclusion, exclusion), and data analysis and tables.
- The proposed journal or meeting and deadlines need to be specified.
- Priority will be deterrmined by *[STUDY]* Executive Committee and *[STUDY]* Statistical and Coordinating Center.
- Status communicated to investigator/working group.

2. Timeline

If the authors have not made substantial progress (as defined by the *[STUDY]* Executive Committee) on the analysis within 6 months or the Publications Committee has not received an abstract, presentation, or manuscript within one year after approval of the analysis plan, the Executive Committee will review the progress on that plan and may offer first authorship to others in the writing group. An exception will be when final data are not available. In that case, the first author will have one year from the time that the data first became available or approval date, whichever is later.

I. *[STUDY]* PAPERS

- Prior to preparation of the manuscript, send to *[STUDY]* Executive Committee the title, abstract, authors, proposed journal.
- Authors are to be proposed by working groups.
- All participants will be listed as co-authors (*[STUDY]* Study Group).
- The manuscript will be reviewed by *[STUDY]* Executive Committee before submission to verify accuracy of the data.

J. *[STUDY]* ABSTRACTS, POSTERS AND PRESENTATIONS

- Abstracts, posters and/or presentations will be of outcome (1^o or 2^o hypotheses) by the entire study group.

- All abstracts posters and presentations must be based on an approved analysis plan.

- Deadlines: Authors who plan to submit an abstract must notify the Coordinating Center 3 weeks in advance of the abstract deadline. Drafts of abstracts and posters and outlines of presentations including the data and conclusions must be received by the Coordinating Center at least 10 working days before the abstract deadline or date of presentation. Executive Committee reviewers must indicate their approval or disapproval and suggested revisions within 5 working days from the fax date of the abstract or presentation. A committee member may withhold approval pending revision. In such cases, authors must respond to the comments of the committee member. For abstracts, approval of at least 2 of the reviewers, with no reviewers disapproving, is required. Failure to respond to request for approval within the time limit will be taken as abstention. Authors and presenters will be notified about approval and recommended changes within 5 working days of the mailing or fax date. Send to *[STUDY]* Executive Committee the title, presenter, audience, and data content.

- For national or regional meetings the authors need to send to *[STUDY]* Executive Committee for review the abstract, authors, meeting, deadline date, and presentation date for final review of accuracy.

Request for use of data from the *[STUDY]* database

Date of Request	
Investigator Name	
Investigator Address	
Investigator email:	
Investigator Direct Line:	
Description of proposed Presentation/Manuscript:	
Data elements needed for Presentation/manuscript:	

All publications/presentations must acknowledge:
This study was supported in part by the National Institute of Neurological Disorders and Stroke of the National Institute of Health grant number *[Grant Number]*.
Any publications/presentation using genetic results must acknowledge:
Genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to the Johns Hopkins University, Contract Number *[Grant Number]*.

PUBLICATION POLICY – UK EXAMPLE

PUBLICATION POLICY FOR XXXXXX Study
AUTHORSHIP POLICY

1. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals (see references) and are in accordance with the rules of the International Committee of Medical Journal Editors.

a. Group authorship

Group authorship will be appropriate for some publications, such as main reports. This will apply when the intellectual work underpinning a publication 'has been carried out by a group, and no one person can be identified as having substantially greater responsibility for its contents than others'.[1] In such cases the authorship will be presented by the collective title - The XXXXXX Trial Group - and the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. In some situations one or more authors may take responsibility for drafting the paper but all group members qualify as members; in this case, this should be recognised using the byline 'Jane Doe *and* the Trial Group'.[2] Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the byline would read 'Jane Doe *for* the Trial Group'). [2]

b. Individual authorship

Other papers, such as describing satellite studies, will have individual authorship. In order to qualify for authorship an individual must fulfil the following criteria[1]:

i. Each author should have participated sufficiently in the work represented by the article to take public responsibility for the content.

ii. 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.

Participation solely in the collection of data is insufficient by itself and those persons who have contributed intellectually to the article but those contributors do not justify authorship may be acknowledged and their contribution described.[1]

c. Determining authorship

Tentative decisions on authorship should be made as soon as possible.[1] These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Steering Committee.

2. AUTHORSHIP FOR PUBLICATION ARISING FROM XXXXXX

a. Operationalising authorship rules

We envisage two types of report (including conference presentations) arising from the XXXXXX trial and its associated projects:

i. *Reports of work arising from the main XXXXXX trial* - If all grant-holders and research staff fulfil authorship rules, group authorship should be used under the collective title of 'The XXXXXX Trial Group'; if one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to 'Jane Doe and the XXXXXX Trial Group'.

ii. *Reports of satellite studies and subsidiary projects* - Authorship should be guided by the authorship rules outlined in Section 1 above. Grant-holders and research staff not directly associated with the specific project should only be included as authors if they fulfil the authorship rules. Grant-holders and research staff who have made a contribution to the project but do not fulfil authorship rules should be recognised in the Acknowledgement section. The role of the XXXXXX Trial Group in the development and support of the project should be recognised in the Acknowledgement section. The lead researcher should be responsible for ratifying authorship with the Project Management Group.

For reports which specifically arise from the XXXXXX trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to 'Jane Doe for the XXXXXX Trial Group'. If individual members of the group are dissatisfied by a decision, they can appeal to the Management Group for reconciliation. If this cannot be achieved, the matter should be referred to the Steering Group.

b. Quality assurance

Ensuring quality assurance is essential to the good name of the trial group. For reports of individual projects, internal peer review among members of the Project Management Group is a requirement prior to submission of papers. All reports of work arising from the XXXXXX trial including conference abstracts should be peer reviewed by the Project Management Group.

The internal peer review for reports of work arising from the XXXXXX project is mandatory and submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. The Project Management Group will be responsible for decisions about submission following internal peer review. If individual members of the group are dissatisfied by decisions, the matter may be referred to the Steering Group.

The Project Management Group undertake to respond to submission of articles for peer review at the Project Management Group Meeting following submission (assuming the report is submitted to the trial secretariat in Aberdeen at least two weeks prior to the meeting).

REFERENCES

1. Huth EJ (1986). Guidelines on authorship of medical papers. *Annals of Internal Medicine*, **104**, 269-274.

2. Glass RM (1992). New information for authors and readers. Group authorship, acknowledgements and rejected manuscripts. *Journal of the American Medical Association*, **268**, 99.

Example Co-sponsorship Agreement

Allocation of Co-sponsorship Responsibilities for the ??? Trial

Between:

??? (Central Office location)
and
?? (site)
and
??? (Site Collaborator)

All responsibilities allocated ✓, <u>must be</u> initialed to indicate acceptance

Responsibilities	Central Office		Site		Collaborator	
1. Assess the quality of the research	✓		✓			
2. Assess the quality of the research environment premises [1]	✓		✓			
3. Ensure appropriate experience of the site Collaborator(s) [2]	✓		✓			
4. Ensure arrangements, systems and resources will allow the collection of high quality, accurate data and the appropriate data analysis and data protection	✓		✓			
5. Ensure that arrangements are in place for the research team to access resources and support to completely deliver the research	✓		✓		✓	
6. Ensure that arrangements are in place to review significant developments	✓					
7. Ensure arrangements are in place to monitor the research for compliance or agree with another organisation to provide the facility	✓					
8. Ensure provision has been made for insurance or indemnity	✓		✓			
9. Ensure the research proposal respects the dignity, rights, safety and well-being of participants and the relationship with care professionals	✓		✓			

Responsibilities	Central Office		Site		Collaborator	
10. Ensure that the research proposal is worthwhile, of high scientific quality and represents good value for money	✓		✓			
11. Ensure that all scientific judgements made in relation to responsibilities set out here are based on independent and expert advice	✓					
12. Ensure that appropriate arrangements are in place for the registration of the trial	✓					
13. Ensure that assistance is provided to any enquiry, audit or investigation related to the trial	✓		✓		✓	
14. Ensure that arrangements are proposed for disseminating the findings	✓		✓			
15. Ensure adequate financing of the project	✓					
16. Ensure adequate arrangements for the long term storage of Trial Source Data and Patient Health records			✓		✓	
17. Management of Intellectual Property	✓					
18. Write the protocol	✓					
19. Ensure documented risk assessment of significant hazards associated with the protocol	✓					
20. Ensure appropriate scientific review of the proposed protocol	✓					
21. Ensure statistical advice is sought	✓					
22. Ensure Research Ethics Committee approval obtained before starting	✓				✓	
23. Ensure Trust R&D approval before commencement					✓	
24. Write study specific procedures [3]	✓				✓	
25. Set up and maintain a Trial Master File and essential documentation	✓				✓	
26. Notify protocol amendment(s) to Research Ethics / R&D [4]					✓	

Responsibilities	Central Office		Site		Collaborator	
27. Notify early discontinuation of trial to Research Ethics / R&D [4]					✓	
28. Notify end of trial within 90 days to Research Ethics / R&D [4]					✓	
29. Notify R&D of Study Start and End Dates					✓	
30. Take appropriate safety measures in consultation with the other parties	✓		✓		✓	
31. Keep auditable records of all adverse events	✓				✓	
32. Ensure that all SAEs are recorded and reported according to local and regulatory requirements	✓				✓	
33. Ensure that Site Collaborators are informed of SAEs	✓					
34. Produce an annual safety report on the research trial and submit to R&D [5]					✓	
35. Ensuring adequate arrangements for the long term storage of Trial Master File and essential documentation	✓				✓	
36. Notify R&D of all study publications annually [6]					✓	
37. Submit annual reports on trial progress to the R&D Office					✓	

Notes:

1. Quality of premises assessed by Central Office through Centre Survey
2. Experience of Site Collaborators assessed by Central Office through collection of CVs
3. Overall study specific procedures by Central Office; local issues by Site Collaborators
4. Notice of protocol amendments, early discontinuation of trial, and end of trial provided to Site Collaborators by Central Office
5. Safety information provided to Site Collaborators by Central Office: notification of all SAEs, Data Safety Monitoring Board reports (if any), notification of results of other similar trials
6. Trial progress information provided to Site Collaborators by Central Office: monthly recruitment and follow-up tables, monthly newsletter

DECLARATION OF ACCEPTANCE OF CO-SPONSORSHIP ARRANGEMENTS
for the ??? Trial

Between:

??? (Central Office)
and

??? (Site)
and
??? (Site Collaborator)

In signing this agreement the above parties are confirming that:

- This research trial will be conducted in accordance with the Research Governance Framework for Health & Social Care 2005 The parties confirm that where they have agreed that responsibilities shall be allocated otherwise than in accordance with the Framework this shall not compromise the standards or quality of the research nor the safeguards for those, including the public, who participate in the research.
- Where applicable this research trial will be conducted according to all regulatory requirements of International Conference on Harmonisation GCP/GMP, the UK Competent Authority (MHRA) and Directive/2005/20/EC.
- It is understood that if serious non-compliance, research misconduct and/or fraud are identified through routine or regulatory monitoring the trial will be closed.

I confirm that I have read and agree to accept the responsibilities as detailed and initialled in the
Allocation of Co-sponsorship Responsibilities for the ??? Trial

Signature for (Central Office)

_____	_____	_____
Print name	Signature	Date

Signature for (Site)

_____	_____	_____
Print name	Signature	Date

Signature of the Site Collaborator

_____	_____	_____
Print name	Signature	Date

Sample Agreement for US Central Office and non-US site

AGREEMENT

This Agreement is by and between [CENTRAL OFFICE], [the site] [which may be part of a bigger organization] for the purpose of support to the [study]. The [STUDY] is funded by the National Institutes of Health/National Institute of Neurological Disorders and Strokes Grant No. ??? attached hereto as Attachment C.

1. **Statement of Work**. On behalf of [SITE], the [?? UNIT] will function as the central point of contact for administrative tasks related to [STUDY] in ???. The [SITE] will act as administrative agent of [CENTRAL OFFICE] by performing specific activities identified in Attachment A.

2. Period of Performance. The period of performance under this Agreement shall be from February 1, 2006 through January 31, 2007. Expenditures incurred beyond January 31, 2007 are contingent upon availability of federal funding and will be authorized by written amendment to this Agreement.

3. Payment Amount. The estimated payment for [SITE]'s services provided under this Agreement is identified in the budget attached hereto as Attachment B. The annual estimated amount of $___ US Dollars is contingent on availability of funds and will be paid proportional to overall recruitment by nine proposed centers. Such amount shall not be exceeded without written Amendment to this Agreement. In addition and pursuant to Exhibit One, Enrolling Center Template, funding will be provided through [SITE] for payment to Enrolling Centers.

4. Key Personnel. Project activities under the [SITE] shall be under the direction of the [SITE] Director, ???. [SITE] shall notify [CENTRAL OFFICE] in writing of any changes of the [SITE] Project Director. Any successor proposed by [SITE] to replace the [SITE] Project Director must have the prior written approval of [CENTRAL OFFICE].

5. Fiscal Considerations.

5.1 Submission of Invoice: [CENTRAL OFFICE] will pay the [SITE] according to payment schedule attached hereto as Attachment B, in arrears, upon submission of an invoice to [CENTRAL OFFICE] at: ???. Such invoices shall be in duplicate (a certified original and one copy) and shall reference the [CENTRAL OFFICE] Agreement Number 122343/122182. Invoice amounts shall be calculated and shown in US Dollars. The basis for such calculation and conversion to US Dollars shall be the Euro value of ____€ (as of March 9, 2006 per http://www.oanda.com/convert/classic).

5.2 Final Payment: The final payment under this Agreement will be based upon receipt of and acceptance by [CENTRAL OFFICE], all services, information, and/or supplies required herein.

6. Reporting Requirements. Reports shall be submitted to [CENTRAL OFFICE] at such time and in such format as the [CENTRAL OFFICE] Project Director and [SITE] Project Director shall agree and as outlined in Attachment A.

7. Publications. [??? UNIT]] acknowledges that the work to be conducted under this Agreement is part of a multi-center [study]and that an independent joint publication is anticipated to be authored by the investigators in the multi-center [STUDY]. Therefore, [??? UNIT] agrees not to independently publish the any results of the [STUDY] until the multi-center publication has been made.

8. Termination. Either party may terminate this Agreement upon thirty (30) days' written notice to the other party. Termination by either party does not relieve the Enrolling Center of the responsibilities of the follow-up phase of the Study as detailed in the Protocol. In the case of termination by [CENTRAL OFFICE], the Enrolling Center will be reimbursed for all non-cancelable commitments under Article 5, Payment Schedule.

9. Compliance Assurances and Certifications. [??? UNIT] and [SITE] certify, by signing this document that the following assurances and certifications that apply to the [CENTRAL OFFICE] prime grant are met. Such assurances and certifications required by the [SITE] shall include but are not necessarily limited to:

a. Human Subjects. Compliance with the requirements of federal policy concerning the safe-guarding of the rights and welfare of human subjects who are involved in activities supported by Federal funds.

b. Patents, Licenses, and Inventions. Compliance with the Standard Patent Rights clauses as specified in 37 Code of Federal Regulations (CFR), Federal Acquisition Regulation (FAR) System or United States Code (U.S.C.) CFR, Part 501, FAR 57.227-11, or U.S.C. 203, whichever is appropriate and applicable.

c. Non-Delinquency on Federal Debt. AWARDEE specifically certifies that neither it nor any person to be paid from funds under this Agreement is delinquent in repaying any U.S. Government debt as defined by Office of Management and Budget (OMB) Circular A-129.

d. Misconduct in Science. Compliance with Final Rule as published at 70 CFR 37010, May 17, 2005, which in Spain corresponds to Subpart A of Part 50 of Title 42 CFR, as well as the Final Rule published in 32446 if Title 54 CFR on August 8, 1989.

e. Restrictions on Lobbying. Compliance with PL 101-121, Title 31, Section 1352, which prohibits the use of U.S. Government funds for lobbying on connection with this particular Agreement.

f. Conflict of Interest. Compliance with the National Institutes of Health (NIH) requirement to maintain a written standard of conduct and comply with 42 CFR Part 50, Subpart F.

10. Site Visits and Programmatic Audits. Designated representatives of [CENTRAL OFFICE], and/or the federal government may inspect and review progress of the work performed pursuant to the Agreement and for compliance with NIH/NINDS rules and regulations and International Conference on Harmonization/ Good Clinical Practices (ICH/GCP). Access shall be granted to facilities used or otherwise associated with the work performed and to all relevant data generated under this Agreement. All such inspections shall be conducted in such a way as to not unduly delay the progress of work and [CENTRAL OFFICE] shall give reasonable notice prior to conducting such inspections. Inspection by [CENTRAL OFFICE] shall not relieve the Enrolling Center of its responsibility to fully and formally report the details of the work set forth herein.

11. Indemnification. [CENTRAL OFFICE], to the extent authorized under the Constitution and laws of the State of ??, shall indemnify and hold [??? UNIT] harmless from liability resulting from the negligent acts or omissions of [CENTRAL OFFICE], its agents or employees pertaining to the activities to be carried out pursuant to the obligations under this Agreement; provided, however, that [CENTRAL OFFICE] shall not hold [??? UNIT] harmless from claims arising out of the negligence or willful malfeasances of [SITE], its officers, agents, or employees, or any person or entity not subject to [CENTRAL OFFICE]'s supervision or control.

[??? UNIT] shall indemnify and hold [CENTRAL OFFICE] harmless from liability resulting from the negligent acts or omissions of [??? UNIT], its agents or employees pertaining to the activities to be carried out pursuant to the obligations under this Agreement; provided, however, that [??? UNIT] shall not hold [CENTRAL OFFICE] harmless from claims arising out of the negligence or willful malfeasances of [CENTRAL OFFICE], its officers, agents, or employees, or any person or entity not subject to [SITE]'s supervision or control.

12. Independent Contractor. In the performance of this Agreement, [SITE] shall be deemed an independent contractor and, as such, no employees or staff of [SITE] shall be entitled to any benefits applicable to employees of [CENTRAL OFFICE].

13. Assignment. [??? UNIT] shall not assign, transfer, or subcontract its interest or obligations hereunder without the written consent of [CENTRAL OFFICE].

14. Notices. Any notices to be given under this Agreement shall be made to the signatories of this Agreement.

15. Termination. [CENTRAL OFFICE] may terminate this Agreement upon thirty (30) days' written notice to [??? UNIT]. [SITE] will be reimbursed for its costs to date of termination and non-cancelable obligations properly incurred prior to the date of termination, provided, however, that such costs shall not exceed the amount allowed under this Agreement and that a report of progress to date of termination has been submitted to [CENTRAL OFFICE].

16. Amendment. This Agreement may be amended only by joint written agreement between the parties.

17. Additional Provisions. This Agreement is made because of the U. S. Department of Health Human Services, Public Health Service, National Institutes of Health (NIH) Research Project Cooperative Agreement No. ??? that was awarded to [CENTRAL OFFICE]. The general provisions of that grant are incorporated into this Agreement as Attachment C. Where there is a conflict between those provisions and this Agreement, this Agreement will govern. [??? UNIT] agrees to abide by these provisions, including the appropriate administrative and cost guidelines. Where approval is required from NIH, such approval shall be sought from [CENTRAL OFFICE]. Under no circumstances is the right to grant a no-cost extension of the termination date given to the [??? UNIT] under this Agreement.

In witness whereof, the parties hereto have executed this Agreement as of the day and year first written.

Signatures of all parties

Attachment A
Statement of Work
Specific Activities

Private Foundation of [SITE]
([??? UNIT])

On behalf of [SITE], the [??? UNIT} will function as the central point of contact for administrative tasks related to [STUDY] in ??. The [??? UNIT] will act as the administrative agent of [CENTRAL OFFICE] by distributing financial reimbursement to participating Enrolling Centers in ?? and provide research data entry services for the Enrolling Centers.

Contracting and Payment of Enrolling Centers.

a. Contract with Enrolling Centers on behalf of [CENTRAL OFFICE]. Such contracts shall be in conformance with the template provided as Exhibit One to this Attachment A. This template may be translated to Spanish; any translation is subject to [CENTRAL OFFICE] approval prior to execution by the Enrolling Center. Termination of contracts with Enrolling Centers can be made only at the direction of the [CENTRAL OFFICE].

b. Issue monthly payments to the Enrolling Centers upon receipt of Reimbursement Reports from the [CENTRAL OFFICE] Coordinating Center and receipt of pass-through payment from [CENTRAL OFFICE]. Provide reconciled monthly financial disclosure of payments to Enrolling Centers, sent to [CENTRAL OFFICE] within 60 days of transacted payments.

Data Entry and Monitoring.

a. Collect and/or receive case report forms from Enrolling Centers and perform data entry of patient information as described in the Manual of Operations.

b. Respond to data queries from [CENTRAL OFFICE]-assigned Study Manager and feedback the resolution procedures to Enrolling Center(s).

c. Monitor source documentation at Enrolling Centers at least quarterly per [STUDY] procedures and provide reports of site visits and other monitoring activities to the [CENTRAL OFFICE] Coordinating Center on a quarterly basis.

Regulatory Documentation.

a. Represent [STUDY] to submit the protocol to the health ministry and centralize the IRB/EC approval process for each Enrolling Center
b. Forward copies of all health ministry and IRB/EC approval letters with informed consent forms to the [CENTRAL OFFICE] initially and upon update.
c. Assist Enrolling Centers to obtain NIH Federal Wide Assurance and forward copies assurances to [CENTRAL OFFICE].
d. Assist Enrolling Center key personnel to obtain certification in Human Subjects Protection and forward copies to [CENTRAL OFFICE] Coordinating Center.

Equipment and materials.

a. Receive and distribute neuropsychology materials and blood pressure equipment.
b. Cooperate with ??? who will facilitate importation of clopidogrel and placebo from the [STUDY] Drug Distribution Center in ???.
c. Conduct drug inventory every two weeks and enter into web-based drug inventory system to ???.

Other.

a. Participate in routine conference calls with [STUDY] Coordinating Center.
b. Provide location and amenities for training seminar to facilitate training of Enrolling Centers
c. Provide a telephone number to site investigator for immediate contact (available 24 hours/day, 7 days/week).

Exhibit One
Enrolling Center Template

AGREEMENT

This Agreement is made between the [SITE] and _____ (Enrolling Center) as a result of a subcontract from ([CENTRAL OFFICE]) and based upon a grant from the National Institutes of Health/National Institute of Neurological Disease and Stroke (NINDS) Grant No. ??? (Research Grant) award incorporated herein and attached to this Agreement to conduct a study entitled Secondary Prevention of Small Subcortical Strokes ([STUDY] Study).

1. Key Personnel. The [CENTRAL OFFICE] PI is ???.
The [SITE] PI is ???.
The Enrolling Center PI is _____.

2. Statement of Work. The Enrolling Center agrees to use all reasonable efforts to conduct the [STUDY] described in the Protocol incorporated herein and attached to this Agreement. The scope of work shall include screening patients, randomizing eligible patients, blood draws, the collection and submission of data, test results, radiology films, and other data as required. Any change in the Enrolling Center PI will be referred to [CENTRAL OFFICE] through [SITE] and be subject to the approval of the [CENTRAL OFFICE]. The Enrolling Center and [SITE] will ensure that IRB review is current through the study and that the research is conducted in accordance with applicable federal regulations.

3. Reports. The Enrolling Center shall submit any reports of unanticipated or pre-specified adverse events to the Statistical Center, within 24 hours in accordance with the requirement in the study protocol. In addition, the Enrolling Center may be asked to furnish other reports, at such times and in such form as reasonably requested by [SITE] and/or [CENTRAL OFFICE] during the term of this Agreement (e.g., progress regarding recruitment, reprints of MRI/MRA, certification of training in the Protection of Human Subjects, IRB/EC updates and renewals, FDA and Health Ministry approvals/updates, informed consent documents and other regulatory documents),.

4. Enrollment. The Enrolling Center agrees to enroll study participants as specified in the Protocol. The Enrolling Center shall obtain and retain in its files an informed consent for each patient enrolled. Should enrollment fall significantly below the projected enrollment rate or if the Enrolling Center consistently violates the Protocol, this Agreement may be terminated at the discretion of the [CENTRAL OFFICE] PI and in accordance with the provisions of Article 9 of this Agreement. In the event that an Enrolling Center is terminated in accordance with this Agreement, [SITE] or [CENTRAL OFFICE] reserves the right to obtain follow-up data from Enrolling Center study participants; participant consent forms should be constructed to reserve the follow-up rights of the Enrolling Center.

5. Payment Schedule. [SITE] agrees to make payments as follows:

Patient Costs
At randomization $____ USD
At follow-up visit $ ___ USD
(reimbursements for randomization and follow-up patient visits is contingent upon submission of data management forms to [SITE])

MRI/MRA $ ___ USD
(used only in rare cases, subject to prior authorization by [CENTRAL OFFICE] PI via email)

Payments to be made under this Agreement will be generated by [SITE] when patient documents have been received and reviewed as complete in accordance with the Protocol or other payment milestones have been reached. Invoice documentation from the Enrolling Center, unless specifically requested, is not required.

Ownership of equipment supplied by [SITE] for the express purpose of this study shall remain part of [CENTRAL OFFICE] controlled assets inventory and may be subject to return upon termination or completion of the [STUDY] Study.

6. Site Visits and Audits. Designated representatives of [SITE], [CENTRAL OFFICE] and/or the federal government may inspect and review progress of the work performed pursuant to the Agreement and for compliance with the U.S. Food and Drug Administration, local Ministry of Health, International Conference on Harmonization (ICH) guidance and regulations for Good Clinical Practice (GCP) under Title 21 of the of the U.S. Code of Federal Regulations (CFR). Access shall be granted to facilities used or otherwise associated with the work performed and to all relevant data generated under this Agreement. All such inspections shall be conducted in such a way as to not unduly delay the progress of work and [SITE] or [CENTRAL OFFICE] shall give reasonable notice prior to conducting such inspections. Inspection by [SITE] or [CENTRAL OFFICE] shall not relieve the Enrolling Center of its responsibility to fully and formally report the details of the work set forth herein. Should the Enrolling Center receive notice of inspection or review or if it is inspected or reviewed by the U.S. Food and Drug Administration or the local Ministry of Health, the [CENTRAL OFFICE] PI shall be immediately notified.

7. Confidentiality. The Enrolling Center will insure that all study records will be treated as confidential and will be stored in a secure area. Study records will be stored at the Enrolling Center for at least three years after study termination. Enrolling Center agrees to be bound by patient confidentiality laws of its country and, where applicable, to the United States Health Insurance Portability and Accountability Act of 1996 (HIPAA).

8. Publications. Enrolling Center acknowledges that the work to be conducted under this Agreement is part of a multi-center [study] and that an independent joint publication is anticipated to be authored by the investigators in the multi-center [STUDY] Study, including the Enrolling Center PI. Therefore, Enrolling Center agrees not to independently publish the results of the [STUDY] Study, but in no event shall Enrolling Center be so restricted after expiration of twelve (12) months after completion of study enrollment at all enrolling sites, or until such time as the multi-center publication has been made.

9. Termination. Either party may terminate this Agreement upon thirty (30) days' written notice to the other party. Exercise by [SITE] of its rights under this Article is subject to the approval of [CENTRAL OFFICE]. Termination by either party does not relieve the Enrolling Center of the responsibilities of the follow-up phase of the Study as detailed in the Protocol. In the case of termination by [CENTRAL OFFICE], the Enrolling Center will be reimbursed for all non-cancelable commitments under Article 5, Payment Schedule.

10. Term. The performance of this Agreement will extend from the effective date of February 1, 2006 through January 31, 2007. Contingent upon the availability of funding, it is anticipated that the study will renew annually through January 31, 2008. However, no further funding beyond that already provided herein will be authorized without further written agreement.

11. General Provisions.

11.a. Independent Contractor. In the performance of this Agreement, Enrolling Center shall be deemed to be an independent contractor and, as such, no employees or staff of Enrolling Center shall be entitled to any benefits applicable to employees of [CENTRAL OFFICE] or [SITE].

11.b. Assignment. Enrolling Center shall not assign, transfer, or subcontract its interest or obligations hereunder without the prior written consent of [CENTRAL OFFICE] and [SITE].

11.c. Notices. Any notices due under this Agreement shall be given to the signatories of the Agreement unless otherwise stated in this Agreement.

11.d. Amendment. This Agreement maybe amended only by joint written agreement between the parties.

11.e. Terms and Conditions. It is agreed that all terms and conditions of the Research Grant will apply to the Enrolling Center in the conduct of the work under this Agreement. Where approval is required from NINDS, such approval shall be sought from [CENTRAL OFFICE] through [SITE]. Under no circumstances is the right to grant a no-cost extension of the termination date given to the AWARDEE under this Agreement.

The parties hereby accept and agree to the terms and conditions of this Agreement.

[SITE] Project Director
I have read this Agreement and understand my obligations hereunder.

By_____
Name__ _____

Date_____

Enrolling Center: **_____**

By_____
Name_____

Title_____ _____

Date_____

Exhibit A—NGA plus special terms Exhibit B—Study Protocol

ACRONYMS

ACRP – Association of Clinical Research Professionals
CC – Coordinating Center
CI – Chief Investigator
CoC – Certificates of Confidentiality
CMS – Centers for Medicare and Medicaid Services
CMP – Clinical Monitoring Plan
COI – Conflict of Interest
CFR – Code of Federal Regulations
CDER – Center for Drug Evaluation and Research
CDISC – Clinical Data Interchange Standards Consortium
CIOMS – Council for International Organizations of Medical Services
CRA – Clinical Research Associate or monitor
CRF - Case (Clinical) Report form
CRISP – Computer Retrieval of Information on Scientific Programs
CRO – Contract Research Organization
CSR – Center for Scientific Review
CTA - Clinical Trial Authorization/Application
CTIMP - Clinical Trial of an Investigational Medicinal Product
CTS – Clinical Trial Specialist
DCC – Data Coordinating Center
DERA – Division of Extramural Research Activities
DHHS – Department of Health and Human Services
DIA – Drug Information Association
DIN – Drug Identification Number
DMC/DSMB - Data Monitoring Committee/Data and Safety Monitoring Board
DMP – Data Management Plan
DSMP – Data and Safety Monitoring Plan
EC – Ethics Committee
ECOG – Eastern Co-operative Oncology Group
EDC – Electronic Data Capture
EIN – Federal Entity Identification Number
EU – European Union
EudraCT – European Clinical Trials Database
FDA – Food and Drug Administration
FDAA – Food and Drug Administration Act Amendment
FIC – Fogarty International Center
FPFV – First Patient, First Visit
FSR – Financial Status Report
FWA – Federal Wide Assurance
GCP – Good Clinical Practice
GMO – Grants Management Officer
GMP – Good Manufacturing Practices
HC – Health Canada
HSC – Health and Social Care
HHS – Health and Human Services
HIPAA – Health Insurance Portability and Accountability Act

ICH – Good Clinical Practice
ICMJE – International Committee of Medical Journal Editors
IM – Investigator Meeting
IMP – Investigational Medicinal Product
IND – Investigational New Drug
IP – Investigational Product
IRB – Institutional Review Board
ISF – Investigator Site File
ISRCTN – International Standard Randomized Controlled Trial Number
MHRA – Medicines and Healthcare products Regulatory Agency
MINC – Medical Identification Number for Canada
MOP – Manual of Operations
NCIC – National Cancer Institute of Cancer
NIH(R) – National Institutes of Health (for Health Research)
NINDS – National Institute of Neurological Disorders and Stroke
NOA – Notice of Award
NRES – National Research Ethics Service
OER – Office of Extramural Research
OHRP – Office of Human Research Protections
OSMB – Observational and Safety Monitoring Board
PHAC – Public Health Agency of Canada
PHS – Public Health Service
PI – Principal Investigator
PMP – Project Management Plan
QC – Quality Control
QMP – Quality Management Plan
QOL – Quality of Life
R & D – Research and Development
RA – Research Assistant
RN – Research Nurse
RCT – Randomized Controlled Trial
REC (B) – Research Ethics Committee (Board)
RMP – Risk Management Plan
SAE – Serious Adverse Event
SAP – Statistics Analysis Plan
SC – Steering Committee
SC – Study Coordinator
SMO – Site Management Organization
SMP – Safety Management Plan
SOPS – Standard Operating Procedures
SOW – Statement of Work
TMF – Trial Master File
TSC – Trial Steering Committee

USEFUL RESOURCES, WEB LINKS AND PUBLICATIONS

Regulatory Authorities:

- US Food and Drug Administration (FDA) - http://www.fda.gov/
- FDA past inspections - http://www.fda.gov/ICECI/EnforcementActions/ucm222557.htm
- The Medicines and Healthcare products Regulatory Agency (MHRA) (UK) - http://www.mhra.gov.uk/#page=DynamicListMedicines

Regulatory Resources for Trials Conducted With Health Canada

- E6. ICH Guideline on Good Clinical Practice - http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php
- Division 5 of the Food and Drug Regulations - http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/reg/1024-eng.php
- Guidance 0068 - Guidance for Records Related to Clinical Trials - http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/docs/gui_68-eng.php
- Guidance for Clinical Trial Sponsors - http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec-eng.php

Regulatory Resources for Trials Receiving US Federal Funds

- http://www.hhs.gov/ohrp/policy/index/index.html

Ethics:

- FDA - www.fda.gov/AboutFDA/WorkingatFDA/Ethics/default.htm
- NIH - http://ethics.od.nih.gov
- National Research Ethics Service (NRES) (UK) - http://www.nres.npsa.nhs.uk/NRES
- Integrated Research Application System (UK) - https://www.myresearchproject.org.uk/SignIn.aspx (system for applying for the permissions and approvals for health and social care / community care research)
- NRES (UK) amendments - http://www.nres.npsa.nhs.uk/applications/after-ethical-review/notification-of-amendments/
- Declaration of Helsinki - http://www.wma.net/en/30publications/10policies/b3/

Research & Development:

- NHS R&D Forum - http://www.rdforum.nhs.uk (network and support organisation for those involved in planning and managing research in the UK NHS).
- UK NIHR Coordinated System for gaining NHS Permission (NIHR CSP) http://www.crncc.nihr.ac.uk/about_us/processes/csp

Pharmaceutical information:

- Drug Information Association (DIA) - http://www.diahome.org/DIAHOME/Home.aspx
- Association of Clinical Research Professionals (ACRP) - http://www.acrpnet.org/

EU Clinical Trial Legislation:

- EUdraLex guidelines - http://ec.europa.eu/health/documents/eudralex/index_en.htm (rules governing medicinal products in the EU. Volume 10 contains legislation and guidance documents applying to clinical trials)
- European Clinical Trials Directive 2001/20/EC - http://www.cardiff.ac.uk/racdv/resgov/Resources/CT%20Directive%202001.20.ec.pdf

Good Clinical Practice:

- International Conference on Harmonisation (ICH) GCP (E6 Guidelines) -http://ichgcp.net/

Medical Devices for Human Use:

- The Medical Devices Regulations 2002 - http://www.legislation.gov.uk/uksi/2002/618/contents/made

Safety reporting

- FDA - http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm
- UK MHRA - http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm
  UK National Research Ethics Service safety reporting - http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/

Clinical Trials Registration:

- Ottawa Statement on Trial Registration - http://ottawagroup.ohri.ca/
- WHO international trial search platform - http://apps.who.int/trialsearch/ (note: this search portal is not a clinical trials registry).
- International Standard Randomised Controlled Trial Number (ISRCTN) registration - http://www.isrctn.org/
  Clinical Trials.gov - http://clinicaltrials.gov/ (a service of the US National Institute of Health)
- Australian New Zealand Clinical Trials Registry - www.anzctr.org.au
- Nederlands Trial Register - www.trialregister.nl
- Clinical Trials Registry – India - http://ctri.nic.in/Clinicaltrials/login.php
- German Clinical Trials Register - https://drks-neu.uniklinik-freiburg.de/drks_web/

Databases of trials:

- UK Clinical Research Network Portfolio Database - http://public.ukcrn.org.uk/search/The search facility
- http://www.controlled-trials.com/mrct/ - Database of current trials (Current Controlled Trials website)
- European Clinical Trials database (EudraCT) - https://eudract.ema.europa.eu/ (database of all clinical trials commencing in the Community from 1 May 2004 onwards. It has been established in accordance with Directive 2001/20/EC).
- European Clinical Trials Register - https://www.clinicaltrialsregister.eu/ (EU Clinical Trials Register website is part of EudraPharm, the Community database of authorised medicinal products. Provides information on clinical trials of medicinal products with or without a marketing authorisation. The website provides public access to information extracted from the EU clinical
- trial database EudraCT.)
- WHO international trial search platform - http://apps.who.int/trialsearch/
- IFPMA Clinical Trials Portal – Drug Company Trials - http://clinicaltrials.ifpma.org/clinicaltrials/no_cache/en/myportal/index.htm

Publication information and Open access electronic journals

- International Committee of Medical Journal Editors (ICMJE) guidelines - http://www.icmje.org/urm_main.html
- Consort Statement - http://www.consort-statement.org/consort-statement/
- New England Journal of Medicine - http://www.nejm.org/
- The Lancet - http://www.thelancet.com/

- British Medical Journal - http://www.bmj.com/
- Applied Clinical Trials - http://www.appliedclinicaltrialsonline.com/appliedclinicaltrials
- Trials Journal - http://www.trialsjournal.com/

Search for Evidence:

- The Cochrane Library - http://www.thecochranelibrary.com/view/0/index.html
- National Institute for Clinical Excellence (NICE) - http://www.nice.org.uk/ - (UK independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health).
- Centre for Reviews and Dissemination - http://www.york.ac.uk/inst/crd/index.htm (part of the UK National Institute for Health Research (NIHR)

Consumer involvement:

- Centerwatch - http://centerwatch.com/
- INVOLVE - http://www.invo.org.uk/ (UK advisory group which supports greater public involvement in NHS, public health and social care research)
- People in Research - http://www.peopleinresearch.org/ (a UK Clinical Research Collaboration project)
- TwoCan Associates - http://www.twocanassociates.co.uk/index.php (help voluntary and statutory organisations to involve service users, patients, carers and the public)
- James Lind Alliance - www.lindalliance.org

Useful Toolkits/resources for managing clinical trials:

- Clinical Trials Tool Kit - http://www.ct-toolkit.ac.uk/ (route maps that navigate you through the regulations).
- Experimental Medicine Tool Kit - http://www.em-toolkit.ac.uk/home.cfm (supports risk assessment and devising risk proportionate management strategies).
- Data and tissues Tool Kit - http://www.dt-toolkit.ac.uk/home.cfm
- UK Stem Cell Tool Kit - http://www.sc-toolkit.ac.uk/home.cfm
- The Guardian Clinical Research Zone - http://www.guardian.co.uk/healthcare-network-nihr-clinical-research-zone (includes links to health care professionals and a participant speaking about their experiences)
- American Society of Clinical Oncology (ASCO) - Standards & Attributes of Exemplary Clinical Trial Sites - www.asco.org/ASCOv2/Research+Resources/Research+Activities/Clinical+Trial+Resources
- Cancer Therapy Evaluation Program (CTEP) - http://ctep.cancer.gov/
- National Cancer Institute (NCI) - Accural.net Clinical Trials - https://accrualnet.cancer.gov/
- Partnership-driven Resources to IMprove and Enhance Research (PRIMER) - ResearchToolkit.org - http://www.researchtoolkit.org/

Common Data Elements:

- National Cancer Institute (NCI) - Cancer Biomedical Informatics Grid (caBIG) - Cancer Data Standards Registry and Repository (caDSR) - https://cabig.nci.nih.gov/community/concepts/caDSR/

Certification Offered:

- Association of Clinical Research Professionals (ACRP) (membership required) http://www.acrpnet.org/MainMenuCategory/Certification.aspx
- Society for Clinical Data Management (SCDM) (membership required) http://www.scdm.org/certification/

- Society for Clinical Research Associates (SOCRA) (membership required) http://www.socra.org/html/certific.htm

Free Project Management Tools:

- GantProject - http://www.ganttproject.biz/
- OpenProj - Open Project - http://www.serena.com/products/openproj/

Data Protection

- UK Department of Health: Guidance to the NHS on the Data \Protection Act 1988 - http://www.dh.gov.uk/en/Managingyourorganisation/Informationpolicy/Recordsmanagement/DH_4000489 Department of Health: Guidance to the NHS on the Data Protection Act 1998
- Information Commissioner's Office Guide to data protection - http://www.ico.gov.uk/for_organisations/data_protection/the_guide.aspx

Designing Questionnaires

- University of Leeds (UK) Guide to the Design of Questionnaires - http://iss.leeds.ac.uk/info/312/surveys/217/guide_to_the_design_of_questionnaires

Education and Training

- International Conference on Harmonisation (ICH) GCP (E6 Guidelines) - http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf
- GCP Training online (Infonetica) - http://www.gcptraining.org.uk /
- UK Clinical Research Network (training available for studies registered on their portfolio) - http://www.crncc.nihr.ac.uk/training/index
- Pharma School - http://www.pharmaschool.co/
- UK NIHR valid informed consent resources - http://www.crncc.nihr.ac.uk/training/courses/other/vic_resources.htm

Glossary of Clinical Trials Terms

- Clinical Trials. Gov Glossary - http://clinicaltrials.gov/ct2/info/glossary
- Data and Tissues Tool Kit Glossary - http://www.dt-toolkit.ac.uk/glossary.cfm

International Collaboration

- European Clinical Research Infrastructure Network (ECRIN) - http://www.ecrin.org/
- KKS Network (Germany) - http://www.kks-netzwerk.de/index,en,.html
- Swiss CTU Network - http://www.scto.ch/en/CTU-Network.html

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