Society for Clinical Trials 31st Annual Meeting

Workshop P5
Trial and Site Management for
Multi-Center Trials

Sunday, May 16, 2010
8:00 AM - 12:00 PM
Harborview Ballroom D

Society for Clinical Trials

Pre-Conference Workshop Evaluation
Baltimore, Maryland
May 16, 2010

WORKSHOP 5 – Trial and Site Management for Multi-Center Trials

1. Overall, did the subject context of this workshop meet your expectations and needs?

   Yes ( )　　　　　　No ( )

   If yes, in what way? If no, why not? _____

   _____

2. Was the content of this workshop of value to you personally or on the Job?

   Yes ( )　　　　　　No ( )

3. Was the content of the workshop:　　　　New ( )　　　New/Review ( )　　Review ( )

4. The level and complexity of this workshop was:

   Too elementary ( )　　　Correct ( )　　　Too advanced   ( )

> **Please complete the following questions by circling the appropriate description using the rating scale listed below.**
>
> **1 = excellent   2 = very good   3 = good   4 = fair   5 = poor**

5. Rate the extent to which this workshop:

   a. Presented content clearly　　　　　　　　　1　　2　　3　　4　　5

   b. Allowed sufficient time for discussion
      and audience participation　　　　　　　　1　　2　　3　　4　　5

   c. Provided useful information　　　　　　　　1　　2　　3　　4　　5

   d. Utilized appropriate teaching methods,
      i.e., audiovisual, handouts, lectures　　　　1　　2　　3　　4　　5

6. Please rate each workshop faculty member:

Name	Knowledge of Subject	Organization/Delivery
John Norrie	1 2 3 4 5	1 2 3 4 5
Alison McDonald	1 2 3 4 5	1 2 3 4 5
Julie Weston	1 2 3 4 5	1 2 3 4 5
Carole White	1 2 3 4 5	1 2 3 4 5

1. Are you currently working in a clinical trial?   (Yes)   (No)

2. What is your job title? _____

3. Do you have any suggested topics for workshops at future meetings? If so, please list below:

    _____

    _____

4. What aspect of the workshop did you like best?

    _____

    _____

5.   What aspect of the workshop would you change if this workshop were offered again?

    _____

    _____

6. Additional Comments: _____

    _____

Workshop 5

**Trial and Site Management
for
Multi-Center Trials**

Faculty

Alison McDonald
**Centre for Healthcare Randomised Trials (CHaRT),
University of Aberdeen**

Senior Trials Manager within a UKCRN registered Trials Unit in the UK, specialising in non-drug interventions

Coordinates a portfolio of publicly-funded national trials

Previous and ongoing experience in trial administration, including budget monitoring

---

Faculty

John Norrie
**Robertson Centre for Biostatistics
University of Glasgow**

Professor and Chair in Clinical Trials and Biostatistics

Experienced trialist in publicly funded and commercially funded trials

Statistician by training

Faculty

Julie Weston

Lawrence S. Bloomberg Faculty of Nursing, University of Toronto

Senior Trial Coordinator at Data Coordinating Centre

Coordinates international multicentre trials

In the past has been research nurse at several sites

Labour & Delivery nurse

Faculty

Carole L White

The University of Texas Health Science Center at San Antonio

Trial Manager of international secondary stroke prevention trial

Conducts own research examining outcomes after stroke for the stroke survivor and the family

Previous work experience includes research nurse, educator, administrator, staff nurse

Format of Workshop

- All the Faculty have collaborated to produce the content
- Presentation of the content will be split among the Faculty
- This means that we will be presenting information that was submitted by other Faculty in addition to our own
- Each Faculty member will present all the material in a section but the other Faculty will be able to answer questions as needed
- This will avoid repetition of content

Who are you?

From clinical centres?

From Data Coordinating Centres?

Other?

Workshop Topics

PART 1
Organization of a Central Office

1. What is a Central Office?
2. Functions
3. Training of Central Office Staff
4. Managing Multiple Grants
5. Other Central Office Tasks
   - Trial Registration
   - Trial Sponsorship
   - On-going Reporting
6. Budgets at Central Office

Workshop Topics

7. Budgets for Clinical Sites
8. Committee Structure
9. Data Collection Options
10. Special Challenges of International Trials
11. Publication Arrangements

Workshop Topics

PART 2
Clinical Site Management

1. Picking Appropriate Sites
2. Assessing Suitability of Sites
3. Staffing at Clinical Sites
4. Training Clinical Site Staff
5. Interacting with Clinical Sites
6. Staff Motivation and Patient Recruitment Strategies
7. Timely Completion of Data Forms
8. Study Record Keeping

Workshop Topics

9. Attrition
10. Study Close Down
11. Paperwork/approvals

Workshop Topics

PART 3
Future Directions

1. Quality Assurance
2. Risk Assessment

NOTE:
- We will be limiting our discussions today to funded studies. How to obtain funding and all the tasks required would be better handled in another session.

Terms/Short forms (1)

Central Office
Also known as: Data Coordinating Centre
Central Coordinating Office
Biostatistic Coordinating Center
- Location that oversees the running of the trial and manages the data

Principal Investigator (PI)
- Person who developed the study and obtained funding

Terms/Short forms (2)

Centre Collaborator (CC)
Also frequently referred to as Principal Investigator when talking about a specific site
- Oversees the running of the trial at a clinical site

Research Nurse/Research Midwife/ Research Assistant (RA)
- Person who enrolls participants; collects, enters and submits data
- Title is often dependent on the requirements of the job (nurse or not) and the background of the person filling the job

PART 1
Organization of Central Office

What is a Central Office?

- It can be an established academic trials unit with access to appropriate disciplines or a department conducting one clinical study with little infrastructure
- No matter the size, there are functions that have to occur there

---

Functions

- In general – oversee all aspects of the trial.
- The actual "hands-on" doing of these tasks will depend on the size of the trial and the size of the central office.

Specific functions:
- Assure regulatory requirements are met on an on-going basis (e.g./ethics approvals; adverse event reporting; submission of documents for IND (investigational new drug) approvals, etc.)
- Manage grant renewals

Specific functions (cont')
- Manage trial budget
- Prepare and distribute trial documents – protocol, procedure manual, data collection forms, etc
- Form and manage committees needed for the trial
- Train clinical site staff
- Oversee day-to-day trial management activities at the clinical sites
- Develop quality assurance procedures for both central office and clinical site tasks

Specific functions (cont')
- Arrange communication methods for clinical sites and central office including meetings, phone conferencing, web applications, etc
- Oversee publication policies and activities
- Provide for randomization of study participants
- Data management of study data including data monitoring
- Statistical analysis, or arrangement for analysis
- Interact with other centres involved in the trial, i.e. Drug Distribution Center, Statistical Center, etc

Who performs these functions?
- For some trials there are a large number of people from many disciplines that need to be involved.
- In others, a much smaller number of people take care of the same functions.
- It is important to involve all the needed people as early as possible.

The group can include one (or more) of the following:

- Trial manager
- Data manager, including management of audio tapes, images etc
- Programmer
- Secretary
- Statistician
- Health economist
- Trialist
- Clinician
- Administrator

One example of a large multidisciplinary group:

Study: 65 sites in 8 countries with 1850 patients enrolled. Secondary prevention trial for stroke victims. Cognitive assessments and MRIs are done on all participants.

Staff: 12 (some part-time)
2 neurologists (PI and Co-I); administrator (with an assistant); trial coordinator; secretary; coordinator of cognitive materials; coordinator of imaging; neuroradiologist; neurologist; hypertension consultant and pharmacologist consultant.

One example of a small group:

Study: 20 sites in 2 countries with 5002 participants enrolled. All trial enrollment and data entry is done on a web system by the sites.

Staff: 2
Nurse researcher (PI) and trial coordinator

Training of Central Office Staff

- In this section we will talk about training the Central Office staff to do their own jobs
- Depending on the job, training centre staff may be part of it. We will cover this training later in this workshop.

What training is required and/or provided for Central Office staff?

- This is a tricky issue. In the UK regulations now dictate that training has to be 'fit for purpose' but it is not always clear what that training would be or how to access.
- One example is GCP training. All staff working on clinical trials require this training but there are no accredited courses.

Some Options for GCP Training

- On-line course – Infonetica - http://www.gcptraining.org.uk/
- UK Clinical Research Network has training available for studies that are registered in their network. GCP courses (workshop format) for various groups of trial staff (new staff, experienced staff, pharmacy staff and pediatric staff) are currently being offered.
- Private consultants can do courses but these can be quite expensive

- Training can be done from within the institution that houses the central office, e.g. courses on booking travel, Microsoft Excel, Microsoft Access, budget management, and meeting planning.
- There is always the dilemma of whether to develop in-house training or rely on what is available elsewhere. The best solution is probably to use a combination of both.

- It is very important to have a crisis plan.
- You must have information recorded and available centrally in the event that someone else has to pick up the work – key people do go off on long-term sick leave and you have to be able to cope without them.

Things to think about regarding training
- Do you want to hire people with experience or do you want to develop skills in new staff?
- Staff need time to complete training
- Keeping training/knowledge up-to-date in rapidly changing environment is very difficult

Managing Multiple Grants

- Increasingly, publicly funded clinical trials are supported by dedicated clinical trials units, that bring all the core competencies (trial managers, statisticians, IT developers, experienced trialists) needed to design, conduct & analyse trials under one roof.
- These trials units then manage a portfolio of clinical trials. Instead of each individual trial in separate 'silos', all trials in the portfolio benefit from a common approach, by dedicated staff

Managing multiple trials – some thoughts:
- By sharing the risk of individual trials across a portfolio, each trial gets what it needs, when it needs it.
- However, each trial should still have a trial manager taking day-to-day responsibility, liaising with support staff.
- Trial tasks usually ebb and flow – use your available expertise where it is needed most.
- Communication between all staff is very important. This will keep everyone informed and likely more satisfied with their work.

Managing multiple grants – planning & organisation is critical …
- Consider using project management software to efficiently manage multiple trials, for:
    - Milestones (e.g. recruitment targets)
    - Staff resources
    - Physical space, equipment etc
- An individual trial has changing demands on staff over time (set-up, stable running, closedown) and rarely go according to plan (!)
- Managing multiple trials is the art of smoothing spikes and avoiding troughs …

Sustainability …
- With trials ending and new ones starting, a trials unit can be a stable home providing a career for trials experts …
- However, funding is still uncertain and lead times for projects can be long .. So need to retain flexibility
- In the UK, accredited UK CRN trials units (17) are being awarded $300-$500k per year in core funding on rolling contracts to develop high quality trials for submission for competitive public funding

Other Central Office Tasks

1. **Trial Registration**
2. **Trial Sponsorship**
3. **On-going Reporting**

1. Trial registration
- Registration – prior to the first randomisation - of all clinical trials ensures that the existence of all clinical trials is revealed – particularly those which were not completed or have 'negative' findings.
- Free access to these registries enables anyone to then check up on a trial's progress.
- Should result in it being less likely that unnecessary trials are undertaken

- The International Committee of Medical Journal Editors (ICJME) has established a requirement that all clinical trials be entered in a public registry before the onset of patient enrollment, as a condition of consideration for publication.
- Registry must be open to all prospective registrants and managed by a not-for-profit organization.
- There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable.

An acceptable registry must include at minimum the following information:
- a unique identifying number
- a statement of the intervention(s) and comparison(s) studied
- a statement of the study hypothesis
- definitions of the primary and secondary outcome measures
- eligibility criteria

- key trial dates (registration date; anticipated or actual start date; anticipated or actual date of last follow-up; planned or actual date of closure to data entry; and, date trial data considered complete)
- target number of subjects
- funding source
- contact information for the principal investigator.

From: De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. Ann Intern Med. 2004;141:477-8.

Website about the international registry initiative (lists acceptable registries)

- http://www.who.int/ictrp/en/

Websites for trial registration:

- http://prsinfo.clinicaltrials.gov
- http://isrctn.org/
- http://www.controlled-trials.com/

2. Trial sponsorship

- Over the past few years sponsorship has been a real issue for trials being conducted in Europe.
- In North America it isn't a direct issue for local sites but it is a very real issue for those trials that have non-North American sites
- The "Sponsor" takes legal responsibility for:
  - Getting the trial properly "authorised" (ethics, scientific integrity etc)
  - The "financial" management of the trial (adequate funds, insurance/indemnity)
  - The safety reporting (patient safety, serious adverse events)

- For commercial studies, the company will be the Sponsor
- For publicly funded studies, usually the government cannot assume the Sponsor's role (e.g. can't provide insurance / indemnity).
- Usually then passes to the host institution (University or hospital). They in turn delegate their responsibilities to the PI and/or trials unit.

- Trials that come under the European Union (EU) Clinical Trials Directive of 2001 (any IMP 'drug' trial) must have a Sponsor.
- Usually, if you need a European centre on board your trial, this will have to be negotiated individually with each country/site.
- The solutions are so different in each country the best way to think of this for a multicentre trial is that you have a constellation of a group of individual studies that have some commonality.

- It can be (is!) frustrating …However, there is encouraging work underway towards common agreements with standard paperwork
- Two examples of sponsorship agreements have been included in your package.
- Some you will see share the sponsorship duties between the central office location (i.e. the PI), the clinical site itself and the PI at the clinical site

---

3. Ongoing Reporting

The three main areas of ongoing reporting are:
- progress reports
- serious adverse events
- significant amendments to the protocol

Progress Reports:
- Progress reports can easily become an organizational problem at a central office.
- They can all fall at the same time and overtax the staff you have.

_____

_____

_____

_____

_____

_____

_____

Things to consider about progress reports:
- Which bodies need a report?
- What data do they need e.g. blinded?
- When / how often do they need it?
- Who should be producing these reports – the statistician; the IT people; a combination of people; one to produce; one to interpret?
- Try to sequence things so that all the reports are not due at the same time.
- Try to produce templates that can be used for more than one study (this isn't as easy as it sounds!)

_____

_____

_____

_____

_____

_____

_____

Serious Adverse Events:
- In drug trials for regulatory purposes (i.e. commercially funded) usual to capture all serious adverse events – and maybe AE's.
- In publicly funded trials reporting is usually more limited e.g. unexpected serious adverse events
- For each trial you have to decide what is expected vs. unexpected. For example in a trial dealing with women in pre-term labour you would expect many of the babies to be born in hospital, and preterm, and some of them will not survive. Neonatal death would thus be 'expected' for this trial.

_____

_____

_____

_____

_____

_____

_____

- What is 'serious'?
- If you are using a marketed drug with a known side effect profile do you have to report all these side effects?
- Is the event related to the trial procedures? If not, do you have to report it? Who decides if it is related?
- Who do you have to report to? The sites need to tell the central office but then do you have to tell the ethics office? the funder? etc.
- Regulations for the UK can be found at: http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/safetyreports

---

Amendments to the protocol:
- When significant amendments are made to the protocol the central office must notify the required parties
- The 'required parties' will vary from study to study.
- The ethics committee will always be one, but you may also have to inform other people especially if drugs are involved in your trial (i.e. FDA, Health Canada)
- In the UK, a significant amendment is: http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/amendments/

Budgets at the Central Office

- How is the coordinating centre ("the central office", the "Trial Office", the "Study Data Centre") run financially?
- This will depend on whether it is a central office for one trial or one that manages multiple trials.

- If it is a central office for one trial – the budget will be a set amount that covers all staff, equipment, services required for that trial. This will probably involve some full-time and some part-time staff.
- If it is a central office that handles multiple trials - some items will be covered completely from a trial budget, while others will be covered by contributions from many grants.

_____

_____

_____

_____

_____

_____

_____

Things to consider about central office budgets:
- Have a clear line of authority/understanding of who is responsible for what for each trial
- Support of an experienced administrative person is very helpful, especially to coordinate central staff members being paid from a combination of grants.
- Be clear about what the conditions are for each grant. These vary between funders.

_____

_____

_____

_____

_____

_____

_____

- Is there flexibility in the budget? i.e. can you move funds between budget categories?
- Be creative – what can be done to maximize financial resources? Treat the budget as per your own finances – investigate cheaper travel/printing companies etc.
- Be sure to consider all aspects of your intervention. Are there items that will be required to carry out the intervention? Where will they come from? Will they be donated or will they have to be purchased? Are they local to sites or will they have to imported/ exported?

_____

_____

_____

_____

_____

_____

- Is there any pharma involvement in the trial? Could this be used to cover the cost of a drug intervention?
- Make sure someone with experience in managing clinical trials budgets is included when grant applications are being considered. They can pick up if there are any hidden costs (e.g. cost of trial registration, licenses to use questionnaires, cost of obtaining/maintaining authorization for a medicinal product)

In general-
- Review all budgets regularly – don't be taken by surprise at the end of the grant period – either with low funds and the chance of running out, or unspent funds that you don't have time to use.
- If a trial is in financial trouble – e.g. recruitment too slow, required resources under priced etc – act sooner rather than later – tell the PI, who should tell the funder – don't leave it until it is too late, hoping things will improve … they might, but probably more likely get worse!

Budgets for Clinical Sites

In general, central money needs to be supplied to the sites to support the work that they do.

And, the clinical sites need to have a plan about how they will use the money coming to them.

Both sides are accountable for what happens to trial funds.

Payments to Sites

There are 2 styles of payment used in most trials – a per-patient enrolled amount or a set amount based on the needs of the site.

Some studies use one style for all the sites while others vary the style of payment depending on the needs and wants of the site.

"Per-patient enrolled" style of payment

- This can be based on the number of patients enrolled alone but then the Central Office is trusting that the site will supply all the data for each case.
- It can be based on a 'per set of data returned' which ensures that completed data are received before payment is made.
- Increasingly the only viable funding model for UK publicly funded studies – allows trials units to deliver recruitment targets by closing out non performing centres

---

- If long term or multiple follow up is part of the study, the per-patient payment can be split and paid out after each follow up visit.
- Some sites find this method of payment too business-like and think it detracts from the feeling of collaborative research

"Set budget amount" style of payment

- This method determines a set payment based on the size of the site.
- There is always the worry that the Central Office may pay money to a site that isn't successful in recruiting patients.
- Popular for research active sites with existing recruitment staff
- Using short term contracts of 3-6 months can help to minimize these problems. The Central Office can drop sites that are not performing before a lot of money is spent.

- Short term contracts also allow the Central Office to increase support for sites that are doing very well.
- A combination of these methods of payments has worked well – a set amount is paid to each site to cover the study coordination activities, staff training etc. and then an additional amount is paid based on the number of patients enrolled.
- This should include a 'get-out' clause e.g. '<x recruits by y months' invokes termination
- Can be useful to give set-up costs

How Sites Spend Money

The contract with the site will stipulate what tasks need to be accomplished with the money provided.

It is up to the site to decide how to best do the tasks at their site.

Most sites will require that trial funds cover all expenses. They can not lose money on your research projects.

Research Nurse (RA) Salary

The main cost at most sites is the research nurse/midwife/assistant/recruitment officer (RA) salary.

Some things to consider are:

- It is very important that this is a paid job. Asking someone to take this on in a volunteer capacity as part of another job does not work.
- Is this existing staff or new recruit? If new recruit, allow time for grading, advert, short listing, interview, acceptance etc…

- Each site will need to decide if the RA job is full-time or part-time (and what %).
- This may be determined by the Central Office if they are paying a set amount per site.
- For trials that are paying on a 'per-case' basis you may have to help the sites figure this out.
  - Set a projected number of participants per month for their site
  - Multiply this by the amount per case you are going to pay them
  - They will know the hourly amount they will be paying a RA
  - They can then see how many paid hours they have for the position

---

- Things to be sure the site is watching for:
  - Be sure they have included any benefit amounts in their hourly rate
  - Encourage them to only pay for the number of hours worked. If they contract with a RA for a set number of hours regardless of recruitment numbers and they don't recruit as quickly as they anticipate, they will end up with a deficit.
  - You don't want to (and in many cases are not allowed to) pay extra to sites that mismanage the money you have sent.

- Budget for annual increases if your trial will go on for several years
- You may have to pay a different 'per-patient enrolled' amount based on the salary of the nurses. In the US there are large differences between states. In one study the per-patient payment ranged from $75 to $200.
- Remember that once recruitment ends there are still tasks the research nurse must do. You may need to pay a close-out payment to cover these. Or you can encourage the sites to keep some money aside to cover these hours.

Other uses for centre funds
- Specific tasks that are required for the specific trial – staff coverage so that trial intervention can be given to an in-patient, taking of samples, etc.
- Postage
- Office supplies – in many cases the trial brochures, posters, data forms, etc are provided centrally so the local office supply needs are minimal.

- Photocopying of consent forms onto local letterhead.
- Payments to trial participants to cover time away from work, travel etc.
- Thank-you token of appreciation for trial participants that have to complete mailed or phone questionnaires (gift cards, coffee coupons, etc.)

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)

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

- 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.

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.

Data Collection Options

There are a wide variety of methods of data collection, data entry and submission.

The goal of all of them is to have accurate data in a timely manner.

Data Collection Principles

- Accurate data begins with the initial data collection and entry but also always involves some type of data query process
- Queries question any data that are either:
  (a) impossible e.g. 1000 given as answer to a blood pressure;
  (b) invalid e.g. 'red' given as an answer to gender;
  (c) unlikely e.g. 115 given as answer to age
  (d) missing

- In most instances the more automated the system the faster the data can be entered and queries can be generated.
- Some queries are handled in 'real-time' as the initial data entry is being done. This is very common in web-based systems.
- But all systems are dependent on humans accurately collecting the data in the first place.
- All data collection systems have different levels of authorization to entry, change and view data.

- All studies will have written procedures for collecting, entering and changing data.
- It is important to remember that research data and data forms are considered in the same way as hospital records, so changes must be properly documented.
- Electronic data entry systems are secure systems with restricted access. They store audit trails for the initial entry of the data and any changes that are made.

Data Backup

- Backing up the data collected is as important as the initial collection.
- Depending on the system of data collection, the clinical sites may have a role to play in backing up its own data.
- This may be electronic backup or making copies of paper forms.

- Centrally there should be a process for routine and frequent backup of all data submitted from the clinical sites.
- Verifying the backup is important as well.
- This involves retrieving data from the backup source and being sure they are the same as the original data that were backed up.

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

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

- 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

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.

- 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.

- 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.

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.

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).

Special Challenges of International Trials

1. Site Selection
2. Ethics Approval
3. Site Set Up and Maintenance
4. Data Management including Randomization service
5. Center funding

Site selection

- Complicated by differences in language and culture, distance and not knowing key individuals at the site
- Use one centre investigator that you have developed a relationship with to help you recruit other sites.
- Promote the study at international meetings to attract sites

---

- Have sites complete a survey to check key points – key people and their contact information; IRB existence and composition; training of staff in GCP and human subjects protection; previous trials experience; expected enrollment numbers.
- If at all possible, visit each new site to ensure the study protocol is clearly understood and that the center is committed to compliance with the study protocol
- If a visit is not possible, be sure to check the standard of care for any procedures that could impact your trial outcomes

Ethics Approval

- Obtain IRB approval centrally and circulate the template for the consent form and the approval letter to the sites. This often speeds up the local process.
- There may be additional approvals required depending on the country – i.e. local Ministry of Health
- Expect that the ethics approval process can take a long time. Twelve to eighteen months at some sites is not uncommon

---

- There may be a process for a country-wide approval in some countries. The UK has this.
- The consent process may have to be adapted to address local cultural needs. For example – in one trial 2 Asian sites deemed it was unethical to tell patients the doctors didn't know which was the best treatment because of the anxiety it would arouse.
- Verbal consent may be needed if a large portion of the patient population at a site is illiterate.

Site set up and maintenance

- It may not be possible to bring international site personnel to the central office for training. The costs are often prohibitive.
- Detailed written manuals and frequent phone and email support can work well instead.
- For countries or regions with a large number of sites, setting up local meetings and having central office staff travel to them can work. In these situations you will need a good local contact to help with the logistics.

- If your central office staff don't speak multiple languages you will need to stipulate that at least one of the center personnel is English-speaking
- Translation of data collection forms used by the trial participants will be needed. Do a back-translation to be sure the content is accurate.
- Courier deliveries of supplies is often more efficient (and traceable) than local postal service

_____

- If you are shipping equipment or medications extra government approvals are probably required.
- Retaining a local customs broker can facilitate the shipment getting to its destination.
- Maintaining regular communication with each site is important to keep them motivated and to feel part of the larger trial group. Monthly newsletters and teleconferences work well.

_____

Data Management including Randomization service
- Be sure your randomization service can be accessed properly from all countries. There can be problems with accessing long distance calling services, activation of all the keys on the phone pad, etc. Internet based systems are probably more universally accessible.
- If your data entry and checking system relies heavily on local computer hardware you may have to provide a more central service for those sites that have limited computer capability.

- Keep in mind that all sites don't conduct trials using the North American model.
  - The important thing is the data quality for randomized patients.
  - However the site plans to do this is OK as long as the result is high quality data.
  - At many international sites there is only the PI and they perform all the roles, including that of the research nurse.

Center funding for international sites
- The expenses at sites may vary considerably.
- At North American sites the biggest budget item is usually salaries.
- But in some countries the cost of technology, e.g. international phone lines, can be very expensive and salaries are very low.

- You must adapt your centre funding strategy to take this into account.
- You can't simply pay the same amount per patient in each country without considering whether: firstly, it is covering all their expenses; and secondly, if the amount is so high in local currency that it could be seen as coercive.
- Wire transfers and yearly payments may need to be considered if the banking or cheque clearing charges are high.

Suggested reference:
Hewson SA, Weston J, Hannah ME. Crossing international boundaries implications for the Term Breech Trial Data Coordinating Centre. Controlled Clinical Trials Volume 23, Issue 1, February 2002, Pages 67-73

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.

- 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

---

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

- 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

_____

_____

_____

_____

_____

_____

_____

**PART 2
Clinical Site
Management**

Picking Appropriate Sites

There are 3 main ways to get clinical sites -

- Choose your own
- Be contacted by a site that wants to collaborate with you
- Be part of a collaborative group where there is a core group of sites

---

Choosing your own sites

- Start with sites that you have collaborated successfully with in the past
- Direct contact from you to the site collaborator works to inform them of your new trial
- You can invite potential collaborators to a meeting prior to submitting the trial for funding. You may then be able to tweak the protocol to better meet the needs of their site

- It is important to remember that not all trials are alike. The current research question has to fit with the staff and system at the site you are approaching
- Each site should consider each trial on its own merit before agreeing to participate.
- You will come to appreciate a site that says they don't think a trial fits for them.
- Very often when you have to talk a site into participating you will end up investing time and money in a site that is not a successful recruiter.

Being approached by a site that wants to collaborate with you

- This is a very positive sign
- If someone at the site has taken the time to seek you out they are usually very interested in the research question
- Be cautious of sites that are doing a lot of trials and not doing well at any of them. Their motivation may be financial rather than true interest.

- Be sure to check if other staff at the site are keen about the study too, especially if they are going to be involved in the recruitment process. The centre collaborator can't do the study on their own. They need the support of others at their site.
- Discuss the practical requirements of being a site to be sure that they can fulfill those.
- Just being interested doesn't mean they will be able to actually carry out the study

- Your time is best spent working out solutions with sites that have approached you, rather than trying to convince ones you have approached yourself.

- In most multicentre trials the sites tend to be very varied, in both capacity and experience.

- Consider using the following to attract interested sites:
    - Listservs e.g. AWHONN (Association of Women's Health, Obstetric and Neonatal Nurses) have a listserv for its members
    - Journals e.g. ongoing clinical trials of interest to the stroke professional community are published on an annual basis - Major Ongoing Stroke Trials 2007;38;1-9 *Stroke*
    - Professional meetings e.g. the annual International Stroke Conference has a poster section titled On-Going Clinical Trials. Brochures advertising for sites were distributed at an annual AWHONN meeting.

- Register your trial, sites can search the registries and then contact you

---

Being part of a collaborative group
- Collaborative groups are organizations that are committed to conducting multi-center trials.
- They are usually set up for specific disease entities.
- These groups can include 30-60 institutions from a variety of countries.
- They can include both tertiary care hospitals and community hospitals.
- In the UK there are clinical networks which are very similar to the US model of collaborative groups.

- Each group has its own application process to become a member and to participate in a specific trials.
- Examples of collaborative groups/clinical networks:

  NCIC – National Cancer Institute of Canada - www.ncic.cancer.ca/

  ECOG - Eastern Cooperative Oncology Group - http://www.ecog.org

  NIHR CRN - www.ukcrn.org.uk/

  NINDS Clinical Research Collaboration - www.nindscrc.com

Assessing Suitability of Sites

- Potential clinical health care providers should have enough uncertainty over the intervention to allow them to fully participate (i.e. refer/enroll participants)

  – that is, avoid centers that are convinced of the benefit of one intervention over others.
- Site has sufficient capacity (including staff, physical space) to take on the new trial
- Site has the required equipment, techniques, or facilities essential for the specific clinical trial. This could be lab facilities, specimen storage, computer and web access, etc.

- Access to the patient population essential for the trial. The potential population needs to be quite large because in many trials the incidence of patient availability sharply decreases when a clinical trial begins and returns to its original level as soon as a trial is completed (Lasagna's law).
- Geographical location and type of organization (University based hospital, community hospital, VA hospital, long-term care facility, outpatient setting) may play a part in this.
- There are no ongoing trials that would compete for the same patient population

- Anticipated time required to initiate the trial
- Budgetary factors. Most trials are not 'money making' ventures for the site and they may have to cover some of the costs themselves.
- The site has stability to see the trial through to the end. For some projects this may be 3-5 years, or longer.
- Ability of the organization to obtain necessary paperwork to participate

Ways to assess suitability

- Questionnaires sent to sites asking about critical components of participation
- Site visit by PI to assess staff enthusiasm and physical capabilities
- Keep database of information about centers approached and used in the past including who declined; who accepted and then failed to recruit; who accepted, recruited and then stopped; and who were good recruiters.

Staffing at Clinical Sites

The key to being a successful site is having the right people.

It happens over and over again that successful sites have research personnel that are dedicated to the project and will problem solve to get the research tasks done.

Sites where the staff think the trial will run itself are often not successful.

Centre Staff

At a clinical site there are usually two types of research staff -

1) Centre Collaborator (Principal Investigator)

2) Research Nurse/ Research Midwife/
   Research Assistant

Centre Collaborator (CC)

- The CC is usually appointed, clinically qualified and, in the Canadian and UK model, unpaid.
- In some instances they are paid for study visits by insurance or the standard health care system
- They are responsible for the overall running of the trial at their site including spending of the budget.
- They are usually the person the Central Office has the first contact with.

Research Nurse/Midwife/Assistant

- The RA is hired to carry out the day-to-day patient recruitment and data collection duties.
- At some large sites, or at sites that are members of a Network, one RA might work for several trials.
- Even though you don't hire research nurses from the Central Office it is important to help sites know what qualities they should look for in the person they hire.

- A good research nurse is different than a good bedside nurse. They should be someone with people skills who can enroll participants but they also need to have the computer and secretarial skills to collect and manage clean data.

Important Qualities of RA

- Imagination and creativity
  - Many recruitment strategies may have to be tried before a smooth system is found for patient recruitment
  - Imaginative and creative ideas will be needed to maintain ongoing staff enthusiasm.
- Self-motivation
  - Challenges will probably come up over the course of the trial and the RA should be able to deal with these, for the most part, on her own

---

- Flexibility
  - In a part-time position the hours of work can vary a lot
  - There may be off-hours recruitment or specimen collection to be done
- Good interpersonal skills
  - Need to work with other members of the research team
  - Need good people skills to enroll participants
- Good organizational skills
  - Tracking of all participants and timely collection of data is required

- Meticulous attention to detail
  - Precise with no cutting corners
  - Asking how they manage their bank checkbook is a great way to assess this. Someone who balances to the penny each month is the one you want.
- Research experience
  - Education is not always as important as the actual hands on experience
  - And we all have to start somewhere. The above personality traits are very important. The actual research tasks can be taught.

How to Train
Clinical Site Staff

- Initial training is always required but on-going support of site staff is equally important.

- It is far better, and more efficient, to spend time and money to properly train all clinical site staff than to try and fix mistakes and bad practices once they have begun.

- Training can be in-person at the site with local senior trial personnel training new staff.
- The Central Office can bring together all the site staff in a central location. This enables bonding and allows site staff to get to know one another.
- The Central Office can send staff to the sites for training. This allows the Central Office to see the physical space where the trial will be run and to meet and encourage clinical staff that may need to support the research effort.

- 'Old' staff can train the new people before they leave
- The new staff member can spend a day at a geographically close experienced trial site. This benefits the new/replacement member of a study team as it enables some networking. It also benefits the existing site. Their role in 'training' boosts their feeling of ownership.
- Tests and quizzes can be done on the web to assess knowledge of the protocol and trial procedures.

Interacting with Clinical Sites

- It is very important for 2-way communication to exist between the Central Office and each site.
- The Central Office needs to know what is going on at each site. Problems can thus be identified quickly and appropriate fixes can be put in place.
- Sites need to feel that their efforts are supported and acknowledged. They will then feel an 'ownership' of the trial.

Importance of Regular Interactions

- Regular contact should be made with each site
- The frequency and method of contact will vary depending on: the needs of the site; the study tasks required of the site; and the staffing available at the Central Office.
- Even though participant enrollment may not occur daily in some trials, regular contact is important to maintain enthusiasm

- Sites participating in their first research trial may not know the questions to ask so contact from the Central Office is important.
- Misinterpretations and errors can be caught quickly and corrected. Confidence in trial procedures may lead to better enrollment numbers.
- Interaction is a two-way street – the Central Office staff will have greater confidence in a site that regularly communicates.
- Tell sites that brief update emails i.e. "I am working on that query" are very welcome.

Type of Interactions with Sites

- Email notifying RA of patient enrollment. This is especially important for trials where clinical staff enroll participants.
- Notification of outstanding data and queries on a regular basis. This can be posted on a web site or email reminders can be sent.
- Notification of upcoming required patient follow-up contacts.

- Communication from sites about any problems with data collection or participant follow-up. The Central Office can draw on the experience of the other sites to hopefully problem solve a solution .
- A "Frequently Asked Questions" section on a web site is useful to share solutions. Sheets of these can be circulated to sites if the web is not available.

- Sites can communicate with each other using chat features on web applications or email listservs.
- The Central Office can use these forums for information sharing as well.
- Regular (often monthly) newsletters can be used to share recruitment numbers.

Things to remember about interacting with sites

- The central office has to do what they say they will do. If you get a query from a site and promise to respond you must do that. Your sites have to trust that you are on top of things centrally.
- The central office staff have to be motivated in order to motivate the sites.

- Treat your sites as collaborators in the total research effort. The more they feel part of a team the more motivated they will be to support the whole research process. They will know that their role is critical to the successful completion of the study.
  - For example, you can have the sites present real life examples of their experiences with recruitment, follow up etc at annual meetings

- Give as much support as possible
  - Try and get to know the site staff as individuals, learn a bit about their individual circumstances and their site set-up
  - Site visits at the outset can be of a benefit to assist with this
  - The central office is then alert to any particular local issues (e.g. one recruitment nurse had to explain the study to potential participants in a broom cupboard).
- Be aware of how many emails are arriving from you. Try to combine all the information into one message if possible.

Methodological work about recruitment

- Aberdeen has the STEPS project *(Strategies for Trials Enrolment and Participation Study)* http://www.hta.nhs.uk/project/1564.asp.
- One of the findings was that staff have to believe that the question being asked is clinically important and that the trial processes are not alien to the collaborators.
- Therefore explaining and ensuring that the need for the study is well understood at the start and that the trial procedures are clear and roles well defined is very important.

Staff Motivation and Patient Recruitment Strategies

- A large part of the Central Office role is to motivate the clinical centre staff to support the study and recruit participants.
- Almost every site will need assistance at some point or another to solve recruitment problems.
- Central team regularly monitor.
- Be flexible – individual strategies for sites.

Patient Recruitment Initiatives

There are really 2 types of patient recruitment initiatives –

1. Targeting the study participants directly.

2. Targeting the staff that will approach patients to participate.

Ideas for targeting the study participants directly

- Make use of the local press to advertise the study.
- The story may be picked up nationally or internationally depending on the health problem and research question.
- There are challenges with the HIPAA regulations in the US/ethics in UK because patients have to contact the researchers directly; the researchers can't contact the patients without permission.

- Use of the web to advertise the study to a patient population actively looking for help with a health problem.
- Website itself and free phone number allow patients to contact the researchers directly.
- To accommodate the visually challenged you can have a voice recording on the website.
- Speak to your IT Dept to ensure search engines pick up your website and have it high in the list of the search results.

- Be sure the explanation it not too specific so no one calls, but also that is isn't so general that the volume of calls is overwhelming.
- Be prepared to deal with disappointment as there will be people who will call the office and found to be ineligible to participate in the study.

- Produce patient brochures and posters that can be put in places that your target population goes – e.g. Doctor's offices, x-ray or ultrasound clinics.
- Regularly update advertising materials
- Provide money to the patient to cover their time and parking costs to attend clinic visits.

How to motivate/thank site staff

- What are your experiences?

- Any new ideas?

Ideas to motivate clinical staff to refer or enroll patients

- In many studies it is not too hard to enroll the patients.
- The challenge is to have the staff approach or refer the patients to the study.
- And even before that, the research staff at each site has to be motivated so they are vigilant and creative in their dealings with colleagues.

- Make personal visits to places that you want to leave brochures and posters. Describe the study to the staff to make them feel part of it. Doctors' secretaries are great allies in this process.
- Give food to the staff to encourage response.
- Keep sites informed - create 'friendly' competition with monthly newsletters showing recruitment goals and how the sites are achieving their goals.

- Make a more structured "thank you" system for the staff – e.g. for every 10 referrals give a movie pass, shopping card, food coupon etc.
- You need to be careful about the level of "thank you" so there is no possibility of the staff pressuring the patients to enroll.
- Gestures of appreciation don't have to be big to be effective. Small things are very welcome.

- The main goal of the "thank you" is to keep the trial on everyone's mind and to show appreciation for effort.
- As with all things repetition becomes uninteresting so the "thank you" programs need to change frequently to keep the staff interested.
- The Central Office needs to acknowledge that it is usually not the local Principal Investigator that is the key person working hard to identify and recruit but that it is usually the nursing team/secretaries that should be thanked and supported.

Motivating research staff

- Just as the central office staff have to be motivated in order to motivate the sites, the research staff at the sites have to be motivated to motivate other staff.
- Gestures of appreciation work very well.
- Some examples of 'thank-you' gifts: travel award to a scientific meeting of their choice for high enrollment; awards for excellent data entry, good follow-up, etc; present at a dinner at the time of an annual meeting

Timely Completion of Data Forms

- The first step is to communicate clearly to the sites what the expectation is.
- Then there needs to be regular communication from the central office to each site to let them know how well they are meeting this expectation.

- Understanding the research process and the importance of having complete data in order to answer the research question will help staff to see the importance of what you are asking them to do.
- You should assume that there will be some problems with timely completion at some of your sites. Even your most reliable sites can run into problems from time to time.

_____

_____

_____

_____

_____

_____

_____

What to do when you identify a problem?

•Assess for problems on a regular basis. Quick identification of the problem sites as a result of weekly or monthly reports lets you intervene before things get out of hand.

•Talk with the site to identify the barriers they are having. This can be something quite specific to that site (e.g. computer problems, heavy work load because of high recruitment numbers, travel problems for trial participants and thus missed follow up visits, new staff not understanding the process, competing trials etc)

_____

_____

_____

_____

_____

_____

_____

- Problem solve with them to come up with a satisfactory solution. This could be: extra computer equipment (laptop) to allow data entry to be done in real-time in the clinic; financial assistance for part-time data entry help; allowing missed visits for time periods when primary outcome data is not being collected; extra training session in trial procedures.
- One approach will not work for all your sites. The barrier(s) and solution(s) are usually very site-specific.

_____

_____

_____

_____

_____

_____

_____

- Solutions that cost extra money or take a lot of central office time can be reserved for those sites that are doing well with their recruitment numbers but have a barrier at the data entry stage.
- However it is often inexperienced sites with small recruitment figures that require more support.
- There are some general things you can do to motivate all sites to collect/enter their data in a timely manner:

- Set up between-site information sharing/problem solving. This can happen at regular meetings (research nurses provided with hard copies of data queries); in a circulated quarterly report showing data completeness by site; etc.
- Pay the site for an enrolled case only after the data have been completed. However sometimes the person doing the data collection is not the one who manages the centre budget so this isn't always a motivator.

Things to remember:
- Communication to sites that are doing a good job of data collection/entry is very important.
- A message saying 'No overdue data – congratulations' lets the site know the central office is looking at their data completion and is also a motivator to do the same good job next month.

- Your trial management system has to be able to deal with data forms and follow up visits that have been missed with no possibility of getting the information in the future.
- These sorts of things cannot come up on every monthly report. Your system has to allow them to be 'acceptable'.

Study Record Keeping

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

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 used, 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.

- 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.

- 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 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.

Attrition

What is it?

"Attrition" in general is any process resulting in not obtaining complete information on a randomised participant as required by the study protocol

- loss to follow up (eg participant emigrates)
- withdrawal (participant no longer wants to take part in the study, or is taken out of the study on their doctor's advice)
- inability to attend all visits (death, serious illness, cognitive impairment)
- visit attended, but not all forms, or not all data within a form, completed

---

Attrition in a more specific sense usually refers to the subset of processes that something can be done about eg

- reducing participant withdrawal for voluntary reasons by keeping them motivated and engaged in the study

- ensuring that even if a patient withdraws from further participation in the study, their routine data is still collected

---

Why preventing it is important

Attrition is unwelcome for the <u>management of the study</u>:

•For the trial manager:
- it will generate queries and much painstaking work, often without satisfactory conclusion. Find out what data are missing and chase it up to try and obtain.

•For the local site manager:
- it adds to the overhead of completing participant follow up and increases the number of awkward interactions with the central office.

- Attrition is then an expensive problem to address, creating additional and often senior level trial manager and local co-coordinator action to address.

Attrition is unwelcome from an <u>analysis point of view</u>:

- Reduces the amount of information in the study, and hence reduces the power of the study to detect important differences
- Almost always will introduce bias into the analysis
  - it is well established that there will usually be a reason that a participant fails to complete the data required; and that we will not know this reason
  - the reason(s) may well have an influence on what treatment effect we are trying to measure
  - in statistical speak, the missing data are informative, and not 'missing at random'

- Attrition can seriously damage the credibility of the results of a trial

- If extensive, at peer review often it will be listed as a major criticism and/or bring into question the robustness of the findings

How to prevent attrition from the central office perspective?

- There is some suggestion that research staff turnover is associated with decreased participant adherence (more attrition).
- Work very hard in the central office to support the clinical coordinators across your sites .
- Be very responsive to their needs and ensure as much as you can their job satisfaction (the central office is obviously not completely responsible for this).

- Cover strategies to avoid attrition at the beginning of the trial during orientation and in on-going ways throughout the trial.

- Invite coordinators that have a good track record to participate in workshops on preventing attrition.

How to prevent attrition from the clinical site perspective?

- Ensure informed consent on entry to the trial – that participants understand well the procedures and what is required.

- Use a non-aggressive recruitment method so that participants do not feel coerced into joining the trial as over time they may resent their participation and end up dropping out.

- Ensure that the site collects good contact information on the participant and at least two other people who would know where the participant was if they were unable to contact the participant.

  This information needs to be reviewed on a regular basis with the patient so that the information is always current – people tend to change their cell providers fairly often and also people are moving more.

- Maintain regular contact with participants (beyond the regular clinic visits) – they need to feel valuable and that you care about their health and not just like a research subject. Also respond promptly to any patient concerns.
- Create a positive environment where there is very good rapport between the participant and the research coordinator – this may mean that the research coordinator is involved in other aspects of the subject's health – helping to schedule other appointments, social worker role, etc. (be sure these 'extras' are allowed within the study protocol).

- Allow the patient as much flexibility as possible while respecting the protocol – be willing to change appointments to accommodate patient needs, etc.
- Maintain continuity in research personnel – if there are several people working on the same study, attempt to keep patients with the same research coordinator.
- Keep participants well informed about the trial and its importance – rather than thinking about consent at the beginning of the trial it is more like 'informed consenting' where the goals of the study are reviewed on a regular basis with patients.

- Newsletters from the Coordinating Center written for the participants and distributed by the sites work well to keep participants involved.
- Including a photo of trial team can make it more personal for the participant
- Acknowledge the patient's efforts and time to participate in the trial. Tokens of appreciation need to be small (so as not to be coercive), but are still very effective.

- Provide recognition of the subject's participation as they reach certain landmarks. This is especially important in trials with long follow up periods. Examples are individualized certificates as subjects reach 5 years of follow-up; coffee gift card at second follow up appointment; etc.
- Provide patients with 'things' that help them bond with the trial – medication bags, pill dispensers, pens –have the logo of the study on them so patients see that they are part of a group.

- If attending a clinic visit (or other trial activity) is prompting a request to drop out of the study try the following:
  – Provide financial assistance for travel to the site
  – Negotiate telephone follow-up or a home visit (where possible)
  – Differentiate the visit from the data collection. Many patients have no problem with data collection, it is the 'trial activity' they don't want to do
  – Attempt to get some information on the patient until the end of the trial rather than have an early termination.

- When a patient does withdraw consent for further participation, get as much information as possible during that last contact. Trial outcome information is the most important but other trial data are useful too.
- Use external data resources e.g. routinely collected national databases, death indexes, web-based search engines, or local hospital databases to 'fill in' key data (e.g. on the primary outcome) by record linkage that has been missed by the internal study data capture. This is especially useful when a patient is lost to follow-up.

Study Closedown

Things to consider:
- Start planning soon after trial starts.
- Create close out plans and review regularly.
- Close out may occur as planned (at the end of follow up for all participants) or it may have to be done early based on unexpected occurrences. If a plan is in place, unexpected close down is not as anxiety provoking.

What to include in the plan:
- How will the trial be closed down? You will need procedures for both a planned and unexpected close down.
  - How will the sites be notified?
  - When will the randomization system be shut down? You don't want to disappoint any potential patients that have been offered the trial but you don't want to enroll over the required number. Setting a specific date and time a day or two after you reach your sample size, and informing sites of this, works quite well.

– What arrangements need to made for study participants – unblinding of study group; how to deal with medications until trial results are known; is an in-person visit required. This may be a two step process – one step when follow up is complete and another when the trial results are known.

– How to ensure that study participants are left with positive feelings about the trial.

- Archiving – both paper and electronic
  - Where to be retained?
  - For what period of time?
  - Who can review it?
  - Are sites responsible for archiving their CRFs?
    (if yes, this needs to be agreed at outset and an archiving budget may have to be provided)

- Dissemination of results
  - Where and when will you have a results meeting? Who will you invite? Will you cover all the travel costs for all sites? One option is to tie the number of participants at the final meeting and the coverage of travel expenses for a site to the number of trial participants they enrolled.
  - How you will notify trial participants? A write up of the trial results in lay terms can be sent to the sites for distribution to the participants. A 'thank-you' from the Principal Investigator is very welcome.
  - What journals do you want to publish in?
  - What conferences do you want to present at?

- Which regulatory authorities need to be informed and within what timelines?

- Are there any contract issues that need to be dealt with?

Staffing issues
- Some staff will migrate early as they see the trial (and their job) coming to an end.
  How will you manage this?

- Staff training may be required to cover new procedures for close out visits; data completion and query resolution policies; unblinding of participants, etc

---

- Study close down can be labour intensive. It is not usually necessary to increase staff but duties will definitely shift – some tasks done during active recruitment will cease and patient tracking, data checking, query resolution tasks will increase.
- It is important for site staff to end their collaboration with the central office on a good note. You may want them to participate in a future trial. A good plan is to provide staff with a resume of their participation.

Data issues

- Data on final cases needs to be collected quickly.
- Query resolution must be done quickly as well. Usually a cut-off date is set for all outstanding queries and those remaining unresolved become missing data.
- Frequent reporting to sites about their progress can help speed things up.
- Data cleaning should be an on-going process over the entire trial but one final check before database closure is important.

- After all data and queries are received and cleaned the dataset is closed. No further changes are allowed at this stage. Proper backup of this final dataset is important.
- Once the dataset is closed the analysis plan can begin.

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:

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.

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)

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.

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).

PART 3
Future Directions

Future Directions

1. Quality Management
2. Risk Assessment

Quality Management

- Trials are now very heavily regulated and governed.
- There is an expectation that trial processes will be undertaken to a high standard
  – document what has been done.
- Patient safety is paramount.
- Also scientific integrity, ethical issues, and the best use of scarce (public) resources.

- Quality assurance is those activities that demonstrate this, eg

  – site visits for source data verification

  – robust central monitoring

But increasingly much more …
- Trials Units need to show they are fit for purpose
  – For example, the registration of UK trials units by the UK Clinical Research Network Collaboration http://www.ukcrc-ctu.org.uk.
  – Applications rigorously assessed by international panel .
  – Registered units reviewed 3 yearly.
  – Expectation that should be registered to undertake publicly funded trials.
  – All staff must work to SOPs.

- In the future, there will (have to) be funding for quality assurance people within accredited trials units.


Risk Assessment

- In any complex project – such as a clinical trial – in which many people from different disciplines are inter-dependently working to a challenging deadline under a tight budget, it is important to identify and manage the risks
- Risks:
  - What can go wrong?
  - What are the vulnerabilities?
  - What is the magnitude of the consequences?
  - How likely are they to happen?

- Some of the **risk factors** to be considered are:
  - **Ethical** review; Scientific **peer** review?
  - Difficulties or incapacity to give **informed consent**
  - Adequately **funded**? Properly **staffed**?
  - **Safe** (licensed?) interventions
  - **Randomisation** (allocation concealment)
  - **Blinding**?
  - Support of **registered Trials Unit**
  - **Qualified and experienced** investigators?
  - **GCP** trained staff?
  - **Quality** management systems (quality control & quality assurance?)

- Risk assessment: from whose perspective?
  - Society (e.g. stem cell, gene therapy)
  - Funder / Sponsor
  - Researcher
  - Patient
- Risk assessment – when?
  - Before the start
  - Ongoing as trial evolves

- Risk assessment - for the trial manager?
- Informs 'Monitoring Plan'
  - e.g. on site data source verification
  - Remote central statistical monitoring – identify and then target / visit sites that are 'out of control'

- Monitoring 'proportionate to risk'
  - Regulators / governments will accept this
- Say what you are going to do, then do it

- Clinical Trials Toolkit - www.ct-toolkit.ac.uk
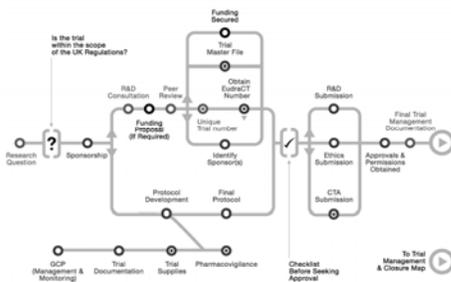
Contact Information

Alison McDonald	a.mcdonald@abdn.ac.uk
John Norrie	johnn@stats.gla.ac.uk
Julie Weston	julie.weston@utoronto.ca
Carole White	Whitec2@uthscsa.edu

Workshop -   Trial and Site Management for Multi-Center Trials

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

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:**

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

In many cases your institution will have many NIH projects underway and will have received a Federal-Wide Assurance (FWA) number. Once an institution has this number your project is automatically covered. You will just need to provide the number to the DCC.

If yours is the first NIH project to be undertaken at your institution the DCC can cover you under their FWA. You will have to sign a special agreement for this to happen. But if your institution is collaborating on multiple NIH studies it must apply for its own FWA number. Here is a web link that covers this situation.
(http://www.hhs.gov/ohrp/assurances/assurances_index.html)

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

The collaborator at your site and all other research personnel must provide this documentation of education. Your institution will stipulate what this education needs to be. It is often some sort of on-line course that can be completed at your 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)

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

If you need to get any of these four numbers the following website will take 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.
- <u>Main papers</u>: Primary hypotheses and outcomes to be presented and published
- by whole *[STUDY]* Study Group
- <u>Other study publications</u>: May be undertaken by smaller groups for the *[STUDY]* Study Group with all participants at the end of the paper.
- <u>Abstracts</u> submitted to national or international meetings.
- <u>Presentations</u> 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]*.

- <u>Authorship of main papers</u>: 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.

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

<u>First authorship of *[STUDY]* papers</u>

- 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.

<u>1. Co-authorship</u>

- 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° or 2° 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:	

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).

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