Society for Clinical Trials 32nd Annual Meeting

Workshop P5
Trial and Site Management for
Multi-Center Trials

Part 1 of 3

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

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

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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

Functioned as Trial Manager of several international secondary stroke prevention trials

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
- Majority of content will be presented in the slide presentation but to allow more time for questions some of the content will be provided in paper handouts
- 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 Sponsorship
   - Trial Registration
   - 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

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.
- We are happy to discuss this at break or after the session for those that have questions

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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)

Also known as: Chief Investigator (CI)

- 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

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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 3000 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 or guidance on how often refresher training should be undertaken.

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 -
  http://www.crncc.nihr.ac.uk/training/index
- Private consultants can do courses but these can be quite expensive

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- 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/maternity 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 England, accredited UK CRN trials units are awarded $250-$400k per year in core funding on rolling contracts to develop high quality trials for submission for competitive public funding - http://www.ukcrc-ctu.org.uk/Pages/default.aspx

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Other Central Office Tasks

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

1. 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/co-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.

- 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

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Risk Assessment
- Undertaken prior to agreement to sponsor
- In any complex project 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 -informs 'Monitoring Plan'
  – e.g. on site data source verification
  – Remote/central monitoring – identify and then target / visit sites
- Monitoring 'proportionate to risk'
  – Regulators / governments will accept this
- Say what you are going to do, then do it, and document what you have done
- there is encouraging work underway to facilitate a risk-proportionate approach: http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf

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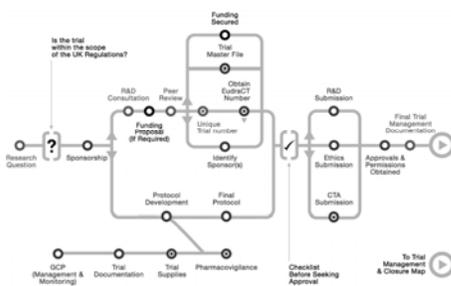- Clinical Trials Toolkit - www.ct-toolkit.ac.uk

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2. Trial registration
- Registration 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
- Aim to ensure that information about the existence and design of clinical trials of all interventions is publicly available
- Acceptable registries include:
- www.clinicaltrials.gov; www.ISRCTN.org; www.anzctr.org.au; www.trialregister.nl; www.umin.ac.jp/ctr/index/htm

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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.

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 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.
- Describe expected adverse events and reporting procedures in protocol
- Regulations for the UK can be found at: http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/safetyreports

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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

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- 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?

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- 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)

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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!

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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

- 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
- Payment type may increase change of successful extension application to funder (apply for no cost/low cost extension)

"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

CONTENT INCLUDED IN HANDOUTS

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' (eg range checks) 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

DETAILS OF EACH ARE IN HANDOUTS

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

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- 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/bring site staff to central office 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/ email/Skype 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
- It may be important for some research staff to be English speaking as data forms and websites are not usually translated
- 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

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- 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

CONTENT INCLUDED IN HANDOUTS

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

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- 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

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- 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

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- Each group has its own application process to become a member and to participate in 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

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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

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- 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

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Ways to assess suitability

- Questionnaires sent to sites asking about critical components of participation
- Site visit by PI/trial manager 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

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.
- Document any training that was done for audit purposes including agenda, participants and minutes

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

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- 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.
- The Central office should look at recruitment numbers regularly so that strategies can be implemented early if there is a problem
- Be flexible – individual strategies for sites.
- Dips during holiday periods should be expected.

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, email contact information 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 contacts you, but also that is isn't so general that the number of contacts is overwhelming.
- Be prepared to deal with disappointment as there will be people who will contact 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 so they are fresh and renew interest
- Provide money to the patient to cover their time and parking costs to attend clinic visits.

Ideas to motivate clinical staff to refer or enroll patients

- Often major challenge 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.

How to motivate/thank site staff

- What are your experiences – what has worked in order to maintain staff motivation and boost patient recruitment?

- Any new ideas?

- 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

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- 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

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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

CONTENT INCLUDED IN HANDOUTS

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 (e.g. 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

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- Attrition in a more specific sense usually refers to the subset of processes that something can be done about, for example:

  - 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

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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
- Lost to follow-up important data for consort: http://www.consort-statement.org/consort-statement/

How to reduce attrition

- 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.
- Consider any evidence eg http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/MR000032/pdf_fs.html

- 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 valued and that you care about their health and not just like a research subject. Also respond promptly to any participant 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 participant needs, etc.
- Maintain continuity in research personnel – if there are several people working on the same study, attempt to keep participants 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 participants.

- 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

- 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.

- If a participant does withdraw consent do you have permission to collect outcome data from central data sources?
- If yes, use these 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)*
  - If storage is required for a long period of time, who is responsible and how will this responsibility be transferred when there is staff changeover?

- 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

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- 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

CONTENT INCLUDED IN HANDOUTS

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