SNACC Mentorship Session
Making My Clinical Research Project a Success

9th October, 2014 Thursday
15:15 – 16:00 PM

Lecture 4: Implementing My Project

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Disclosures

Members in a few trial networks

Involved in several international, multicenter trials

From an site investigator perspective (often frustrating experience)

Congratulations in getting your project funded!

- How to start the project?
  - Relevant documentation
  - Ethics and trial registry
- Optimizing patient recruitment
- Keeping recruitment on track
- Database management
- Monitoring of the trial

Acronym

First (or first few) letters of each word in the title
Pronounceable words
Easy reference
Automatic attitude activation effect
No correlation with study objectives
Works for patients (easier to consent?)
grant reviewers (easier to fund??)

Chest 2002; 121:2023-8

What does IRB look for?

Equipoise (genuine uncertainty on preferred treatment)

N Engl J Med 1987; 317:141-145

Undue suffering / inconvenience

Standards

Common dilemma in Anesthesia Trials

Time sensitive treatment (vs alternative), no time for consent

Patient may not be conscious or able to provide consent

Deferred Consent

Trauma / Emergency surgery at risk of awareness

Family may not be immediately available

Best standard care will be provided

BIS monitor has been approved by FDA US

No harm reported with BIS monitoring

Misconduct

Annual (or more frequent) updates from the PI are required

- Safety monitoring committee
- Unexpected harmful effects (SAE)

PI is primary responsible for the design, conduct and reporting of the research

Regulatory requirements

Patient consent

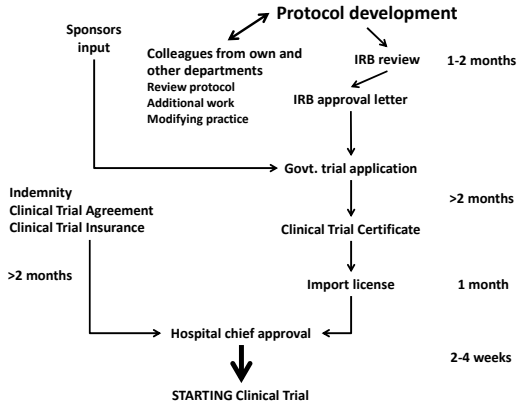
Ethics committee approval

Departmental (yours and others) approval

Clinical trial certificate (from government/FDA)

Hospital chief approval

University approval (clinical trial certificate)



Clinical trial registration

Reduce duplication of efforts

Higher recruitment (Public education)

Disclosure of results

> …call for comprehensive registration of trials as the first step in alleviating selective data presentation on clinical trials in medical literature

Optimizing patient recruitment

- Protocol design
- Patient population (availability)
- Surgical, theatre and ward staff cooperation and collaboration
- Research assistant effort/expertise
- Coordination

Protocol

Objective: Relevant

Patient: Simple inclusion criteria or specific patient population

Procedure: Feasible to patients, anesthetists, surgeons, ward staffs and research assistants

Outcome: Measurable, meaningful

Trial Design

- Factorial design
- Additional measurements / separate hypotheses
  - DWI MRI
  - Coronary CTA
  - Biobank
  - NT-proBNP
  - Chronic postsurgical pain

Patient pool

- Big tertiary hospital has major difficult cases with high morbidity/mortality
- Lack of ambulatory surgery
- Local network of hospitals

Finding the patients

- Advertise to surgeons/colleagues/ward staffs
  - Grand round presentations
  - Co-authors/collaborations/co-investigators

Collaborate with surgeon/colleague

- Help to disseminate information
- Refer patients for study
- Implement findings / recommendations (translational medicine)

Finding the patients

Advertise to surgeons/colleagues/ward staffs
- Grand round presentations
- Co-authors/investigators

- Daily theatre lists (advance booking)
- Emergency lists
- Preanesthetic clinic/consultation

Research assistants

- Recruitment/consent (valid in HK)
- Nurses vs others
  - Psychology graduates (cognitive tests)
  - Trained ICU nurse
  - Summer students - phone follow-up (part-time)
  - Phlebotomists - Blood taking, PSG (hourly pay)
  - Computer/scientific officer (shared by entire department)
  - Clerical staff - copy admission notes
    - audit/follow-up data
- Communications
  - WhatsApp, Facebook - not recommended

Start-up meeting / Agreement

Steering committee

Publication agreement (who are the authors and in what order?)

Clinical trial / Data sharing agreement

Site initiation

- Rationale of the study
- Procedure
- Recruitment strategy
- Endpoint definition
- CRF completion

Data management

Document events (definitions)

Endpoints:

- Primary, Secondary, Safety

Confounding variables:

- Known, ?unknown

Limit the data points to a minimum

Security: de-identified data

Send / fax / email / online transmission to coordinating center

Paper vs Electronic CRF

Paper CRF converted to pdf for indefinite storage

Electronic database system

- Minimize error (date formatting,…)
- Track errors
- Online calculation
- *Expensive*
- *Time consuming to develop and to complete*

Monitoring *outcome*

Events (often adverse)

Serious adverse events - report ≤ 24 hour

- …fatal, life-threatening, permanently disabling or incapacitating or results in hospitalisation, prolongs a hospital stay or is associated with congenital abnormality, carcinoma or overdose

Suspected Unexpected Serious Adverse Reactions (SUSAR)

Causality: unknown, unrelated, …. definitely related

Trial management vs IRB looks after SAE

Unblinding of treatment – procedure

Event adjudication

Important "subjective" endpoints

Event adjudication:

- Add credibility
- Ensure data quality
- Remove noise/bias

Difficult adjudication based on little documentation

Resource limitation (cost and time)

Auditing

Wrong data
- Missing
- Data entry error – systematic, isolated
- Falsification
- Fabrication

Onsite monitoring – random or entire cohort

Statistical monitoring

Analysis plan / Statistician

Involve a statistician early (planning stage)

Statistical Plan

Tables Demographic

Confounding variables

Regression analysis on the effect of confounders

Consolidated Standards of Reporting Trials

http://www.consort-statement.org/home/

Graphs to illustrate the endpoints

Interim Analysis

Goal is to ensure that trial is safe and warrants continuation
- Interim analyses involve relatively few data points
- Inferences can be imprecise
- Increase chance of errors
- Interim results are conveyed to investigators may introduce bias
- We look for strong evidence in one or another direction

Substudies

More cost-effective (than another RCT)

Explain findings

Multicenter involvement / Funding

Faster recruitment

Ethnic difference

Global impact

Generalizability (district vs tertiary referral hospital)

Multiple funding models

JAMA 2012; in press
Anesthesiology 2012; 116:1169-75

Conclusions

1. Acronym
2. Regulatory requirements
3. Clinical trial registration
4. Data management
5. Monitoring, Event adjudication, Auditing
6. Analysis plan / Statistician
7. Start-up meeting / Agreement
8. Interim analysis
9. Substudies
10. Multicenter involvement / Funding