Planning and Running a Clinical Trial: Site perspective

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European Society of Cardiology

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I have the following potential conflict(s) of interest to report

<table>
<thead>
<tr>
<th>Type of affiliation / financial interest</th>
<th>Name of commercial company</th>
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<tbody>
<tr>
<td>Receipt of grants/research support:</td>
<td>AstraZeneca, Bayer Healthcare, MSD, Resverlogix, KOWA, Pfizer</td>
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<tr>
<td>Receipt of honoraria or consultation fees:</td>
<td>Bayer Healthcare, MSD, Pfizer, Novo Nordisk</td>
</tr>
<tr>
<td>Participation in a company sponsored speaker’s bureau:</td>
<td>Pfizer, Novo Nordisk</td>
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Trials that Changed Medicine: CHF

CONSENSUS I
Cumulative Probability of Death in the Placebo and Enalapril Groups

Cumulative Probability of Death

Placebo
Enalapril

40% Reduction
P = 0.002


1987
ACS: Cumulative Hazard Rates for CV Death/MI/Stroke

- **Placebo**
- **Clopidogrel**

Cumulative Hazard Rates

- Months of Follow-up: 0, 3, 6, 9, 12
- No of Pts:
  - Placebo: 6303, 5780, 4664, 3600, 2388
  - Clopidogrel: 6259, 5866, 4779, 3644, 2418

RRR = 20%

p < 0.001

ACC, Mar 2001
AF: Stroke or Systemic Embolism

Dabigatran 110 vs. Warfarin
- Non-inferiority p-value: <0.001
- Superiority p-value: 0.34

Dabigatran 150 vs. Warfarin
- Non-inferiority p-value: <0.001
- Superiority p-value: <0.001

Margin = 1.46

HR (95% CI)

Dabigatran better
Warfarin better

ESC, 2009
EMPAREG: Effect of SGLT2 inhibition in Diabetes Mellitus

A Primary Outcome

B Death from Cardiovascular Causes

C Death from Any Cause

D Hospitalization for Heart Failure

EASD, 2015
Trial Objectives – How did These Trials Succeed?

• Objectives should be relevant and important

• Objectives should be clear and well defined
  • Do ACE-inhibitors improve survival in HF patients?
  • Is DAPT superior to aspirin alone for reducing CV events?
  • Is dabigatran non-inferior to warfarin for preventing stroke/SE in pts with AF? And is dabigatran superior to warfarin?
  • Can antiglycemic drug choice impact on long-term outcome in DM patients?
The Site: PI and Research Team

• PI
  • MD with trial experience
  • PI is the lead scientist for a particular, defined research project, such as a laboratory study or clinical trial
  • PI may be at site level, or at country level
Duties of the PI During the Trial

• Check/sign informed consent sheets
• Check/sign CRFs (case report forms)
• Report SAEs and endpoints within 24 hours
• Read/sign safety report forms
• Take ample time for monitor visits
• Be prepared for audits (sponsor, local, government, international)
• THE PI IS RESPONSIBLE FOR EVERYTHING IN THE TRIAL
The Research Team

• Sub-investigators
  • Staff members, residents, trainees
  • All must have GCP training
  • Have delegated role in the trial, as specified by the PI

• Study Co-ordinators
  • Nurses
  • Biotechnicians
  • Other- social workers, other

• Administrative and secretarial support
Residents and Trainees

Pros:
- Early access to latest treatment strategies
- Access to top investigators and lectures
- Exposure to research methods
  - Protocol, ICF, GCP
  - Criteria, definitions
  - Statistics plan
  - Attention to detail, CRF

Cons:
- Less independent thought
  - Done already by others
- Less independent research and innovation
  - Less time available
- Less critical questioning
  - Do as you are told!
- Fewer publications
The Site: Must Have Adequate Facilities

- **Working space**
  - Team and monitors

- **Storage space**
  - Drug (IP), trial files, patient files

- **Storage facilities**
  - Store IP – Pharmacy? Research unit?
  - Refrigeration for IP
  - Refrigeration for biologic samples - -20? -80?

- **Equipment**
  - Routine equipment available - EKG, BP, scales, tapes, other

- **Local labs may be required**
Trial Master File (TMF), Patient Records, Privacy
Drug Storage, Lab Equipment

Temp-controlled centrifuges
The Site – Administration and Communication

- Electronic communication essential for most trials
  - Email, fax, copiers, scanners
  - Web communication
  - CRF and data transfer usually depends on Electronic Data Capture (EDC)
  - Connection availability and speed (institutional firewalls can be challenging)

- Site training
  - All personnel need to be trained in communication with discreet user IDs

- Paper based research trials for smaller/local trials
A Well Equipped Office Complex
The Site: Patients

- **Site should have access to appropriate patients**
  - Inpatient study (eg ACS, Acute HF)
  - Outpatient study (eg primary or secondary prevention)
  - Referral base

- **Enrollment expectations and commitment**
  - Realistic commitment
  - Competition for patients and resources must be taken into account
  - Track record
  - Financial viability
Trial Procedures

• Identify the patient
  • Inclusion and exclusion criteria must be met, but more importantly, patient must have:
    • Understanding
    • Motivation
    • Availability for trial procedures and visit timelines

• Informed consent (ICF)
  • Do it correctly
  • Do it before any research dictated activities
  • Challenging when there are language issues
  • ICF errors are the commonest issues in FDA trial audits
Trial Procedures

• Follow the Protocol
  • Record the findings
  • Dispense the treatment
  • Plan visit schedule
  • Update the CRF as soon as possible (4-5 days)

• Update the Family Practitioner and Record System
  • Letter to family practitioner
  • Documentation and trial info in patient record system
Clinical Trials: Ethics Committee

• The ethics committee (EC; IRB; “Helsinki” committee) is responsible for ensuring patient safety

• Composition of IRB
  • Scientists and researchers
  • Experts in the field
  • Pharmacists/pharmacologists (where relevant)
  • Institutional administrators
  • Public representative(s)
  • Legal opinion
Role of the Ethics Committee

The ethics committee is responsible for ensuring patient safety

- Ethics of the protocol
- Competence of the investigators and staff
- Informed consent language and process
- Ensure that there is an updated investigator brochure with proper information for investigators

Reviewing trial progress

- Number of patients in trial
- Adverse and serious adverse events
- Input from DSMB
- Protocol violations

Approval is usually renewable on an annual basis after review of trial progress
Clinical Trials: Financing

• Non-funded

• Institutional, health system funding

• Research grant

• Contract research with a sponsor
  • Commercial entity or industry sponsored
  • Governmental or University sponsored
Role of a Clinical Research Organization

- For most large-scale trials, a professional research organization is mandated by the sponsor to manage the trial
  - Site selection and feasibility
  - Contracts
  - Submissions to IRBs
  - Initiation visits
  - Monitoring
    - Ensure data authenticity by checking source data
    - Ensure data completeness
    - Problem solving
Role of the Monitor

- **Monitoring is a method to ensure trial integrity**
  - Verify patient numbers
  - Verify compliance with trial protocol
    - Patient selection
    - Trial procedures
    - Event reporting
  - Verify storage and use of investigational product (IP)

- **Monitor may provide advice/assistance to site**
  - Interpretation of the protocol
  - Problem solving in cases of system malfunction (usually computer or shipping issues)

- **Monitoring level may vary**
Role of the Monitor – Potential Issues

• The monitor represents the CRO (and/or sponsor) and has conflicting motivation to that of the site team
  • Defensive perspective
  • Motivation is beaurocratic rather than medical
  • CRO and sponsor are motivated by profit

• NONETHELESS

• Good working relationship between site and monitor is essential to the success of the project
Adjudication (critical events committee, CEC)

- Adjudication ensures uniformity in interpretation of clinical events
- Adjudication can change outcome - but should not!
- Central or national?
  - National means no translations
  - Better understanding of local records and interpretation
- Total or partial?
  - Concordance rate between investigator and CEC?
  - Automated system can reduce load by more than 50%
Patient retention

- **No patient ever leaves a trial**

- **Degrees of “compromise”**
  - Less drug or no drug
  - Fewer visits, more telephone
  - Less telephone contact? Once a year or end of study essential
  - Vital status should ALWAYS be sought – its in public domain

- **True total withdrawn consent – rare, in writing only?**
Consequences of Lost to Follow-up or Withdrawn Consent

2000 patients in trial

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<tr>
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<td>1000</td>
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</tr>
<tr>
<td>Event/death</td>
<td>200</td>
<td>150</td>
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RRR = 25%, p=0.004

Lost to follow-up or withdrawn consent = 5% (50 each arm)

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<tr>
<td>Calc rate</td>
<td>200+0=200</td>
<td>150+50=200</td>
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RRR = 0%, NS
How to Ensure a Successful Trial

- Plan well in the beginning so that pts don’t get lost
  - ICF to allow tracking
  - Contact persons
  - E-treats and tricks inherent in study
- Watch out for missed or late visits
  - Reliability?
  - Drug supply problem
- Motivate investigators and patients
  - TCs, meetings
  - Patient groups – meetings and information
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