Clinical trials: Protocol document

Professor Tom Marwick MBBS, PhD, MPH
1. Protocol document

2. Data collection plan
   • Who collects each piece of data? When is it collected?
   • How is it routed to the database for analysis?

3. Protocol monitoring plan
   • Describes periodic monitoring reports (Patient entry, on drug, off drug, off study, toxicity, and primary endpoint)
   • Quality control mechanisms

4. Analysis plan
   • 1st draft before study begins, finalize before interim analyses
   • Outlines major elements of the analysis
   • Establishes primary vs. secondary vs. exploratory analyses
Use of Coronary Artery calcium score to Guide management of Hereditary Coronary Artery Disease

Comparison of CCS and Framingham score to predict 3y plaque burden in pts with a F/H of CAD
1. Background/rationale
2. Objectives (Aims, hypothesis)
3. Overview of study design
4. Eligibility (inclusion/exclusion)
5. Enrolment procedures
6. Clinical evaluation/imaging
7. Randomization
8. Treatment regimens (incl titration, stopping)
Does anyone care? Should they?
1. Start with an epidemiology introduction
2. How this study addresses an important problem in CVD
3. If the aims are achieved, how will scientific knowledge or clinical practice be advanced?

Acknowledge potential problem areas.

Do you have preliminary data? This is the best way of dealing with feasibility questions!
• Research question
• Hypothesis – remember it’s a statement. “Elevator pitch” – can you put it in a sentence?
• Study aims – how you will test the hypothesis
• Your audience (ethics committee, grant panel etc) have dozens of applications to read, some written in Swahili.
• Be kind to them!
Avoid the collection of too much data!!!
• Typically <100 variables used in paper but often 1,000 variables collected on study forms!!
• “Abstract/tables/figures model” to focus on key data items
• Collection of dose modifications, concomitant medications and low grade adverse events can overwhelm the research staff

Basic types of Case Report Forms (CRFs)
• Snap-shot – single point in time
• Follow-up – “one visit to next visit”
• Summary – summarize over time from baseline
7. Follow-up schema (graphical)
8. Endpoints – distinguish 1º and 2º
9. Safety, DSMB, stopping rules
10. Data collection and management
11. Statistical analysis
12. Data/safety monitoring
13. Informed consent
<table>
<thead>
<tr>
<th>Study procedures (month)</th>
<th>Screening</th>
<th>Titration</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>24</th>
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<tbody>
<tr>
<td>Informed Consent</td>
<td>X</td>
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<tr>
<td>Clinical review - Medical History</td>
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<tr>
<td>- Heart Failure Assessment (NYHA)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>- Concomitant Medications</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>- Vital Signs (BP, HR, RR)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>- Physical Exam</td>
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<td>- 12 Lead ECG</td>
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<tr>
<td>Exercise testing with VO$_2$</td>
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<tr>
<td>AE/SAE Assessment</td>
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<td>X</td>
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<tr>
<td>Echocardiogram (incl strain)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Labs - Chem Panel incl eGFR)</td>
<td>X</td>
<td>X</td>
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<td>Dispense Study Drug</td>
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<td>Medication Compliance (pill counts)</td>
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<td>HRQoL measures (AQoL, EQ-5D)</td>
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</table>

Be very careful that this matches text and budget as you go through iterations! Some reviewers use this exclusively.
• Outcome measure used to make the decision regarding overall result of the study. Defined prior to study initiation. Basis for sample size determination.

• BE CAREFUL, this may “make or break”! If your primary goes down, you cannot market on your secondary!

• Ideally each trial has one primary endpoint
  – If > 2 primary endpoints, study lacks a clear objective
  – Most regulatory authorities and journals insist on a single primary endpoint identified before study begins.
• Contains the essence of the study results
• Clinically/biologically important
• Measurable for each patient
• Timing – not too soon (treatment has time to work) and not too late (other factors can cloud the results)
• Primary endpoints should occur frequently enough for study to have adequate statistical power
• Two primary endpoints should not be highly correlated with each other
• Generally best if primary endpoint is a major event/finding
1. Proportion of patients with a successful outcome (e.g. “response” is a binary outcome: “response” versus “no response” for each patient). Characterized by the “response rate” - $P$

2. Time to an event (failure) (e.g. “time to death”, “time to disease recurrence” or “time to a grade 3 toxicity”). Characterized by the “hazard rate” – $\lambda$

3. Average value of a quantitative parameter (e.g. “average of a laboratory parameter” or “average quality of life score” defined on a group of patients). Characterized by the “mean” - $\mu$
Initial review
- Schema page
- Primary objectives
- Primary endpoint definition
- Statistical considerations/sample size section
- Patient selection criteria

Secondary order of review
- Study design section
- Parameters table
- Background/rationale – Is the study design justified
- Consent form
Welcome to the CONSORT Website

CONSORT stands for Consolidated Standards of Reporting Trials and encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomized controlled trials.

The CONSORT Statement

The main product of CONSORT is the CONSORT Statement, which is an evidence-based, minimum set of recommendations for reporting randomized trials. It offers a standard way for authors to prepare reports of trial findings, facilitating their complex and transparent reporting, and aiding their critical appraisal and interpretation.

The CONSORT Statement comprises a 25-item checklist and a flow diagram. The checklist items focus on reporting how the trial was designed, analyzed, and interpreted, the flow diagram displays the progress of all participants through the trial. The CONSORT "Explanation and Elaboration" document explains and illustrates the principles underlying the CONSORT Statement. We strongly recommend that it is used in conjunction with the CONSORT Statement. In addition, extensions of the CONSORT Statement have been developed to give additional guidance for RCTs with specific designs, data and interventions.

Endorsement of the CONSORT Statement

The CONSORT Statement is endorsed by prominent general medical journals, many specialty medical journals, and leading editorial organizations. CONSORT is part of a broader effort to improve the reporting of different types of health research, and indeed, to improve the quality of research used in decision-making in healthcare.

This website contains the current definitive version of the CONSORT 2010 Statement and up-to-date information on extensions.
<table>
<thead>
<tr>
<th>PAPER SECTION</th>
<th>Item</th>
<th>Description</th>
<th>Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE &amp; ABSTRACT</td>
<td>1</td>
<td>How participants were allocated to interventions (e.g. &quot;random allocation&quot;, &quot;randomised&quot;, or &quot;randomly assigned&quot;).</td>
<td>2</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>2</td>
<td>Scientific background and explanation of rationale.</td>
<td>3-5</td>
</tr>
<tr>
<td>METHODS</td>
<td>3</td>
<td>Eligibility criteria for participants, settings and locations where the data were collected.</td>
<td>8</td>
</tr>
<tr>
<td>Participants</td>
<td>4</td>
<td>Precise details of the interventions intended for each group and how and when they were actually administered.</td>
<td>8</td>
</tr>
<tr>
<td>Interventions</td>
<td>5</td>
<td>Specific objectives and hypotheses.</td>
<td>5</td>
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<tr>
<td>Objectives</td>
<td>6</td>
<td>Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).</td>
<td>9</td>
</tr>
<tr>
<td>Outcomes</td>
<td>7</td>
<td>How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.</td>
<td>9-10</td>
</tr>
<tr>
<td>Sample size</td>
<td>8</td>
<td>Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification).</td>
<td>8</td>
</tr>
<tr>
<td>Randomisation Sequence generation</td>
<td>9</td>
<td>Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.</td>
<td>8</td>
</tr>
<tr>
<td>Randomisation Allocation concealment</td>
<td>10</td>
<td>Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.</td>
<td>8</td>
</tr>
<tr>
<td>Randomisation Implementation</td>
<td>11</td>
<td>Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.</td>
<td>9</td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td>12</td>
<td>Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.</td>
<td>10</td>
</tr>
</tbody>
</table>
RESEARCH PROJECT
Preparing a budget

1st Priority
- Data manager (40%-50% total cost)
- Tests/drugs for the trial (beyond standard care)
- Study coordinator (10%-20%)

2nd Priority
- Research nurses (10%-20%)
- PI salary (Study Chair) (10%)
- Statistician (20%-30%)

3rd Priority
- Other clinicians (<5%)
- Programmer (5%)
- DBA (5%) and others

2 rules of thumb
- Overall phase III clinical trial budget ~ $1,000-2,000 per patient or more
- Data manager, statistician, programmer, DBA, database costs, and other data management center costs ~ 12%-15% of overall clinical trial budget
• Career development
• Your time
• Someone else’s time – technical, stats
• Disposables, drug/placebo
• Machine time
• New equipment

BUT - many valuable studies are performed with no funding
Appropriate training
Appropriate experience level in practice
Appropriate experience level in research
Appropriate help – complementary, integrated

Define your team!
Complementary skills – nobody can do everything!
• Does the scientific environment in which the work will be done contribute to the probability of success?

• Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements?

• Is there evidence of institutional support as demonstrated in the department head letter?

Are you in the best setting to do this work?

• If not, link up with someone – shared authorship in a good journal is better than rejection!