Statistical Analysis Plans

PROFESSOR CARROL GAMBLE
UNIVERSITY OF LIVERPOOL
Clinical Trials

Lots of different types of clinical trials
  ◦ Various interventions
  ◦ Pharmaceutical/drugs regulated

Regulated environment
  ◦ Subject to inspections
  ◦ Recreation=transparency
# TABLE OF CONTENTS

I. INTRODUCTION .................................................................................................................. 1
  1.1 Background and Purpose ............................................................................................... 1
  1.2 Scope and Direction ...................................................................................................... 2

II. CONSIDERATIONS FOR OVERALL CLINICAL DEVELOPMENT .................................. 3
  2.1 Trial Context .................................................................................................................. 3
    2.1.1 Development Plan .................................................................................................. 3
    2.1.2 Confirmatory Trial ................................................................................................ 4
    2.1.3 Exploratory Trial ................................................................................................... 4
  2.2 Scope of Trials .............................................................................................................. 4
    2.2.1 Population ............................................................................................................ 4
    2.2.2 Primary and Secondary Variables ....................................................................... 5
    2.2.3 Composite Variables ............................................................................................ 6
    2.2.4 Global Assessment Variables .............................................................................. 6
    2.2.5 Multiple Primary Variables ............................................................................... 7
    2.2.6 Surrogate Variables .............................................................................................. 7
    2.2.7 Categorized Variables ......................................................................................... 7
  2.3 Design Techniques to Avoid Bias ................................................................................ 8
    2.3.1 Blinding ............................................................................................................... 8
    2.3.2 Randomisation ..................................................................................................... 9

III. TRIAL DESIGN CONSIDERATIONS ............................................................................. 11
    3.1 Design Configuration ................................................................................................. 11
      3.1.1 Parallel Group Design ....................................................................................... 11
      3.1.2 Crossover Design .............................................................................................. 11
      3.1.3 Factorial Designs ............................................................................................... 12
    3.2 Multicentre Trials ....................................................................................................... 12
    3.3 Type of Comparison .................................................................................................. 14
      3.3.1 Trials to Show Superiority ............................................................................... 14
      3.3.2 Trials to Show Equivalence or Non-inferiority .................................................. 14
      3.3.3 Trials to Show Dose-response Relationship ...................................................... 16

IV. TRIAL CONDUCT CONSIDERATIONS ...................................................................... 18
    4.1 Trial Monitoring and Interim Analysis ....................................................................... 18
    4.2 Changes in Inclusion and Exclusion Criteria ............................................................ 19
    4.3 Accrual Rates ........................................................................................................... 19
    4.4 Sample Size Adjustment ........................................................................................... 19
    4.5 Interim Analysis and Early Stopping ......................................................................... 19
    4.6 Role of Independent Data Monitoring Committee (IDMC) ..................................... 21

V. DATA ANALYSIS CONSIDERATIONS ........................................................................ 21
    5.1 Prespecification of the Analysis .............................................................................. 21
    5.2 Analysis Sets ............................................................................................................ 22
      5.2.1 Full Analysis Set ............................................................................................... 22
      5.2.2 Per Protocol Set ............................................................................................... 23
      5.2.3 Roles of the Different Analysis Sets ................................................................... 24
    5.3 Missing Values and Outliers ................................................................................... 24
    5.4 Data Transformation ............................................................................................... 25
    5.5 Estimation, Confidence Intervals and Hypothesis Testing ..................................... 25
    5.6 Adjustment of Significance and Confidence Levels ................................................. 26
    5.7 Subgroups, Interactions and Covariates .................................................................. 26
    5.8 Integrity of Data and Computer Software Validation ............................................... 27

VI. EVALUATION OF SAFETY AND TOLERABILITY .................................................. 27
    6.1 Scope of Evaluation .................................................................................................. 27
    6.2 Choice of Variables and Data Collection .................................................................. 27
    6.3 Set of Subjects to be Evaluated and Presentation of Data ........................................ 28
    6.4 Statistical Evaluation ............................................................................................... 29
    6.5 Integrated Summary ............................................................................................... 29

VII. REPORTING .................................................................................................................. 29
    7.1 Evaluation and Reporting ........................................................................................ 29
    7.2 Summarising the Clinical Database ........................................................................ 31
      7.2.1 Efficacy Data ..................................................................................................... 31
      7.2.2 Safety Data ....................................................................................................... 32

GLOSSARY ............................................................................................................................ 32
For each clinical trial contributing to a marketing application, all important details of its design and conduct and the principal features of its proposed statistical analysis should be clearly specified in a protocol written before the trial begins. The extent to which the procedures in the protocol are followed and the primary analysis is planned a priori will contribute to the degree of confidence in the final results and conclusions of the trial.
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When designing a clinical trial the principal features of the eventual statistical analysis of the data should be described in the statistical section of the protocol.
Statistical Principles

For each clinical trial contributing to a marketing application, all important details of its design and conduct and the principal features of its proposed statistical analysis should be clearly specified in a protocol written before the trial begins. The extent to which the procedures in the protocol are followed and the primary analysis is planned a priori will contribute to the degree of confidence in the final results and conclusions of the trial.

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The statistical analysis plan may be written as a separate document to be completed after finalising the protocol.
For each clinical trial contributing to a marketing application, all important details of its design and conduct and the principal features of its proposed statistical analysis should be clearly specified in a protocol written before the trial begins. The extent to which the procedures in the protocol are followed and the primary analysis is planned a priori will contribute to the degree of confidence in the final results and conclusions of the trial.

When designing a clinical trial the principal features of the eventual statistical analysis of the data should be described in the statistical section of the protocol.

The statistical analysis plan may be written as a separate document to be completed after finalising the protocol.

Formal records should be kept of when the statistical analysis plan was finalised as well as when the blind was subsequently broken.
Bias

The presence of bias may seriously compromise the ability to draw valid conclusions from clinical trials (or any study).

Definition ICH E9:
- The systematic tendency of any factors associated with the design, conduct, analysis and evaluation of the results of a clinical trial to make the estimate of a treatment effect deviate from its true value.

Statistical analysis plans have been identified as one approach to reduce selective reporting of outcomes and analyses
- Decisions made *apriori* less likely to be biased
- Replication via the level of detail specified
- Did you do what you said you were going to do?
- Did you do anything extra?
- Implications for interpretation
Statistical Analysis Plans and the peer review process

Leading journals may request SAP when submit final results paper

SAP published as standalone report or linked to protocols
- Often published within supplementary material
- Example of increasing transparency

<table>
<thead>
<tr>
<th>Publication Journal</th>
<th>Publish SAPs</th>
<th>Submission</th>
<th>Guidance</th>
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Guidance on the content of SAPs

Understand need for SAPs

Guidance on Statistical Principles and Clinical Study Reports

Experience shows level of detail on SAPs varies considerably
  ◦ Roles on Oversight committees
  ◦ Review of published SAPs

UKCRC registered CTU Network
  ◦ Priority for stats group
  ◦ Obtained funding from Medical Research Council Hubs for Trials Methodology Network
Developing Guidance

Search for existing guidance

Survey of registered UKCRC CTUs

Two round Delphi Survey

- Expert consensus meeting

Piloted guidance on 5 trials
Developing Guidance - Search for existing guidance

Major RCT funding bodies
- identified from list of funders actively supporting RCTs within UKCRC registered CTUs

Regulators (MHRA, FDA)

Journals
- Leading medical journals: BMJ, JAMA, NEJM, Lancet
- Journals publishing SAPS: Trials, Critical Care and Resuscitation & International Journal of Stroke
- Checked references of relevant publications and documents
Developing Guidance - Survey

Survey of registered UKCRC CTUs

- Do they write SAPs?
- When?
- Who writes them?
- Who is the intended audience?
- Collection of SOPs and SAP examples
Assumptions

The SAP is not a standalone document and should be read in conjunction with the clinical trial protocol;

The clinical trial protocol should be compliant with the principles of the SPIRIT 2013 Statement;

The SAP is to be applied to a clean or validated dataset for analysis.
Developing Guidance-Delphi survey

Two round Delphi Survey

Round 1
- list of components generated from SAPs and SOPs returned from survey
- Participants scored each item 1-9
  - 1 to 3 = ‘not important’, 4 to 6 = ‘important but not critical’ and 7 to 9 = ‘critical’
- Able to suggest items for inclusion in round 2

Round 2: for each component
- participants presented with the number and percentage of participants who chose each score.
- Participants were shown their score from round 1, and provided with an option to revise their score or keep it the same
Developing Guidance-Delphi survey

76 Participants approached representing:
- UKCRC CTU, contributors to CONSORT and SPIRIT guidelines, methodologists, contributors to pharmaceutical industry, journal editors and regulators.

<table>
<thead>
<tr>
<th>Consensus classification</th>
<th>Description</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Consensus in</td>
<td>Consensus that component should be included in the SAP Guidance Document</td>
<td>70% or more participants scoring as 7 to 9 AND &lt;15% participants scoring as 1 to 3</td>
</tr>
<tr>
<td>Consensus out</td>
<td>Consensus that component should not be included in the SAP Guidance Document</td>
<td>70% or more participants scoring as 1 to 3 AND &lt;15% of participants scoring as 7 to 9</td>
</tr>
<tr>
<td>No consensus</td>
<td>Uncertainty about importance of component</td>
<td>Anything else</td>
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Developing Guidance-Delphi Survey

Round 1 of the Delphi was sent to 73 participants of whom 56 completed the round with 54 also completing round 2

Experts met to discuss areas of ‘uncertainty’
- clinical trials unit senior statisticians, regulators (MHRA), statisticians in the pharmaceutical industry, and journal editors
- Following the consensus meeting: consensus in on 63 items, consensus out on 30 items and 17 items that the expert panel felt are important but do not necessarily need to be included

Critical review and piloting
- Critical review at a UKCRC statisticians meeting led to some items combined leaving 55
- Piloting across 5 trials
# Guidance document - 6 sections

<table>
<thead>
<tr>
<th>Section/Item</th>
<th>Index</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Section 1: Administrative Information</strong></td>
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<tr>
<td>Title and Trial registration</td>
<td>1a</td>
<td>Descriptive title that matches the protocol, with ‘Statistical analysis plan’ either as a fore runner or sub title, and trial acronym (if applicable)</td>
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<td></td>
<td>1b</td>
<td>Trial registration number</td>
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<tr>
<td><strong>SAP Version</strong></td>
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<td>SAP version number with dates</td>
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<td><strong>Protocol Version</strong></td>
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<td>Reference to version of Protocol being used</td>
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<td>4a</td>
<td>SAP revision history</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>Justification for each SAP revision</td>
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<td></td>
<td>4c</td>
<td>Timing of SAP revisions in relation to interim analyses etc.</td>
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<tr>
<td><strong>Roles and Responsibility</strong></td>
<td>5</td>
<td>Names, affiliations, and roles of SAP contributors</td>
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<tr>
<td><strong>Signatures of:</strong></td>
<td>6a</td>
<td>- Person writing the SAP</td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>- Senior statistician responsible</td>
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<tr>
<td></td>
<td>6c</td>
<td>- Chief investigator/clinical lead</td>
</tr>
<tr>
<td><strong>Section 2: Introduction</strong></td>
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<tr>
<td><strong>Background and rationale</strong></td>
<td>7</td>
<td>Synopsis of trial background and rationale including a brief description of research question and brief justification for undertaking the trial</td>
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<tr>
<td><strong>Objectives</strong></td>
<td>8</td>
<td>Description of specific objectives or hypotheses</td>
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Statistical Analysis Plans - summary

‘We had planned to do this before we saw the data’ is the best defence against data dredging
‘You only did this because the data showed....’

Improves transparency

Detailing your analysis plans early:
◦ ensures you are collecting all the data you need
◦ maintains a focus on the objectives of the study
◦ can prevent collection of unnecessary data (Data Protection Act)

Very specific to clinical trials but the principles can be extrapolated

Guidance under consideration for publication

We will aim to have a reference to this guidance on the CONSORT and EQUATOR websites

This work is now being extended to Health Economic Analysis Plans (HEAPS)
Question

Thinking about your own PhD:

Do you think you will need to develop a separate document outlining your analysis plan?

What are the difficulties in being so detailed up front?

What would the benefits be for you?