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

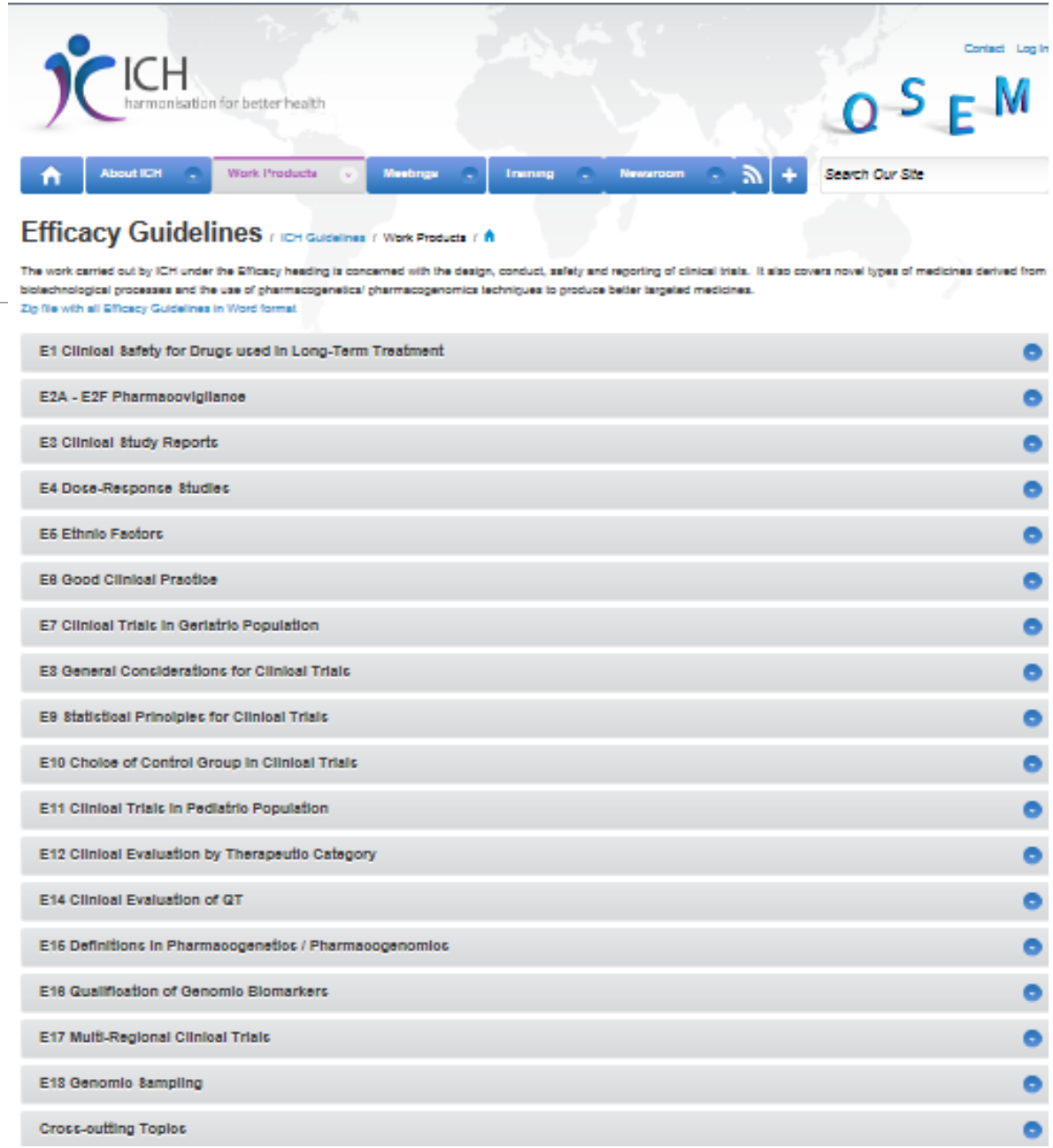

TABLE OF CONTENTS

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 Categorised 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
3.4 Group Sequential Designs 16
3.5 Sample Size 16
3.6 Data Capture and Processing 18
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 Validity 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

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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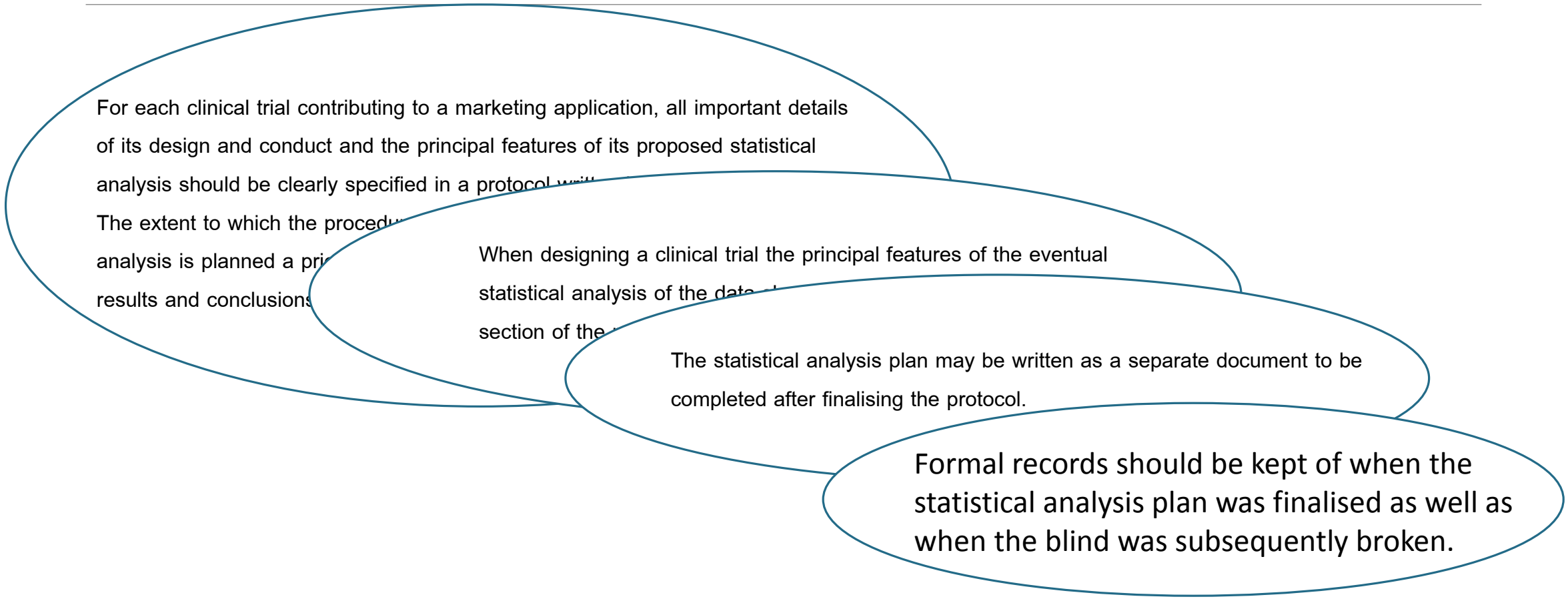
section of the protocol.

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

Statistical Principles



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

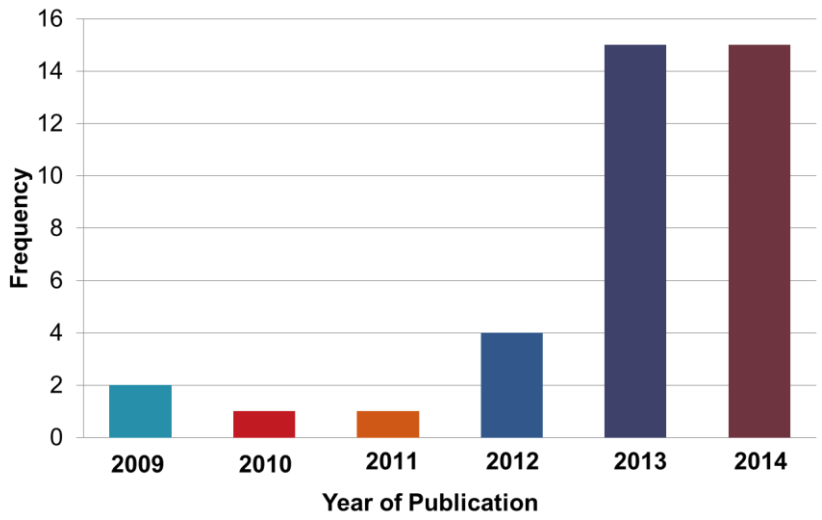
- Decisions made *apriori* less likely to be biased
- Replication via the level of detail specified
- Did you do what you said you were going to do?
- Did you do anything extra?
- Implications for interpretation

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



Publication Journal	Publish SAPs	Submission	Guidance
Trials	✓	×	×
JAMA	×	✓	×
BMJ	×	×	×
NEJM	✓	✓/×	×
Lancet	×	×	×

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.

Consensus classification	Description	Definition
Consensus in	Consensus that component should be included in the SAP Guidance Document	70% or more participants scoring as 7 to 9 AND <15% participants scoring as 1 to 3
Consensus out	Consensus that component should not be included in the SAP Guidance Document	70% or more participants scoring as 1 to 3 AND <15% of participants scoring as 7 to 9
No consensus	Uncertainty about importance of component	Anything else

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

Section/Item	Index	Description
Section 1: Administrative Information		
Title and Trial registration	1a	Descriptive title that matches the protocol, with 'Statistical analysis plan' either as a fore runner or sub title, and trial acronym (if applicable)
	1b	Trial registration number
SAP Version	2	SAP version number with dates
Protocol Version	3	Reference to version of Protocol being used
SAP Revisions	4a	SAP revision history
	4b	Justification for each SAP revision
	4c	Timing of SAP revisions in relation to interim analyses etc.
Roles and Responsibility	5	Names, affiliations, and roles of SAP contributors
Signatures of:	6a	- Person writing the SAP
	6b	- Senior statistician responsible
	6c	- Chief investigator/clinical lead
Section 2: Introduction		
Background and rationale	7	Synopsis of trial background and rationale including a brief description of research question and brief justification for undertaking the trial
Objectives	8	Description of specific objectives or hypotheses

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?