Estimands: PSI/EFSPI Special Interest group

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Agenda

- PSI/EFSPI Special Interest Group
  - Discussion Framework
- What is the real problem we are trying to solve?
- Case study
- Key messages
  - Definition and development of Estimands
  - Implementation
  - Education and communication
- Closing remarks

PSI/EFSPI Special Interest Group: Estimands

- Addendum to ICH E9 was proposed relating to Estimands and sensitivity analyses: October 2014
  - Arisen on the back of “Missing data” debate
  - Validity of “MAR” assumption for patients who discontinue
- EFSPI/PSI offered assistance via Special Interest Group
  - Goal: Form an industry consensus on the subject matter.
  - Request for volunteers: August 2014
  - Meeting: 18 February 2015

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Oliver Keene	GSK	
Ray Harris	Eisai	
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Chrissie Fletcher	Amgen	ICH Representative
Frank Bretz	Novartis	ICH Representative
Juan Abellan-Andres	Grunenthal	
Magnus Kjaer	AstraZeneca	
Søren Andersen	Novo Nordisk	

ICH
harmonisation for better health

Final Concept Paper
E9(R1): Addendum to Statistical Principles for Clinical Trials
on
Choosing Appropriate Estimands and Defining Sensitivity Snalyses in Clinical Trials
dated 22 October 2014
Endorsed by the ICH Steering Committee on 23 October 2014

Type of Harmonisation Action Proposed

To develop new regulatory guidance, suggested to be an Addendum to ICH E9, which promotes harmonised standards on the choice of estimand in clinical trials and describes an agreed framework for planning, conducting and interpreting sensitivity analyses of clinical trial data. As with ICH E9, the Addendum will focuses on statistical principles related to estimands and sensitivity analysis, not on the use or acceptability of specific statistical procedures or methods. While a variety of mid-stage and late-stage clinical trials may be in scope, the primary focus of the Addendum will be on confirmatory clinical trials.

Statement of the Perceived Problem

- ***Incorrect choice of estimand and unclear definitions for estimands lead to problems in relation to trial design, conduct and analysis and introduce potential for inconsistencies in inference and decision making.***

Inferences about the true efficacy and safety profile of a medicinal product are drawn from estimated effects in confirmatory clinical trials. A clinical trial protocol and analysis plan

Sample questions: Definition and development of Estimands

- What is an Estimand and what should an Estimand statement be based on?

- The ICH Concept Paper provides example Estimands:
  - (Difference in) mean outcome improvement for all randomised participants
  - (Difference in) outcome improvement in those who adhere to treatment

  Can a generic set of Estimand be developed or will each study require a different set of Estimands? What would be the common Estimand statements from an efficacy and safety perspective?

  - By Therapeutic Area
    - Does Oncology have unique and interesting problems?
  - By stage of study
    - POC studies important to assess if a compound is active and has a treatment effect
    - Efficacy vs Effectiveness

- What Estimands are needed for decision making?

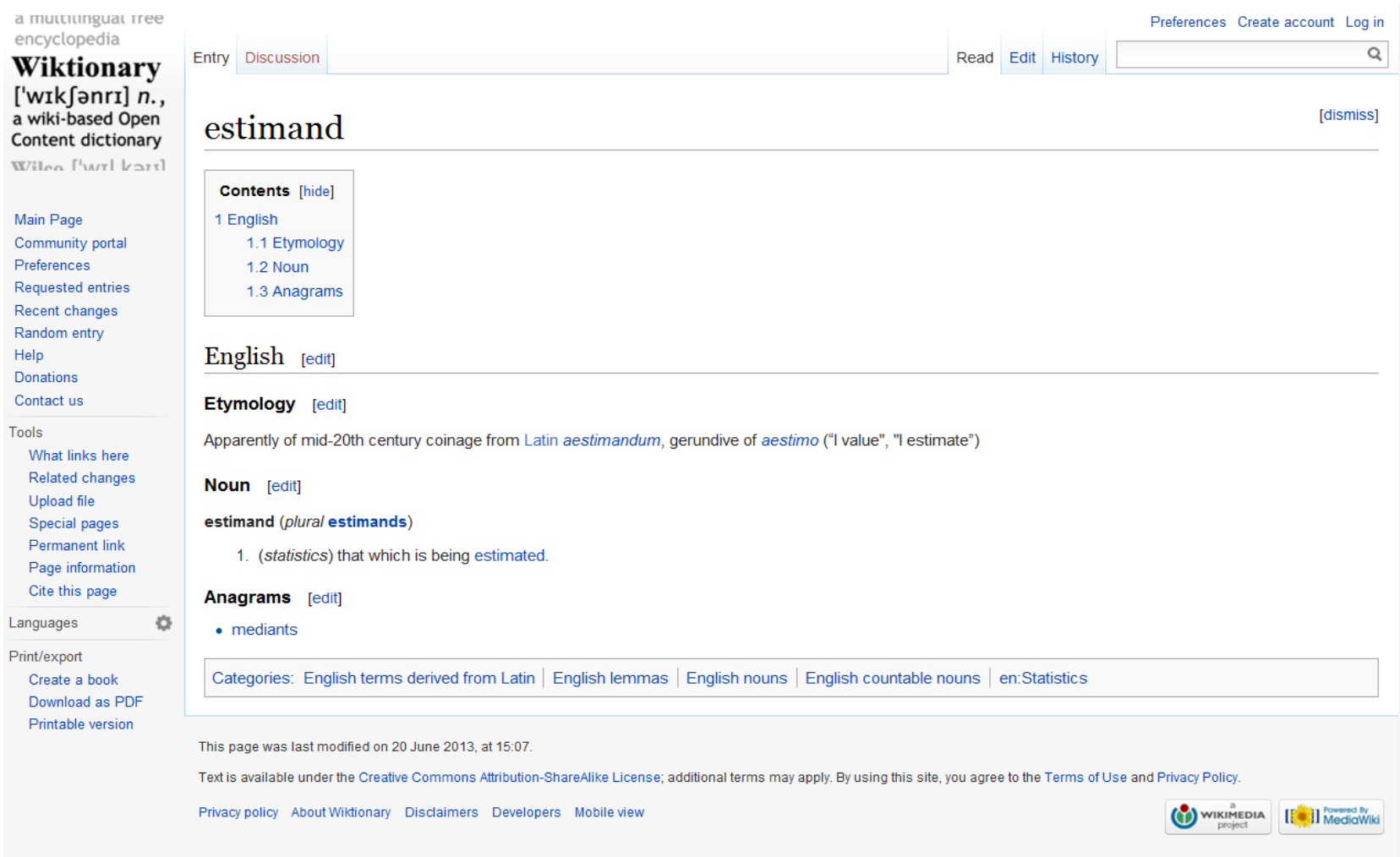
Sample questions: Implementation

- What level of detail relating to the study objectives should be included in any Estimand statement and provided in the protocol and/or the Statistical Analysis Plan?
- How many Estimand statements should be defined per study?
- Should Estimands only be defined for the primary efficacy analysis?
- Should separate Estimands be defined at the integrated level and then be cascaded to individual studies?
- What is the role of sensitivity analyses for a given Estimand? In particular: Which assumptions can be varied within a sensitivity analysis without changing the Estimand?

Sample questions: Education and communication

- What are the advantages and disadvantages of using the proposed Estimand concept when designing clinical trials?
- Are statisticians and non-statisticians on board with the Estimand concept? If not, what needs to happen for the cultural change to be successful since Estimands start with the trial objectives?
- How do you explain Estimands to non-statisticians involved in the drug development process?

Definition



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[dismiss]

estimand

Contents [hide]

1 English
1.1 Etymology
1.2 Noun
1.3 Anagrams

English [edit]

Etymology [edit]

Apparently of mid-20th century coinage from Latin *aestimandum*, gerundive of *aestimo* ("I value", "I estimate")

Noun [edit]

estimand (*plural* **estimands**)

1. (*statistics*) that which is being estimated.

Anagrams [edit]

- mediants

Categories: English terms derived from Latin | English lemmas | English nouns | English countable nouns | en:Statistics

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National Academy of Science Report (2010)

The trial protocol should explicitly define

a) the objective(s) of the trial;
b) the associated primary outcome or outcomes;
c) how, when, and on whom the outcome or outcomes will be measured; and
d) the measures of intervention effects, that is, the causal estimands of primary interest.

These measures should be meaningful for all study participants, and estimable with minimal assumptions.

What is the problem we are trying to solve?

- Frequently study objectives lack of clarity and/or details
  - "….. To compare the efficacy and safety of…."
- Result in misalignment between planned study design and/or statistical methods, and what is required to be estimated for the primary objectives/questions of interest
- The assumptions being made in the analysis are not clear
- Sensitivity analyses supporting the primary analysis for the primary endpoint can also be misaligned to the primary objectives/questions of interest
- Need to improve clarity between objectives and what is planned to be estimated (Estimands)

Definition - Estimand

An Estimand can be thought of as a more detailed objective statement

An Estimand reflects what is to be estimated to address the scientific question of interest posed by a trial.

The choice of an Estimand involves:

- **Population of interest**
- **Endpoint of interest**
- **Measure of intervention effect**

Reference: Bretz Akacha

Definition - Estimand

Population of Interest

- Population for which we are assessing the scientific question of interest
  - Intended post-approval population
- Not to be confused with ‘study population’ or ‘analysis population’

Measure of Intervention of Effect

- Taking into account potential confounding due to post- randomization events, e.g.
  - non-compliance
  - discontinuation of study
  - discontinuation of intervention
  - treatment switching
  - rescue medication
  - death etc.

Case Study

- Randomized, two-arm (drug A and drug B) diabetes trial in patients with type 2 diabetes mellitus (T2DM)
- Endpoint is change of HbA1c levels from baseline after 24 weeks of randomization
- HbA1c levels are measured at baseline and at 4, 8, 12, 16, 24 weeks
- For ethical reasons, patients are switched to rescue medication once their HbA1c values are above a certain threshold
- Regardless of switching to rescue medication all (!) patients are followed up for the whole study duration, i.e.
  - there are no missing observations in this study
    - => Estimand is independent of how missing data are handled
    - Estimating the Estimand in the presence of missing data becomes a technical rather than interpretation question
  - patients never discontinue their study medication, unless they start rescue medication

Case Study: Experience

- Group started with defining the study objectives
  - Comparison of Drug A and Drug B in type 2 Diabetes

- Attention then turned to Estimands and how the study results would be used
  - Support statements targeted at patients, payers or regulators?

- Subsequently the following Estimands were identified; the comparison of
  - (drug A+ rescue) versus (drug B+ rescue)
  - drug A whilst on treatment versus drug B whilst on treatment

- Led the team to iterate back to objectives/study design and ask
  - Was it the response at the end of the study or the average response throughout the study or at end of treatment.

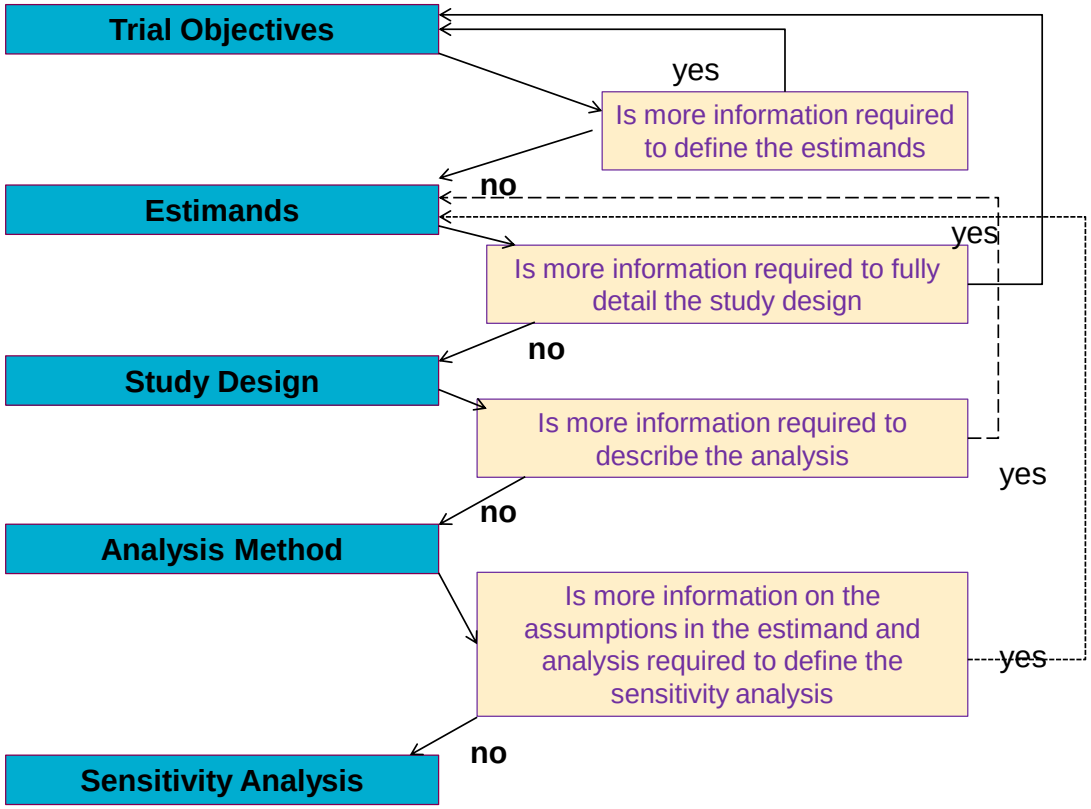
Case Study: Experience

- Indicated a further refinement of the objectives
- Comparison of Drug A and Drug B in type 2 Diabetes but including realistic assessment if patients drop-out of the study; (i.e. ignore rescue medication, but refers to switches of treatment).
- What does ignore rescue medication mean – Estimands can help by detailing how this is handled.
- Illustrates consideration of how Estimands will help to clarify study objectives! And can impact design decisions

Case Study: Learnings

- There are many possible Estimands for a set of objectives
- The selection of the Estimand will be dependent on how the results from the study will be used
  - Support statements targeted at patients, payers or regulators?
- Close examination of proposed Estimand(s) will result in refinement of
  - Study objectives
  - Treatment comparison of interest (e.g. efficacy ‘de jure’ or effectiveness ‘de facto’)
  - Study population
  - Definition of the endpoint, (e.g. end of treatment, or average response)
- Unambiguous wording of Estimands and their associated assumptions is essential for clarity
- Refinement of the objectives may lead to refinement of the study design
  - Data collection post discontinuation of investigational product
  - Definition of treatment for patients who discontinue investigational product
  - Duration of treatment before receiving rescue medication

Proposed Framework



Holzhauer et al (2015) Choice of estimand and analysis methods in diabetes trials with rescue medication

Population	Reflecting post-approval target population
Variable and time point	HbA1c as a measure of average glucose control over the preceding 5-12 weeks assessed after 24 weeks of randomization
Measure of Intervention effect	Treatment difference of the originally assigned treatments at randomisation based on • In case of intake of rescue medication hypothetical values if rescue medication had not been given, because interest is in the treatment assigned at randomisation rather than treatment regimens including rescue medication as needed • In case of discontinuation of study treatment actual off treatment values, because we are interested in the effect of assigned randomised treatment and patients discontinuing treatment, for example, due to an adverse event would not have continued treatment in real clinical practice, either; • For losses to follow up hypothetical values as if patients had continued to take part in the trial including continued intake of randomised treatment

Implications

- Patients are followed up even after study treatment
- Potential Analysis Approaches
- HbA1c
  - Completer analysis
  - Carry forward last pre-rescue value
  - Data after meeting rescue criteria consider Missing At Random
    - Mixed effect repeated measures
    - Multiple imputation
- Other
  - Rescue medication as an outcome
    - Responder analysis
    - Rank-based methods
    - Quantile regression

What do stakeholders want?

Different stakeholders have different objectives so would likely require different estimands for a study; for example

- Regulators
  - How a treatment works whilst the patient takes it
  - Evaluation of different treatment policies
- Payers
  - What would have been the treatment effect if the patient hadn't switched from the randomised treatment
  - How the effect of a treatment varies depending on the order in which it is taken relative to other treatments
- Patients
  - What will happen to me if I start this treatment
  - What will the treatment benefit/risks be if I take all the treatment as directed
- Sponsors
  - Show patients who take their medication as part of a treatment policy benefit.
  - How the treatment works in clinical practice, extrapolating from the clinical trial environment

“De facto” and “de jure” Estimands

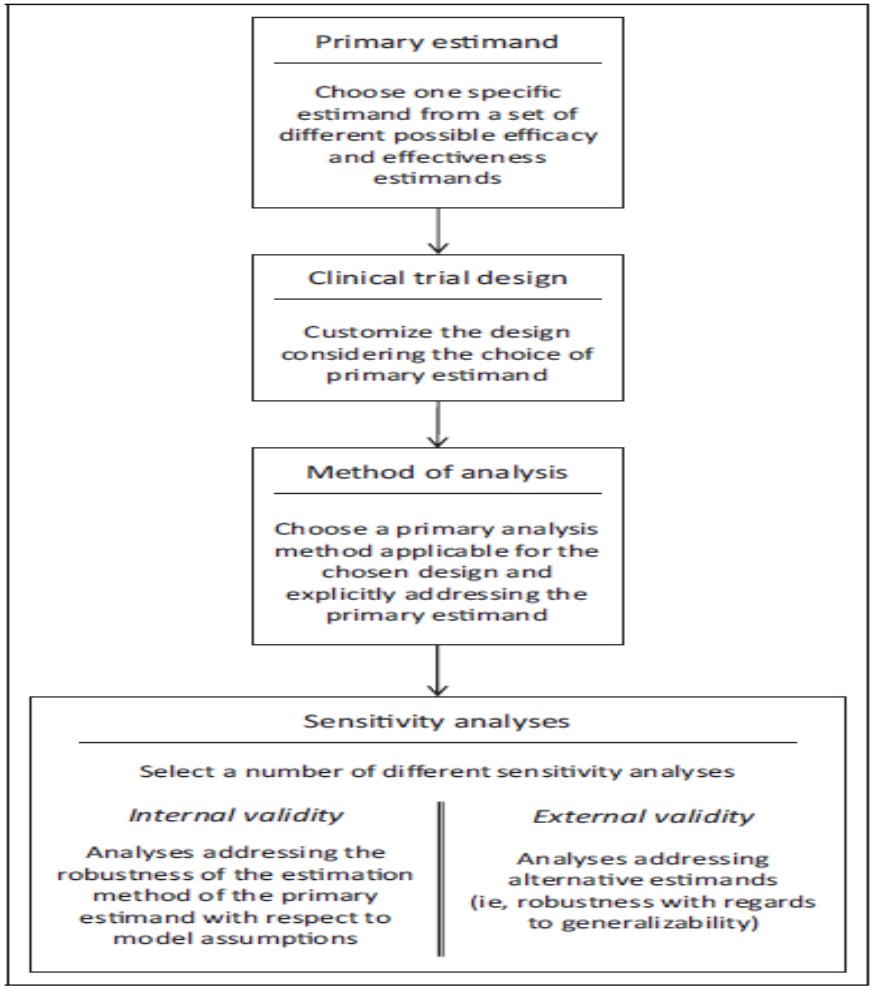
- Some literature discusses
  - ‘de jure’ Estimands
    - Sometimes referred to as ‘efficacy’
  - ‘de facto’ Estimands
    - Sometimes referred to as ‘effectiveness’

- Consensus that “de facto” Estimands should not constitute the sole basis for regulatory decision making for confirmatory trials.

- “De jure” Estimands provide important information to a patient and prescriber on efficacy if the treatment is taken as directed.

- Estimands need to link to the study objectives and/or the decision making process

Sensitivity Analyses



Reference Leuchs et al

Implementation : Sensitivity Analyses

- Sensitivity analyses might estimate the same Estimand or they might estimate different Estimands.
- Is estimating different Estimands a sensitivity analysis?
- Some claim that it is isn't in the true sense of sensitivity.
  - But it may be of direct interest to the researcher.
- One suggestion included “nested sensitivity analyses”

Education and communication

- A cultural change and a new way of thinking will be required.

- To successfully implement both a
  - Pull from the regulators will be required
    - Are starting to demand more rigour
  - Push from informed industry representatives and expert groups
    - To promotes best practise and standards.

- Concern was expressed that ICH E9 may be the wrong place for this addendum
  - ICH E8 may be a better location as there may be expected to be broader readership.

Education and communication

- Study objectives will benefit from being defined more clearly and the Estimands framework allows the inclusion of additional level of detail that will improve understanding clarity and transparency.

- Careful consideration of what data to collect post discontinuation is still needed by all involved in clinical research.
  - After discontinuation data collection may focus only on primary efficacy and safety.
  - However consideration is needed to other data essential to contextualise the primary endpoints and safety eg concomitant therapy, other events.

- Greater understanding and clarity of Estimands is important for interpretation and to provide consistent framework for decision makers

Key Points: Definition of Estimands

- The “problem statement” that Estimands are trying to solve needs to be clearly formulated
  - Estimands are designed to address deficiencies in study design and objectives and their linkage to the primary analysis
  - Provide a consistent framework for decision making

- A workable definition of Estimands is available, but there is a need for an analogous definition for use when defining objectives.

- Estimands are a multi-disciplinary team problem and require understanding and engagement from all disciplines involved in study design, conduct and analysis.
  - Good shared examples would be a beneficial.

Key Points: Implementation

- Agreement that standard Estimands are not required but a framework is required for developing objectives, Estimands, and design.
  - Process flow is; Objectives, Estimands, Study design, Statistical methods, Sensitivity Analyses.
  - An iterative process in that close examination of the Estimands will typically lead to refinement of objectives and study design.

- Clinical trials are multi-faceted and expensive and it is unrealistic to restrict a study to have a single Estimand.

- Clearly defined Estimands are generally required for label claims. In all protocols there should be a description of how the Estimands address the objective

- Therapeutic guidelines could provide details of specific Estimands for specific design types in that therapeutic area.

Key Points: Sensitivity Analyses

- Leuchs provides a good definition of sensitivity analysis, comprising internal vs external sensitivity analyses.
  - Refined to comparing different estimates of the same parameter (internal) versus comparing estimates of different parameters (external)

- No fixed number of sensitivity analyses is recommended: the sensitivity analyses should provide confidence that the conclusions of the study are robust and it is a matter of judgment in each circumstance as to how many are required.

Key Points: Decision Making and Reporting

- “De facto” Estimands should not constitute the sole basis for decision making in clinical development for confirmatory trials.
- “De jure” Estimands may provide important information to a patient and prescriber on efficacy if the treatment is taken as directed.
- Publications should discuss the assumptions in the selection of the Estimand and clearly identify the Estimands being reported.
- ICH E9 may be the wrong place for this addendum as it was recognised that broader leadership is required to implement these changes in practice.
  - Alternative could be addendum to ICH E3 or E6 instead as this has a broader audience.
- The statistical community need to raise awareness and understanding of the impact of using different Estimands on the interpretation and decision making processes in drug development

Closing Remarks

- A cultural change and a new way of thinking will be required

- No shared understanding of Estimands amongst statisticians
  - Is handling of missing data key or a technicality?
  - Step 1 is to promote a common understanding amongst the statistical community.

- Estimands are a multi-disciplinary team problem.

- To successfully implement both a
  - Pull from the regulators will be required
    - Are starting to demand more rigour
  - Push from informed industry representatives and expert groups
    - To promotes best practise and standards.