How to Document Estimands

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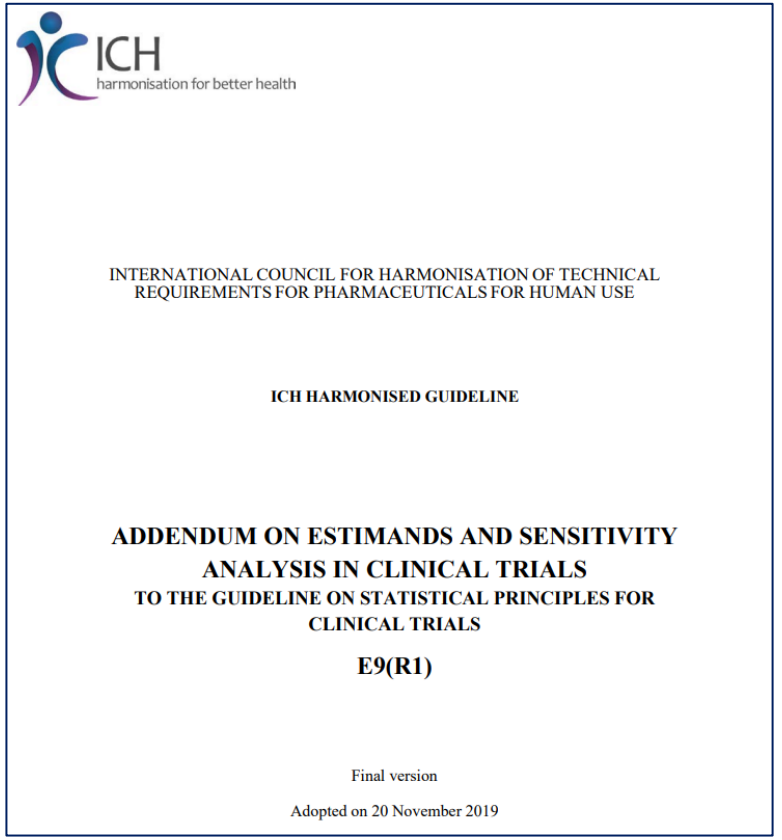
Outline

- Documenting estimands in the trial Protocol
- Documenting estimands in the Statistical Analysis Plan (SAP)
- Trial reporting
- Changes to the estimand during the trial

Documenting estimands - Protocol

- *"A trial protocol should define and specify explicitly a primary estimand that corresponds to the primary trial objective"*

- *"The protocol and the analysis plan should pre-specify the main estimator that is aligned with the primary estimand and leads to the primary analysis, together with a suitable sensitivity analysis to explore the robustness under deviations from its assumptions"*


ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

Final version

Adopted on 20 November 2019

Documenting estimands - Protocol

- *“Estimands for secondary trial objectives (e.g. related to secondary variables) that are likely to support regulatory decisions should also be defined and specified explicitly, each with a corresponding main estimator and a suitable sensitivity analysis”*

- *“Additional exploratory trial objectives may be considered for exploratory purposes, leading to additional estimands.”*

Documenting estimands - Protocol

- ICH E9(R1) does not mandate where in the protocol estimands should be described

- Nor how estimands should be described

Transcelerate protocol template

- Available from:

https://www.transceleratebiopharmainc.com/assets/clinical-content-reuse-solutions/

High-level description

Table of Contents

Transcelerate protocol template

Estimands:

- It is recommended that objectives and endpoints be presented together in a table (see example) to ensure all endpoints are aligned with an objective. Further, it is recommended to include the definition(s) of the estimands below the table.

Objectives	Endpoints
Primary	
•	•
Secondary	
•	•
[Tertiary/Exploratory/Other]	
•	•

[Primary estimand / coprimary estimands / Multiple primary estimands]

<Start of example text>

The primary clinical question of interest is:

What is the [population-level summary] in [endpoint] in [patients with [condition/disease]/individuals] treated with intervention X vs. intervention Y regardless of discontinuation of investigational intervention for any reason and regardless of initiation of rescue medication or change in background medication (dose and product)?

The estimand is described by the following attributes:

- *Population:*

  [patients with [condition/disease]/individuals]
- *Endpoint:*

  change from baseline to [timepoint] in [health measurement/outcome]
- *Treatment condition:*

  the investigational interventions regardless of discontinuation for any reason, with or without rescue medication or change in background medication (treatment policy strategy).
- *Remaining intercurrent events:*

  The intercurrent events "intervention discontinuation for any reason" and "initiation of rescue medication or change in background medication (dose and product)" are addressed by the treatment condition of interest attribute. There are no remaining intercurrent events anticipated at this time.
- *Population-level summary:*

  difference in mean changes between treatment conditions

Rationale for estimand: [rationale].

Example - protocol

The primary clinical question of interest is:

What is the mean difference in the change from baseline in EASI at week 12 in patients with severe chronic eczema (as defined by trial inclusion/exclusion criteria) treated with biologic compared to placebo (150mg e.o.w) **regardless of** discontinuation of investigational intervention for any reason or initiation of rescue medication or topical therapy.

Example - protocol

The primary clinical question of interest is:

> What is the mean difference in the change from baseline in EASI at week 12 in patients with severe chronic eczema (as defined by trial inclusion/exclusion criteria) treated with biologic compared to placebo (150mg e.o.w) **regardless of** discontinuation of investigational intervention for any reason or initiation of rescue medication or topical therapy.

The estimand is described by the following attributes:

- **Population:** patients with severe chronic eczema (as defined by trial inclusion/exclusion criteria)
- **Endpoint:** change from baseline in EASI at week 12
- **Treatment condition:** biologic compared to placebo (150mg e.o.w) regardless of discontinuation for any reason or rescue medication or topical therapies (**treatment policy strategy**).
- **Remaining intercurrent events:** The intercurrent events "intervention discontinuation for any reason" and "initiation of rescue medication" and "initiation of topical therapies" are addressed by the treatment condition of interest attribute. There are no remaining intercurrent events anticipated at this time.
- **Population-level summary:** Difference in mean changes between treatment conditions

Rationale for estimand: To compare biologic against placebo as would be observed in routine practice.

Transcelerate protocol template

Secondary estimand(s)

<Start of example text>

The clinical question of interest is for the secondary objective [label]:

What is the difference in the proportion of [patients with [condition/disease]/individuals] achieving [response criterion] where discontinuation of investigational intervention for any reason is considered to be a failure (non-response) treated with intervention X vs. intervention Y regardless of initiation of any additional rescue intervention, such as [medication/surgery/behavioral]?

The estimand is described by the following attributes:

- *Population:*

  Patients with [condition/disease]

- *Endpoint:*

  Achievement of [rescue criterion], where discontinuation of investigational intervention for any reason is considered to be a failure (composite strategy)

- *Treatment condition:*

  The investigational interventions with or without any other any additional rescue intervention, such as [medication/surgery/behavioral] (treatment policy strategy)

- *Remaining intercurrent events:*

  The intercurrent event "discontinuation of investigational intervention for any reason" is addressed by the endpoint attribute using the composite strategy. The intercurrent event "any additional rescue intervention, such as [medication/surgery/behavioral] is addressed by the treatment condition attribute using the treatment policy a strategy. There are no remaining intercurrent events anticipated at this time

- *Population-level summary:*

  Difference in proportion of patients with response

Rationale for estimand: [rationale]

<End of example text>

Documenting estimands - SAP

- Protocol/SAP houses the full details of the planned statistical analyses
- Full details of the planned statistical analyses (including sensitivity analysis) should align with the estimand(s)

Documenting estimands - SAP

- Gamble et al 2017 published *Guidelines for the Content of statistical analysis plans in clinical trials (JAMA)*

- Estimands not in content list (pre ICH E9 R1 publication), but recognised:

  "Key initiatives that may influence SAP content include the addendum to ICH E9 on estimands and sensitivity analyses"

JAMA | Special Communication

Guidelines for the Content of Statistical Analysis Plans in Clinical Trials

Carrol Gamble, PhD; Ashma Krishan, BSc; Deborah Stocken, PhD; Steff Lewis, PhD; Edmund Juszczak, MSc; Caroline Doré, BSc; Paula R. Williamson, PhD; Douglas G. Altman, DSc; Alan Montgomery, PhD; Pilar Lim, PhD; Jesse Berlin, ScD; Stephen Senn, PhD; Simon Day, PhD; Yolanda Barbachano, PhD; Elizabeth Loder, MD, MPH

Documenting estimands - SAP

- More recently Homer et al published *An Early Phase Clinical Trials Extension to the Guidelines for the Content of Statistical Analysis Plans (BMJ, 2022)* https://www.bmj.com/content/bmj/376/bmj-2021-068177.full.pdf

- Includes estimand definition

RESEARCH METHODS AND REPORTING

OPEN ACCESS

Check for updates

Early phase clinical trials extension to guidelines for the content of statistical analysis plans

Victoria Homer,[1] Christina Yap,[2] Simon Bond,[3] Jane Holmes,[4] Deborah Stocken,[5] Katrina Walker,[5] Emily J Robinson,[6] Graham Wheeler,[7] Sarah Brown,[5] Samantha Hinsley,[8] Matthew Schipper,[9] Christopher J Weir,[10] Khadija Rantell,[11] Thomas Prior,[12] Ly-Mee Yu,[13] John Kirkpatrick,[14] Alun Bedding,[14] Carrol Gamble,[15] Piers Gaunt[1]

For numbered affiliations see end of the article

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2022;376:e068177 http://dx.doi.org/10.1136/bmj-2021-068177

Accepted: 10 January 2022

This paper reports guidelines for the content of statistical analysis plans for early phase clinical trials, ensuring specification of the minimum reporting analysis requirements, by detailing extensions (11 new items) and modifications (25 items) to existing guidance after a review by various stakeholders.

trials have implications for all related subsequent clinical trials. As such, these studies must be performed to the highest standards of rigour and quality, to ensure that correct decisions are taken forward.

Historically, phase I clinical trials were conducted without extensive statistical involvement and conformed to rule based designs (eg, the 3+3 design to determine the maximum tolerated dose).[2 3] Recent recommendations propose that phase I studies should use model based designs[4] such as the continual reassessment method,[5-8] or model assisted designs such as a modified toxicity probability interval design.[9] Randomised dose finding phase I clinical trials (eg...

Documenting estimands - SAP

- Estimand definition

  List and describe each primary and secondary estimands including details of:

  Item 26a:
  Treatment (including treatment combinations).

  Item 26b:
  Population.

  Item 26c:
  Variable of interest.

  Item 26d:
  Intercurrent event handling strategy.

  Item 26e:
  Summary measures

Final publication

- No trials in 2020 in 6 leading journal presented full description of the estimand in publication or supplementary information
- 4 attempted but failed to include one or more attribute
- Improvement needed to ensure no room for misinterpretation
- Will be challenging due to restricted word count – make use of supplementary appendix and make sure reference estimand location in main text

Final publication

- Example:

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 18, 2021 VOL. 384 NO. 11

Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

ABSTRACT

BACKGROUND

Obesity is a global health challenge with few pharmacologic options. Whether adults with obesity can achieve weight loss with once-weekly semaglutide at a dose of 2.4 mg as an adjunct to lifestyle intervention has not been confirmed.

METHODS

In this double-blind trial, we enrolled 1961 adults with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition), who did not have diabetes, and randomly assigned them, in a 2:1 ratio, to 68 weeks of treatment with once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or placebo, plus lifestyle intervention. The coprimary end points were the percentage change in body weight and weight reduction of at least 5%. The primary estimand (a precise description of the treatment effect reflecting the objective of the clinical trial) assessed effects regardless of treatment discontinuation or rescue interventions.

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Kushner at Northwestern University Feinberg School of Medicine, 645 N. Michigan Ave., Suite 530, Chicago, IL 60611, or at rkushner@northwestern.edu.

*A complete list of investigators in the STEP 1 trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on February 10, 2021, at NEJM.org.

N Engl J Med 2021;384:989-1002.
DOI: 10.1056/NEJMoa2032183

Statistical analysis

"Two estimands — the treatment policy estimand (traditional intention-to-treat analysis, with effects assessed regardless of treatment discontinuation or rescue intervention) and the trial product estimand (effects assessed if the drug or placebo was taken as intended) — were used to assess treatment efficacy from different perspectives and accounted for intercurrent events and missing data differently, as described previously.[16] All analyses in the statistical hierarchy were based on the primary treatment policy estimand (details on analysis methods are provided in the Supplementary Appendix). All reported results are for the treatment policy estimand, unless stated otherwise."

Changes to estimand

- Unplanned intercurrent events may occur (e.g. COVID-19!)
- Their impact on the estimand should be evaluated
- A change in the primary estimand would usually require a protocol amendment
- Where not possible to amend protocol explain :
  - how the unforeseen intercurrent events were handled in the data analysis and interpretation
  - impact on what the revised analysis estimates versus the pre-specified estimand

Changes to estimand

- If trials impacted by Covid-19 for guidance see….

Estimands and their Estimators for Clinical Trials Impacted by the COVID-19 Pandemic: A Report from the NISS Ingram Olkin Forum Series on Unplanned Clinical Trial Disruptions

Kelly Van Lancker[1, 2], Sergey Tarima[3], Jonathan Bartlett[4], Madeline Bauer[5], Bharani Bharani-Dharan[6], Frank Bretz[7,8], Nancy Flournoy[9], Hege Michiels[2], Camila Olarte Parra[4], James L Rosenberger[10], and Suzie Cro[11]

https://arxiv.org/pdf/2202.03531.pdf

A four-step strategy for handling missing outcome data in randomised trials affected by a pandemic

Suzie Cro, Tim P. Morris, Brennan C. Kahan, Victoria R. Cornelius & James R. Carpenter

BMC Medical Research Methodology **20**, Article number: 208 (2020) | Cite this article

Summary

- Protocol should include:
  - primary estimand definition that corresponds to the primary trial objective
  - the main estimator that is aligned with the primary estimand
  - sensitivity estimator(s) aligned with the primary estimand
  - estimands for secondary trial objectives used for regulatory/other *key* decisions, with a corresponding main estimator & suitable sensitivity analysis
- Transcelerate provides useful protocol template
- Analysis plan (protocol/SAP) should include full details of aligning estimators
- Estimands in final trial report will ensure no room for misinterpretation