Implementation of estimands in Novo Nordisk

Søren Andersen
Helle Lynggaard

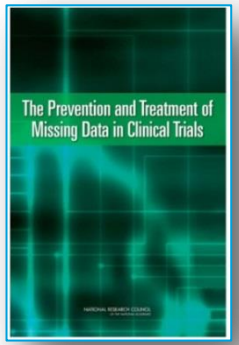
Biostatistics, Novo Nordisk A/S

novo nordisk®

Agenda

- Overview of implementation process
- Cross-functional working group
- Types of estimands used in Novo Nordisk trials
- Impact on process from trial planning to trial results reporting
- Challenges
- After draft ICH E9 (R1) addendum

Overview of implementation process (1 of 2)




ICH
harmonisation for better health

Final Concept Paper
E9(R1): Addendum to Statistical Principles for Clinical Trials
on
Choosing Appropriate Estimands and Defining Sensitivity Analyses 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 focus 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 should include a 'golden thread' linking clear trial objectives with selection and prioritisation of endpoints and hypotheses for statistical testing or targets for estimation. These should, in

2010

2014

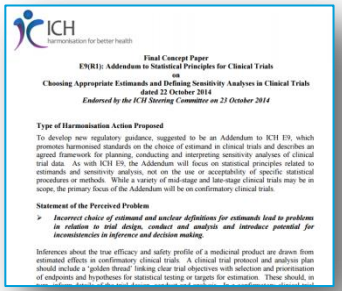
Before 2010: LOCF –
driven by FDA diabetes guideline

After 2010:
FDA no longer accepts LOCF

Novo Nordisk shifts from LOCF to MMRM

NRC: National Research Council, ICH: International Council of Harmonisation, FDA: US Food and Drug Administration
LOCF: last observation carried forward, MMRM: mixed model for repeated measurements

Overview of implementation process (2 of 2)


ICH
harmonisation for better health

Final Concept Paper
E9(R1): Addendum to Statistical Principles for Clinical Trials
on
Choosing Appropriate Estimands and Defining Sensitivity Analyses 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 focus 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.

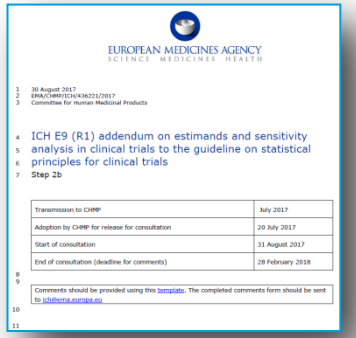
Statement of the Perceived Problem

- ***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 should include a 'golden thread' linking clear trial objectives with selection and prioritisation of endpoints and hypotheses for statistical testing or targets for estimation. These should, in

FDA position papers in Statistics in Medicine, November/December 2015

McEvoy paper October 2015 (FDA stat reviewer for Saxenda®)


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 August 2017
EMA/CHMP/ICH/436221/2017
Committee for Human Medicinal Products

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials
Step 2b

Transmission to CHMP	July 2017
Adoption by CHMP for release for consultation	20 July 2017
Start of consultation	31 August 2017
End of consultation (deadline for comments)	28 February 2018

Comments should be provided using this template. The completed comments form should be sent to ichillema.europa.eu

2014

Saxenda® learnings, approved Dec. 2014
- First project with retrieved data

2015

Regulatory interactions with FDA, EMA, PMDA, Health Canada, CFDA

Novo Nordisk forms cross-functional estimand working group

2016

2017

Biostatistics working group on recommendations for plots and summary tables for different estimands

NRC: National Research Council, ICH: International Council of Harmonisation, FDA: US Food and Drug Administration, EMA: European Medicines Agency, PMDA: Pharmaceuticals and Medical Devices Agency (Japan), CFDA: China Food and Drug Administration

Cross-functional working group

- Representatives from
  - Project Management (1)
  - Regulatory Affairs (2)
  - Medical & Science (2)
  - Biostatistics (5)

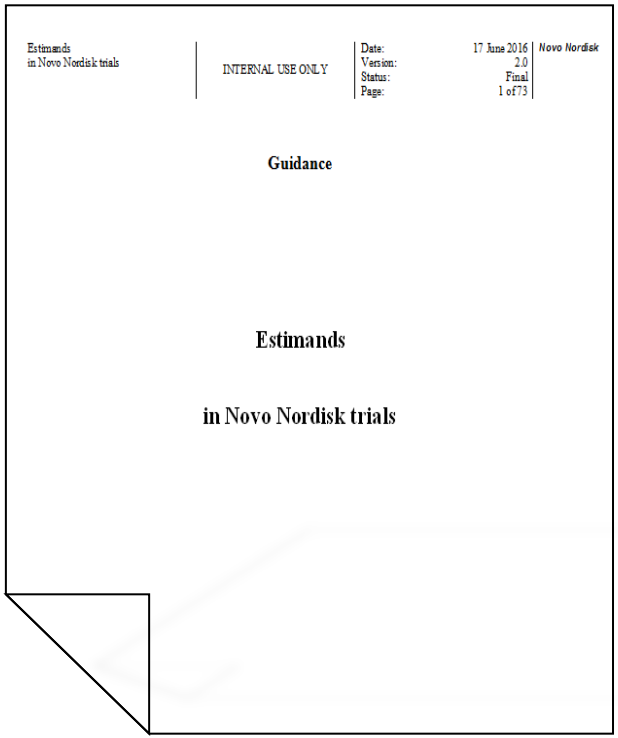
Sources of information

- EFSPI/PSI meetings
- EFPIA workshop (input from clinicians)
- FDA position papers November/December 2015
- Various publications on estimands and imputation of missing data
- Meeting with external statisticians “Advisory Board”, March 2016
  - Scott Emerson (co-author of the NRC report)
  - Jason Connor
  - Ilya Lipkovich (co-author on paper on “attributable” estimand*)

EFSPI: European Federation of Statisticians in the Pharmaceutical Industry, PSI: Promoting Statistical Insights, member of EFSPI
EFPIA: European Federation of Pharmaceutical Industries and Associations, NRC: National Research Council
*A structured approach to choosing estimands and estimators in longitudinal clinical trials. C. H. Mallinckrodt et al. Pharmaceut. Statist. 2012, 11 456–461

novo nordisk®

Deliverable from cross-functional working group



- Current knowledge and recommendations documented in guidance document
  - Terminology
  - Summary of experience
    - Non-inferiority
    - Superiority
    - Placebo/active
  - Feedback from regulatory agencies
- Recommendations endorsed by Novo Nordisk management

Training by working group

- Training of stakeholders involved in trial planning, conduct, analysis and interpretation
  - Medical & Science
  - Biostatistics
  - Clinical Reporting
  - Trial Management
- Other stakeholders
  - Project Management
  - Regulatory Affairs
  - Medical Affairs
  - Market Access

novo nordisk®

Types of estimands used in Novo Nordisk trials

- Until now only one strategy has been used to address all intercurrent events within the estimand description
  - Sensitivity analyses/supplementary analyses has addressed different imputation methods for different intercurrent events
- Based on regulatory feedback we have primarily used/implemented
  - Treatment policy strategy (FDA, PMDA, Health Canada, EMA)
  - Hypothetical strategy (EMA, PMDA, Health Canada, CFDA)
  - Most trials in scope for estimands include both types
- Population-level summary only included in most recent trial protocols
- Estimand generically worded to cover more endpoints

ICH: International Council of Harmonisation, FDA: US Food and Drug Administration, EMA: European Medicines Agency,
PMDA: Pharmaceuticals and Medical Devices Agency (Japan), CFDA: China Food and Drug Administration, NDA: New Drug Application

Impact on trial protocol

- Estimand description is mandatory for therapeutic confirmatory trials and strongly recommended for therapeutic exploratory trials

- Initially, the description of the estimand(s) was included in the statistical section of the trial protocol
  - Now the estimands are described immediately after the trial objectives

Impact on sample size requirements

- Description of anticipated reasons for and proportions of discontinuing trial drug prematurely by treatment group

- Calculation of sample size according to these proportions
  - E.g. by anticipating a worse treatment effect in those who discontinue investigational product prematurely or a better effect in subjects in the placebo group if rescue medication exists

Impact on trial conduct and retention

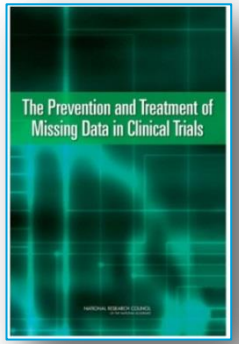
- The repeated request from FDA to respect the ITT principle has lead to increased focus on retention – keep subjects in trial even if discontinuation of trial drug
- Emphasis on importance of minimising extent of missing data - retention central part of training
- The amount of missing data has declined dramatically

Completion rates

Trial type	Trial completion before 2015 (%)	Trial completion after 2015 (%)
Type 1 diabetes	~90	~98
Type 2 diabetes – GLP-1	~80	>90
CVOT	NA	~98
Obesity	~70	>90

CVOT: cardiovascular outcomes trial

Impact on imputation method (1 of 2)




ICH
harmonisation for better health

Final Concept Paper
E9(R1): Addendum to Statistical Principles for Clinical Trials
on
Choosing Appropriate Estimands and Defining Sensitivity Analyses 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 focus 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 should include a 'golden thread' linking clear trial objectives with selection and prioritisation of endpoints and hypotheses for statistical testing or targets for estimation. These should, in

2010 2014

Before 2010:
Primary: LOCF
Sensitivity:
- Completer analysis/PP
  - Non-inferiority
- MMRM

2010-~2015:
Primary: MMRM
Sensitivity:
- reference-based MI,
- Completer analysis/PP
  - Non-inferiority
- LOCF

2015-:
Primary: MI from groups defined by randomised arm, on/off treatment at landmark and timing, if possible
Sensitivity:
- tipping point analysis,
- reference-based MI,
- LOCF

Landmark visit: the visit indicating the time point for the primary assessments, e.g. end-of-treatment
NRC: National Research Council, ICH: International Council of Harmonisation, FDA: US Food and Drug Administration
LOCF: last observation carried forward, PP: per protocol, MMRM: mixed model for repeated measurements, MI: Multiple imputations

novo nordisk®

Impact on imputation method (2 of 2)

- Reference-based MI (unconditional or conditional on observed trajectory)
  - Possibility for rich imputation model
  - Missing data from all visits imputed
- MI from groups defined by randomised arm, treatment status at landmark and timing for discontinuation of treatment
  - The group of similar subjects to impute from may be very small, i.e.
    - Very few missing data and even fewer to return at landmark visit
    - Imputation model should be kept simple to ensure that parameters can be fitted
  - Only missing data at landmark visit imputed
- Responder (binary) endpoints are imputed from the continuous endpoint
  - E.g. HbA1c<7.0% at week 26 is imputed from change from baseline to week 26 in HbA1c

Landmark visit: the visit indicating the time point for the primary assessments, e.g. end-of-treatment
MI: Multiple imputations

Impact on sensitivity analyses

- Aim at explicitly describe assumptions for primary estimator and describe how the sensitivity analyses target these
  - Implicit distinction between sensitivity (aligned to estimand) and supplementary analyse (“other”)

- Tipping point analysis (discussed in the draft ICH E9 (R1) addendum) to address impact of missing data assumptions on results
  - Implemented in the majority of the protocols in scope after 2015

Impact on sub-group analyses

- Impute from overall population and no special imputation from sub-groups
  - Simple and transparent
  - May not always be a satisfactory approach

Impact on non-inferiority trials

- Treatment policy strategy "ITT estimand" consistently requested by FDA
  - problematic for non-inferiority trials – bias towards equivalence
    - Patch: FDA suggested "Koch analysis" – add penalty (non-inferiority margin) to imputed values in investigational treatment arm
    - Novo Nordisk strategy: do not do Koch analysis, but do a tipping point sensitivity analysis
- Different strategies for handling intercurrent events may be relevant for non-inferiority and superiority testing
  - Likely to lead to different point estimates and confidence intervals
  - Complicates shift from non-inferiority to superiority testing
- Draft addendum only briefly discusses non-inferiority
  - Treatment policy strategy carries same concerns as FAS
  - Identify intercurrent events that attenuates treatment effect

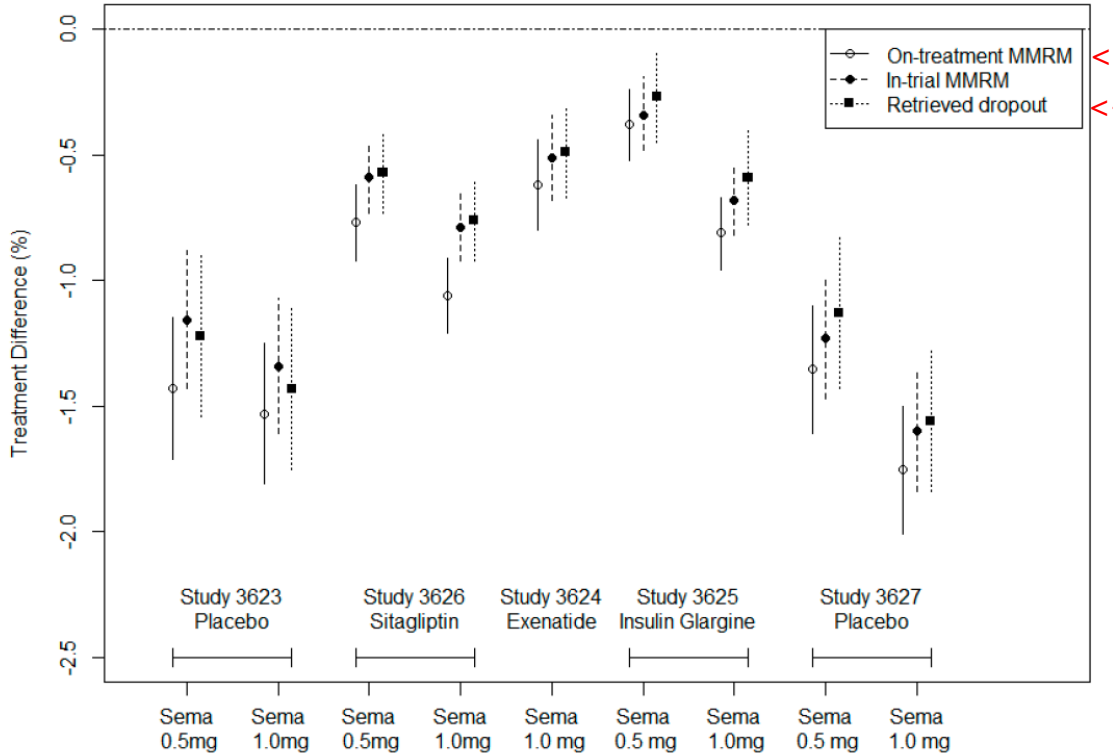
ITT: intention-to-treat, FAS: full analysis set
FDA: US Food and Drug Administration

Impact on plots and summary tables

- In case of more than one estimand (primary and supplemental) the number of tables, figures and listings will grow considerably

- Working group within Biostatistics was formed to align summary tables and figures for different estimands across projects
  - Observed and estimated mean plot over time
    - Impact of imputing only landmark visit
  - Plots illustrating missing data pattern

Impact on effect size – semaglutide s.c. (T2DM)



<-hypothetical

<-treatment policy

s.c.: subcutaneous, T2DM: type 2 diabetes mellitus

Briefing Information for the October 18, 2017 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC), Figure 2, statistical reviewer

Impact on label

- Label supposed to be guidance to prescribing physicians
- "Basis for approval is what comes into the label" (Lisa LaVange, FDA at PSI meeting May 2017)
  - Treatment policy strategy always the most clinically relevant strategy?

FDA: US Food and Drug Administration, PSI: Promoting Statistical Insights

Challenges

- Estimands are still considered to be the responsibility of the statistician by many of our stakeholders
  - How to engage stakeholders?

- Different regulators have different views on which estimand is the most relevant
  - How to conduct multi-regional trials and name one estimand primary?

After draft ICH E9 (R1) addendum

- Other strategies than treatment policy may be relevant and accepted
- Use of different strategies for different intercurrent events
- Very complex estimands – different strategies for different intercurrent events and a much higher number of estimands in protocol
  - Generic wording not possible with population-level summary
  - Trials with primary and a number of supplemental estimands are likely to lead to huge numbers of tables, figures and listings

Selected references

- ICH Expert Working Group (1999) Statistical principles for clinical trials (ICH E9). Statistics in Medicine, 18: 1905-1942.
- Lewis JA. Statistical principles for clinical trials (ICH E9): An introductory note on an international guideline. Statistics in Medicine 1999, 18: 1903-1904.
- EMA (2010), Guideline on Missing Data in Confirmatory Clinical Trials.
- ICH concept paper (2014) E9(R1): Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials
- National Research Council of the National Academies (2010) The Prevention and Treatment of Missing Data in Clinical Trials. Washington, D.C.: National Academies Press.
- A structured approach to choosing estimands and estimators in longitudinal clinical trials. C. H. Mallinckrodt et al. Pharmaceut. Statist. 2012, 11 456–461
- Koch GG. Comments on 'Current issues in non-inferiority trials'. *Statist. Med* 2008; **27**:333-342
- Comments on 'Current issues in non-inferiority trials' by Thomas R. Fleming, Statistics in Medicine, DOI:10.1002/sim.2855. Gary G. Koch. Statist. Med 2008;**27**:333-342
- A regulatory perspective on missing data in the aftermath of the NRC report. LaVange LM and Permuttt T. Stats Med 2015
- A taxonomy of estimands for regulatory clinical trials with discontinuations. Permutt T. Stats Med 2015
- Sensitivity analysis for missing data in regulatory submissions. Permutt T. Stats Med 2015
- McEvoy BW. Missing data in clinical trials for weight management, Journal of Biopharmaceutical Statistics 2016;26(1):30-6
- O'Kelly M & Ratitch B (2014). Clinical trials with missing data: A guide for practitioners. Wiley
- ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (draft, step 2b, 30 August 2017)
- Briefing Information for the October 18, 2017 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC): https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM580460.pdf