Implementation of estimands in Novo Nordisk

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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)

Before 2010: LOCF – driven by FDA diabetes guideline

After 2010:
FDA no longer accepts LOCF

Novo Nordisk shifts from LOCF to MMRM

LOCF: last observation carried forward, MMRM: mixed model for repeated measurements
Overview of implementation process (2 of 2)

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

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

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

Cross-functional working group

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

- EFSP/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 EFSP
EFPIA: European Federation of Pharmaceutical Industries and Associations, NRC: National Research Council
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
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

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

<table>
<thead>
<tr>
<th>Trial type</th>
<th>Trial completion before 2015 (%)</th>
<th>Trial completion after 2015 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 diabetes</td>
<td>~90</td>
<td>~98</td>
</tr>
<tr>
<td>Type 2 diabetes – GLP-1</td>
<td>~80</td>
<td>&gt;90</td>
</tr>
<tr>
<td>CVOT</td>
<td>NA</td>
<td>~98</td>
</tr>
<tr>
<td>Obesity</td>
<td>~70</td>
<td>&gt;90</td>
</tr>
</tbody>
</table>

CVOT: cardiovascular outcomes trial
Impact on imputation method (1 of 2)

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
LOCF: last observation carried forward, PP: per protocol, MMRM: mixed model for repeated measurements, MI: Multiple imputations
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
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)

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?
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

- 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
- A regulatory perspective on missing data in the aftermath of the NRC report. LaVange LM and Permuttt T. Stats Med 2015
- 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):