Regulatory Hot Topics

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Content

• ICH E9 (R1) Addendum on estimands
• Master Protocols (Basket Trials, Umbrella Trials, Platform Trials)
• Draft Reflection Paper on Quality Attributes
Estimands – Regulatory documents

• Guidelines: considerations on estimands have been incorporated in EMA therapeutic guidelines, e.g. Alzheimer’s disease and Diabetes guidelines. Other guidelines are currently under revision and discussions regarding estimands are taking place.

• Scientific Advice: adoption of the framework and its language are increasing. Since not all possible scenarios can be anticipated in the disease specific guidelines, dialogue between sponsors and regulators (i.e. Scientific Advice) will still be necessary.

• Longer term, implementation of the addendum could be envisaged in other regulatory documents, to include discussions/information of the estimand(s) of interest.
Estimands – Guidelines

• Result of a collaborative effort from regulatory clinicians and statisticians and aim at providing clarity for sponsors and applicants on how the estimand framework can help drug development and evaluation.

• The input includes specification of:
  • the most common intercurrent events that can prevent the observation of the variable or affect its interpretation
  • the treatment effect(s) of interest for the specific disease setting
  • the most suitable strategies to address these intercurrent events
  • considerations on the statistical analysis and sensitivity analysis
  • considerations regarding data collection and handling of missing data
Alzheimer’s Disease GL

- Intercurrent events
  - Section 8.1

- Targets of estimation
  - in AD dementia (sec. 8.1.1) and prodromal AD/pre-clinical AD (sec. 8.1.2)

- Statistical considerations
  - Section 11, including statistical analysis, sensitivity analysis and handling of missing data.

Draft Diabetes GL

- Intercurrent events
  - Section 4.2.1

- Targets of estimation, statistical analysis, handling of missing data
  - Section 4.2.2.1
Example - Handling of “use of symptomatic medication” in prodromal AD trials investigating disease-modifying products

Background:

• An investigational drug supposed to slow-down disease progression

• Patients recruited in the prodromal (i.e. pre-dementia) stage, some expected to progress within the duration of the trial

• All drugs available are symptomatic, none is approved in the EU for prodromal AD (but it happens that patients receive some of them in that stage)

• Only one intercurrent event considered: use of symptomatic medication
### Example – Three strategies considered

<table>
<thead>
<tr>
<th>Treatment-policy</th>
<th>Composite</th>
<th>Hypothetical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Population</strong></td>
<td></td>
<td>Patients with prodromal AD</td>
</tr>
<tr>
<td><strong>B. Variable</strong></td>
<td>Change from baseline to 24 months on an endpoint scale</td>
<td>The variable is binary, where treatment failure is defined as occurrence of at least one between (i) change of X points from baseline to 24 months on a composite scale and (ii) use of symptomatic medication</td>
</tr>
<tr>
<td><strong>C. Intercurrent events</strong></td>
<td>Regardless of whether the use of symptomatic medication occurred</td>
<td>The intercurrent event is captured through the variable definition</td>
</tr>
<tr>
<td><strong>D. Population-level</strong></td>
<td>Difference in mean between placebo and active arm</td>
<td>Difference in proportion between placebo and active arm</td>
</tr>
</tbody>
</table>
Why the treatment-policy strategy was not of interest

Few (unrealistic) assumptions for the sake of an argument.

• Within each arm, all patients will have the same decline

• All patients will start a symptomatic medication as soon as they reach a certain threshold

• The symptomatic treatment would provide a small symptomatic improvement to everyone
Why the treatment-policy strategy was not of interest
Why the treatment-policy strategy was not of interest

Value on the composite scale

The threshold that triggers use of symptomatic medication
Why the treatment-policy strategy was not of interest

Value on the composite scale vs. time (months)

The threshold that triggers use of symptomatic medication

Investigational
Why the treatment-policy strategy was not of interest

- The threshold that triggers use of symptomatic medication.
  - Investigational
  - Placebo + Symptomatic medication

Value on the composite scale

Time (months)
Master protocols - Becoming a hot topic for EU regulatory statisticians

• Master Protocols:
  • Basket Trials
  • Umbrella Trials
  • Platform Trials

• Several subtrials, defined by several target populations (biomarkers, indications, tumour histologies), under a common protocol
Master protocols – Experience so far

- Increasing number of requests for Scientific Advice on master protocols trials
- Approval of Keytruda in all Microsatellite Instability (MSI)-High solid tumours in the USA
- It is fundamental to react to this and start developing “a regulatory view” to answer to this new paradigm
- EMA’s Site and Histology Independent Indications Workshop in December 2017
- Biostatistics Working Party has a dedicated task force regarding that topic
- Oncology Working Party is currently revising the Anticancer guideline and is planning to include this topic with the assistance of the Biostatistics Working Party
# Master protocols – Definitions

<table>
<thead>
<tr>
<th>Type of Trial</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbrella</td>
<td>To study multiple targeted therapies in the context of a single disease</td>
</tr>
<tr>
<td>Basket</td>
<td>To study a single targeted therapy in the context of multiple diseases or disease subtypes</td>
</tr>
<tr>
<td>Platform</td>
<td>To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm</td>
</tr>
</tbody>
</table>
Master protocols – Terminology not so clear

- Example: NCI Match Study
  - Allocate patients based on tumour profiles
  - Enrol patients with different tumour entities
- Woodcock & LaVange (NEJM, 2017): Umbrella Trial

- Define the trial constitutive elements rather than put a label on the design
Master protocols – Trial constitutive elements

• Rationale for master protocol (combined study vs a series of studies)
• Phase of study (exploratory vs confirmatory)
• Dependent vs independent sub-studies
• Pooled analysis vs separate analyses
• Common indication vs separate indications
• Adaptive design (adaptive vs fixed design; pre-specified vs ad-hoc; type of adaptations)
Master protocols – Type I error control

• No multiplicity adjustment is required if the subtrials are essentially independent trials, each testing a different, independent hypothesis.

• Multiplicity adjustment is required if the subtrials test dependent hypotheses

• Consistent with current guidance on multiplicity adjustment, that requires strong FWER control only within a trial

• Independence is as:
  - no overlap of patients (e.g. no switching from one subtrial to the other)
  - no overlap of treatment (randomization occurs within a given subtrial)
  - no decision taken for one trial can impact the other ones (e.g. early stop for efficacy)
  - the only common points boil down to logistic/ethic/legal aspects
Master protocols – Further topics to be considered

- Sharing control arm
- Overlapping target populations
- Pooling subtrials
Data requirements for approval of a medicinal product versus its biosimilar
Comparison of Quality Attributes

- Min-max
- X-Sigma ($\mu \pm x\sigma$)
- Tolerance intervals
- Equivalence tests for means
Reflection Paper on statistical methodology for the comparative assessment of quality attributes in drug development (Draft)

Draft paper on statistical methodology for the comparative assessment of quality attributes in drug development

Interdisciplinary effort (BSWP, BWP, BMWP, QWP, PKWP)

Published for 1-year public consultation on 1 April 2017

Deadline for comments: 31 March 2018

Related workshop held on 3-4 May 2018

EMA/CHMP/138502/2017
# Reflection paper - Objectives

## Areas of interest
- Pre- and post-manufacturing change
- Biosimilar development
- Generic development

## Scope
- Focus on methodological aspects
- Raise open issues from statistical perspective
- Address questions related to:
  - Objectives of comparisons
  - Sampling strategies
  - Sources of variability
  - Options for statistical inference and acceptance ranges

## Aim
- Establish a common language
- Improve understanding among experts from various disciplines
- **Trigger discussion** vs. impose rules
- Discuss likely limitations hampering statistical inference
- Point out meaningful ways forward
Discussion of methodological considerations

- Objective
- Metric describing differences
- Sources of variability
- Quantification of uncertainty
- Choice of characteristic
- Unit of observation
- Sampling strategy
- Definition & justification of acceptance ranges
Sources of variability and definition of acceptance ranges

- Anticipating/identifying (un)important sources of variability
- Between batch (e.g. site, scale, age, starting material)
- Within batch (e.g. circadian effects, duration)
- Within sample (e.g. assay, preparation, storage)
- Within assay (e.g. measurement error, accuracy)

- Should be defined a priori and independent of sample data
- Conceptually different to statistical intervals derived from actual sample data
- Understanding the operating characteristics
Workshop

- Objective:
  - Discussing comments received during public consultation phase
  - Better understanding challenges seen by industry and opportunities (e.g. illustrated by case studies)
- 1.5 day, 5 sessions, scientific multidisciplinary discussion
- Main topics discussed:
  - Importance of operating characteristics
  - Terminology (e.g. descriptive vs inferential; consistent manufacturing)
  - Shifts and drifts in reference and impact on equivalence test of means
What happens next?

Strengthen the newly emerging multidisciplinary interaction

Finalising workshop report and publication of documents

Creation of a multidisciplinary task force to address comments received and taking them into account for the finalisation of the draft reflection paper

Further implications on other guidelines in areas of interest to be discussed