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Health Products Regulatory Authority

Regulatory update on estimands: learnings, planned guideline updates, recommendations, and asks for industry

Finbarr Leacy PhD CStat, *Health Products Regulatory Authority*

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Webinar 2: Estimands – emerging questions now that we are using the framework
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Speaker Introduction

- Biostatistician/Statistical Assessor at the Health Products Regulatory Authority in Dublin, Ireland
- Alternate member, EMA CHMP Scientific Advice Working Party
- Member, EMA CHMP Biostatistics Working Party

Disclaimer

The views expressed in this presentation are my own personal views and do not necessarily reflect those of the HPRA or EMA.

Introduction

- ICH E9 (R1) was adopted by CHMP in January 2020 and came into effect on 30 July 2020.
- Substantial and growing experience with the framework at EMA level (SAWP, BSWP, CHMP)
- Increasing engagement with the framework at NCA level
- Application of the framework to new, previously unforeseen, scenarios, e.g. COVID-19 pandemic

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Experience to date

Experience at assessment stage – overview

- "Early adopter" applications providing valuable assessment experiences at NCA and EMA level
- Challenges arising in transitional period with respect to studies designed and initiated prior to adoption of addendum
- Knowledge and experience of estimand framework among (clinical) assessors differs across the EU network
- Greater engagement between statistical assessors and clinical assessors indicated

Experience at assessment stage – common issues

- Variability in how estimand is captured in the protocol and SAP
  - ICH M11 should help
- Intercurrent events (IEs) not described in a comprehensive or systematic manner
  - additional relevant IEs often identified by assessment teams, resulting in requests for additional analysis
- Misunderstandings in distinguishing between IEs and missing data, e.g. study withdrawal

Experience at assessment stage – common issues

- Rationale underlying primary estimand definitions for primary and secondary endpoints not provided, e.g.
  - default use of treatment policy strategy for all IEs
  - same estimand definition used for all endpoints

- Rationale for choice of estimands reported in SmPC section 5.1 not provided
  - will not necessarily be the primary estimand

Experience at scientific advice stage – overview

- Estimands are a frequent topic of advice and discussion
- Level of engagement with the estimand framework has varied across therapeutic areas, e.g. lower engagement in oncology
- Missed opportunities to reframe (non-typical) problems using estimand language

Experience at scientific advice stage – common issues

- Common issues impacting quality of advice that can be provided:
  - IEs not described in a systematic or comprehensive way
  - Incomplete description of treatments to be compared
  - IEs not captured at sufficiently granular level, e.g. short term vs long-term use of rescue medication
  - Rationale for a particular strategy for handling IE not provided
  - Same strategy used for all IEs uncritically

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Impact of the COVID-19 pandemic

Methodological implications for ongoing trials

- Points to Consider document first published 25 March 2020

- Explicit statements about utility of the estimand framework introduced in Revision 1 (29 June 2020):

  "The estimand framework provides a comprehensive approach to articulate this impact analysis."

Methodological implications for ongoing trials

- Limited number of requests reviewed by SAWP to date
  - Issues more often related to missing data handling due to missed assessments than IEs such as treatment interruption
- IEs should not be attributed to the pandemic uncritically
- Hypothetical strategy for pandemic-related IEs may (often) be justified but should not be used uncritically
- Changes to (primary) estimand definitions require strong scientific justification
- Importance of systematically capturing deviations and recording related reasons is evident

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Future developments

Potential guideline updates and developments

- Continue to support implementation of estimand framework in therapeutic area guidelines:
  - Finalised: Alzheimer's Disease, Crohn's Disease, Ulcerative Colitis
  - Public consultation: Diabetes Mellitus, Epileptic Disorders

- Opportunity to formalise and elaborate on advice for handling of intercurrent events already implicit in many guidelines

Potential guideline updates and developments

- Better align existing methodological guidelines with estimand framework:
  - Guideline on Missing Data in Confirmatory Clinical Trials
  - Guideline on the Choice of the Non-inferiority Margin
  - Points to Consider on Switching between Non-inferiority and Superiority

Potential guideline updates and developments

- Opportunities to embed estimand framework in discussions on use of Real World Evidence:
  - Guideline on registry-based studies (under public consultation)
  - HMA-EMA Joint Big Data Steering Group work plan outputs

Other topics

- Reporting of estimands in Product Information and EPAR
  - engagement with HCPs on what should be reported in SmPC
  - finding the right balance between what is reported in the SmPC and EPAR
- Novel intercurrent event strategies and/or statistical methodology
- Application to time-to-event endpoints
- Application to novel trial designs

Conclusions

- Full potential of the estimand framework can be realised through strong implementation and engagement activities.
- A promising start, but a long journey ahead.
- Not only a task for statisticians – engaging and motivating our clinical colleagues will be key!

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Thank you.