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

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

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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
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
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
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!
Thank you.