How the estimand framework becomes standard practice in applications, and where we still need to learn

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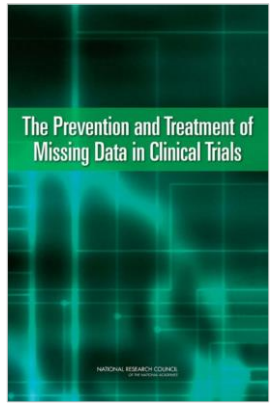
Disclaimer

The views expressed in this presentations are those of the speakers and are not necessarily those of the MHRA, EMA or ICH E9(R1) Expert Working Group.

Background on estimands and why they are important

National Research Council (NRC) published a report on the prevention and treatment of missing data in clinical trials

trial protocol should define 'the measure of intervention effects…'



Draft ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trial was published

Final Addendum and revised training material to be published on ICH website

2010 | **Oct 2014** | **Aug 2017** | **Aug 2018** | **Sep/Oct 2019**


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.***

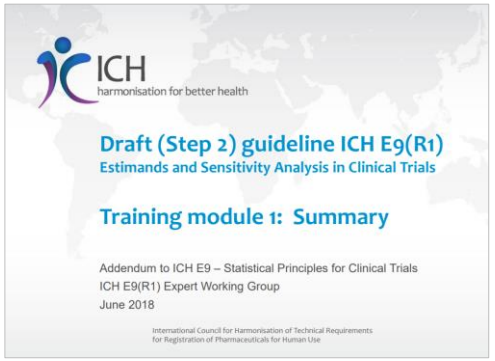
Inferences about the true efficacy and safety profile of a medicinal product are drawn from estimated effects in confirmatory clinical trials. A clinical trial protocol and analysis plan should include a 'golden thread' linking clear trial objectives with selection and prioritisation of endpoints and hypotheses for statistical testing or targets for estimation. These should, in turn, inform details of the trial design, conduct and analysis. In a confirmatory clinical trial data are collected to measure outcomes that quantify the impact of one or more experimental interventions in comparison to a control group, typically over a defined period of time, or until a sufficient number of clinical outcome events have occurred. The trialist is trying to formulate an appropriate and well-defined measure of treatment effect in terms of the data that were intended to be collected. This may then be parameterised, for example to "compare experimental drug X and placebo in terms of improving endpoint Y at time Z for all randomised patients, without regarding adherence to randomised treatment" or to "compare experimental drug X and placebo in terms of improving endpoint Y at time Z for all randomised patients if all patients had remained in the trial and received treatment as planned without rescue medication until time Z". Controversy and confusion exist on the definition and appropriate selection of an appropriate estimand and these two examples should not be taken as preferences or recommendations. These are presented only as illustrations of ***estimands***: the property that is to be estimated in the context of a scientific question of interest, to stimulate discussion in generating the addendum.

A clear definition of an estimand is important not only so that the analysis can be pre-specified in all main aspects, but also since the choice of estimand is linked to important considerations around trial design, conduct and analysis. These include, for example, duration of patient follow-up, adherence to randomised treatment, use of alternative

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICH Secretariat, Chemin Louis-Dunant 15, P.O. Box 195, 1211 Geneva 20, Switzerland

ICH E9(R1) Concept paper, proposing harmonised standards on the choice of estimand in clinical trials and describe an agreed framework for planning, conducting and interpreting sensitivity analyses of clinical trial data.


ICH harmonisation for better health

Draft (Step 2) guideline ICH E9(R1)
Estimands and Sensitivity Analysis in Clinical Trials

Training module 1: Summary

Addendum to ICH E9 – Statistical Principles for Clinical Trials
ICH E9(R1) Expert Working Group
June 2018

International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Training material slide decks published on ICH website

ICH E9(R1) addendum – key messages

- To **properly inform decision making** by pharmaceutical companies, regulators, patients, physicians and other stakeholders, **clear descriptions of the benefits and risks of a treatment** for a given medical condition are necessary.
- The description of an estimand should reflect the clinical question of interest in respect to **intercurrent events (IEs). This is facilitated by the estimand framework, which introduces strategies** to reflect different questions of interest.
- The **statistical analysis** of clinical trial data must be **aligned to the estimand** and should be **subject to sensitivity analysis.** Supplementary analysis may also be useful.
- The framework introduces other **treatment effects not aligned to the ITT principle**, and points to consider for the **design and analysis of trials** to estimate these effects

ICH E9(R1) addendum – key messages

- The addendum **distinguishes treatment discontinuation from study withdrawal** (and IEs from missing data). The **handling of missing data must be aligned to the chosen estimand**.
- **The role and choice of sensitivity analysis is clarified:**
  - Interpretation of trial results should focus on the main estimator for each agreed estimand providing that the corresponding estimate is verified to be robust through the **sensitivity analysis**
  - **Sensitivity analysis** are conducted with the intent of exploring **robustness of departures from assumptions** used in the statistical model for the main estimator so that the estimate derived can be reliably interpreted.
  - **Supplementary analysis** are conducted to more fully investigate and understand the trial data

Construction of an estimand (latest version)

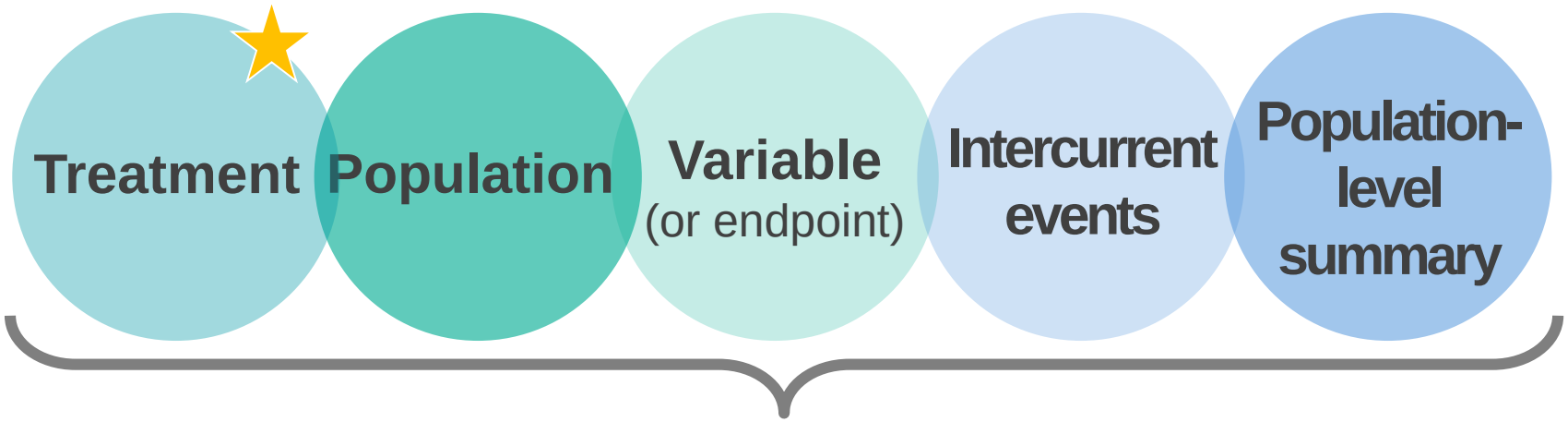
Intercurrent events

Treatment discontinuation, use of additional or alternative treatment, terminal events

Strategies

Treatment policy | Hypothetical | Composite | While on treatment | Principal stratum

Attributes

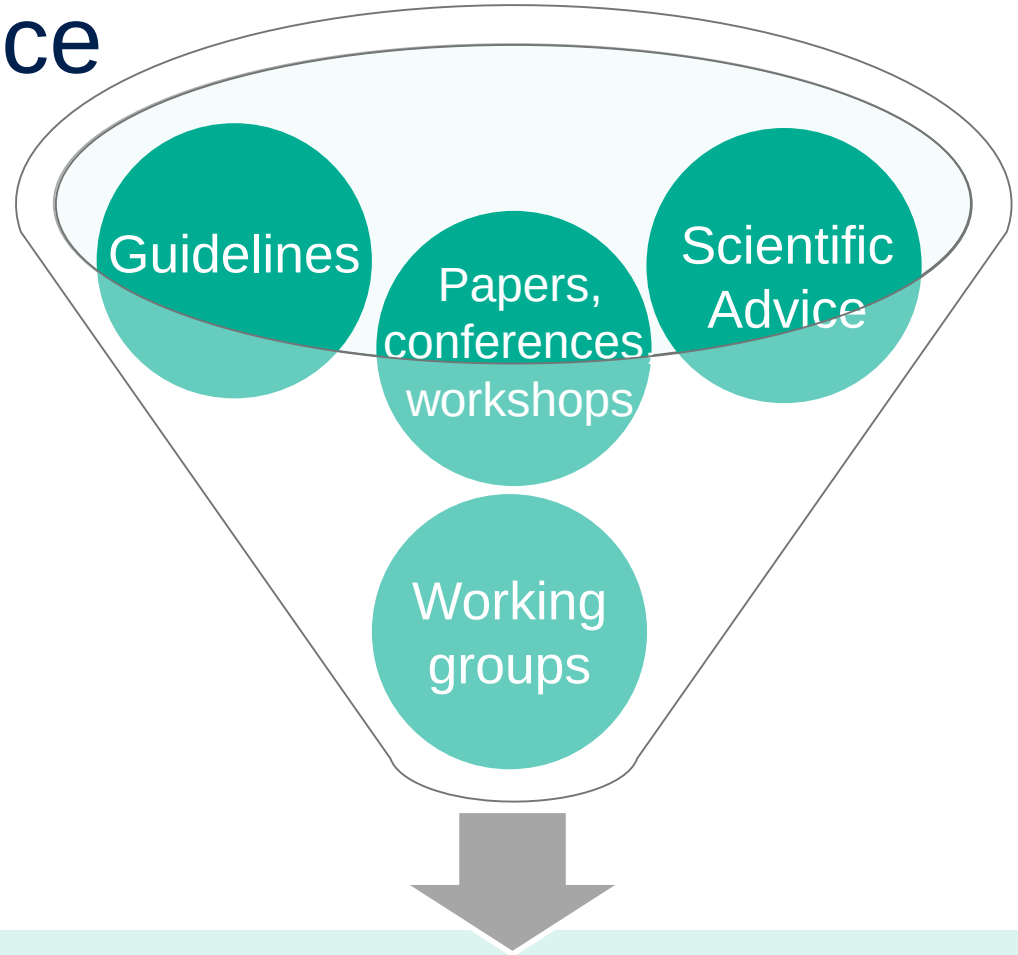


ESTIMAND

Target of estimation, intercurrent events and missing data

- The treatment effect of interest is defined in a way that **determines both the population** of subjects to be included in the estimation of that treatment effect and **the observations from each subject to be included in the analysis** considering **the occurrence of intercurrent events.**
- **Five strategies** of handling intercurrent events when defining the scientific question of interest are described in the ICH E9 (R1), e.g. a treatment strategy would lead to incorporating observed efficacy data after discontinuation
- **A missing data problem** (i.e. data not collected) need **to be addressed in the statistical analysis,** using methods to address the missing data problem that is aligned with the chosen estimand.

Becoming standard practice in the regulatory setting



Guidelines: E9 (R1) Addendum (and training material) and EMA Scientific Guidelines

Scientific Advice: National and Centralised

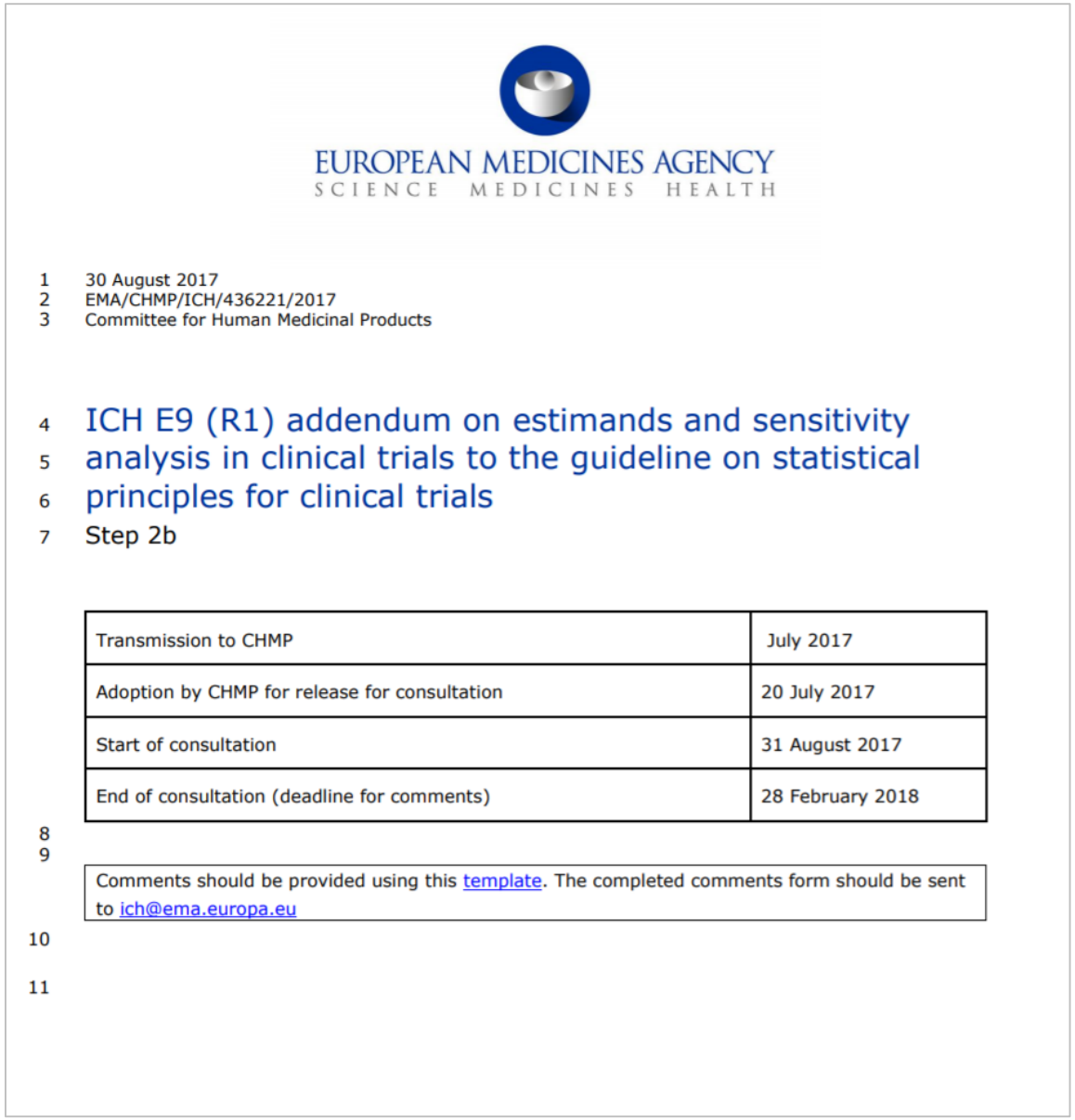
Articles, conferences, workshops: e.g. PSI, FDA-ASCO workshop

Industry working groups: e.g. EFSPI's Estimands in Oncology Applications Special Interest Group

Clear communication of results to facilitate decision making

MAA assessments and EPARs using estimand terminology to describe treatment effect precisely

The ICH E9(R1) Draft addendum



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 ich@ema.europa.eu

CHMP guidance documents referring to the estimand framework

Therapeutic area guidelines

- Alzheimer's disease
- Diabetes (Draft GL)
- Ulcerative Colitis & Crohn's disease
- Epileptic disorders
- Pain
- (…)

Concept papers

- Acute kidney injury

Reflection papers

- Chronic non-infectious liver diseases (PBC, PSC, NASH)

Questions and answers

- Adjustment for cross-over in oncology trials

Available at the EMA website

Scientific Advice (SA)

We performed a search for the word “estimand” in final advice letters during the period 2013-2018. We identified 41 centralised SA and 15 national (UK) SA where the word estimand was mentioned.

Prior to 2017, the word estimand was generally mentioned in relation to the estimate of treatment effect based on **MMRM model**, specifically in relation to inference based on **MAR assumption** when there is differential drop-out between treatment groups.

MMRM model provides estimate of treatment effect that **assumes that all patients completed treatment.**

Examples of questions

1. The **estimand of interest** is the difference in change from baseline in disease activity between treatment groups, as measured by the primary outcome variable at 52 weeks. The primary analysis will be based on adjusted logistic regression with **missing data imputed as failures**.
2. The primary efficacy analysis would be conducted in **an on-treatment fashion** (i.e. only counting on-treatment events and on-treatment follow-up in the primary analysis) based on negative binomial. In sensitivity analyses an **ITT estimand** will also be considered using all observed data for all patients and **imputing missing data using jump-to-control** for those that discontinued due to adverse events, tolerability or lack of efficacy, while imputing under a **missing at random assumption** for all other patients with missing data
3. The **target estimand** is the treatment effect that results in **all patients do not take rescue medication and adhere to treatment**. The primary efficacy endpoint is the change in the primary outcome variable from Baseline to Week 28. **Missing data will be imputed using LOCF**.
4. Does the Agency agree with the proposed statistical methods for the Phase III clinical studies, including the following approaches for: controlling Type I error and for using an efficacy **estimand as the primary analyses for all efficacy variables?**

Composite strategy: example

Scenario: randomised, double-blind, placebo control trial. Primary analysis based on mITT population.

The proposed targeted estimand: the difference between treatment X and placebo in the proportion of patients achieving a response (according to the pre-defined criteria) at 12 months in the target population (defined by the inclusion/exclusion criteria), **regardless of treatment non-compliance, treatment discontinuation or rescue**. **Missing data will be imputed using LOCF**.

Issues:

- **patients without postbaseline data should be treated as non-responders**
- **A treatment-policy strategy is not of primary interest in this disease setting**
- **The relevant target estimand should be based on composite strategy i.e.**

The difference between X and placebo in the proportion of patients achieving response (according to the pre-defined criteria) at month 12 in the target population remaining on treatment who have not taken rescue medication.

Distinguishing IEs and missing data: example

Information provided by the Company for the Scientific Advice:

Drug: Drug X, investigated for the symptomatic treatment

Setting: degenerative disease Y

Endpoints: change in score ABC

Description of the estimand

Population: adults diagnosed with disease X; exclusion criteria: patients intolerant to the drug, with underlying CV severe disease, and psychiatric illness

Variable: Score ABC measured every 4 months for a period of 24 months

Population-level summary: difference from baseline until month 24 in score ABC between investigational treatment and placebo

Distinguishing IEs and missing data: example

Intercurrent event	Strategy	Intercurrent event	Strategy
Missed trial visit due to symptomatic disease crisis	The rate of this event will be minimised in the trial design with telephone follow up. ITT to be used.	Missing score ABC data due to deterioration	This will occur frequently; analysis strategy will depend on whether the decline has been recorded in the score or not. Hypothetical strategy will be used.
Missed trial visit due to side effect	Likely to be rare because side effects are more likely to lead to treatment discontinuation. ITT will be used.	Starting a disease modifying treatment	It is expected that the majority of the patients will already be on this treatment, but it is expected that 15% will start it during the trial; handled using ITT.
Missing data due to efficacy	This will be rare, so ITT will be used.	Missing data due to death before end of follow-up	Death is a competing risk for measurement of the score. The scores up to that time will reflect poor condition. MAR assumption is reasonable, and ITT will be used.

Distinguishing IEs and missing data: example

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Not intercurrent events!

Not missing data!

Estimands in MAAs – EPAR for Segluromet

Estimand

"The estimand for all of the primary hypotheses was the difference in mean A1C improvement at the primary timepoint, in the target population defined by the inclusion / exclusion criteria, if all subjects adhered to therapy without use of rescue medication."

Population

Variable (or endpoint)

Intercurrent events

Population-level summary

Segluromet

INN: ertugliflozin / metformin hydrochloride

Indication: Type 2 diabetes mellitus, as adjunct to diet and exercise

Analysis

Primary analysis: constrained LDA (cLDA) model, with no explicit imputation of missing data

Missing data handling: data after use of rescue is censored

Sensitivity analysis: Tipping-point analysis and jump-to-reference multiple-imputation (J2R)

Supplementary analysis: efficacy analysis including data after the start of rescue therapy

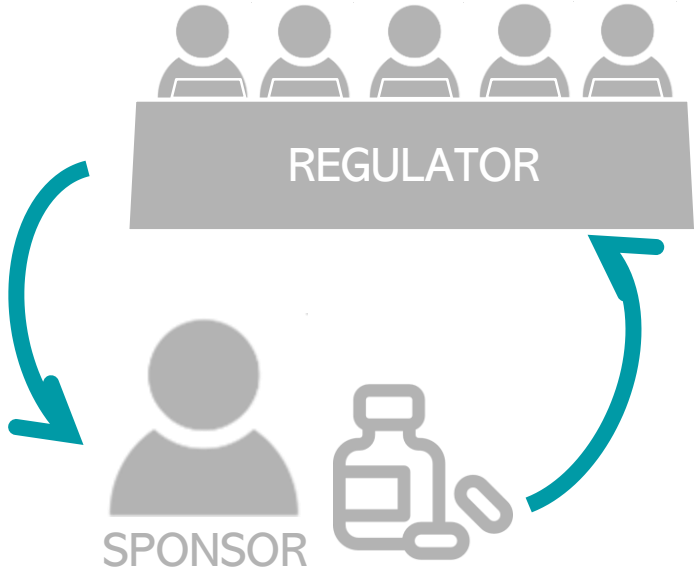
Articles, conferences, workshops…

Where we are now

There is evidence of **increased dialogue between sponsors and regulators,** and discussions outside the regulatory setting (conferences, workshops), on the estimand framework (**WHAT** and **HOW** questions).

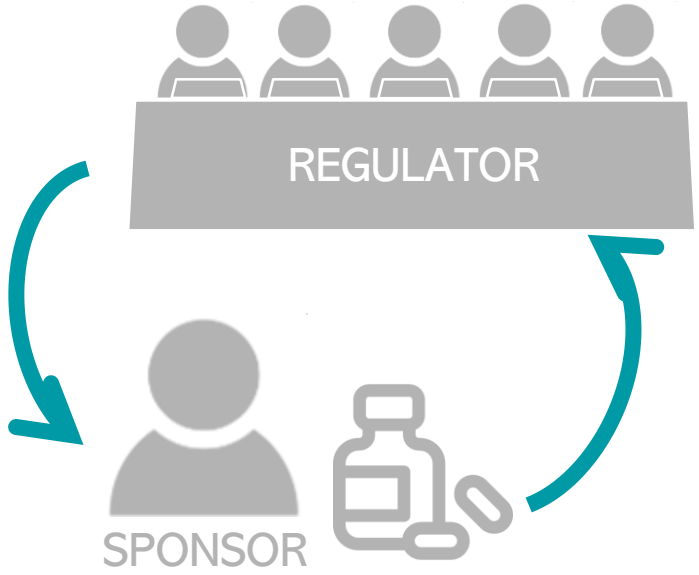
There is a greater understanding of the following:

- The relevance of different strategies in **different disease settings** and depending on **trial objectives**
- **Intercurrent events vs missing data**
- The importance of **collecting all the necessary data** to estimate all the relevant estimands
- Role of **sensitivity** and **supplementary analysis**
- Role of **analysis sets**
- Concept being extended to **safety evaluations**



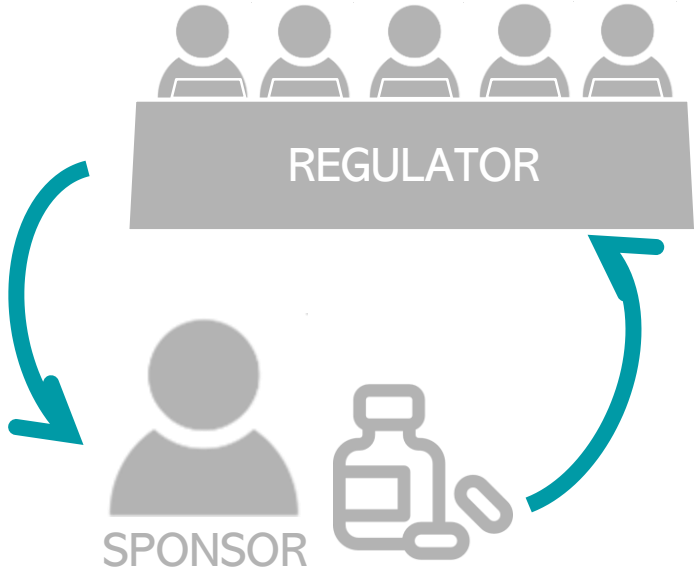
Where we still need to learn

- **Distinguishing missing data from intercurrent events** can still be a challenging task
- How to deal with different strategies being used for **multiple intercurrent events within the same estimand**
- There is still some confusion between **principal stratum strategy** for handling IE and subgroup analysis
- Also, between **while on treatment estimand** and LOCF for imputing missing data
- There is still some uncertainty on the **role of sensitivity** analysis and **supplementary analysis**



Recommendations to improve standard practice

- **Early dialogue with regulators** helps to establish early on which strategies will be relevant for regulatory decision making in a specific setting, avoiding complications at the assessment stage;
- **It is important to** :
  - Ensure that **all potential intercurrent events have been identified** and **the relevant data** for the estimands defined **is being collected**.
  - Consider if the **analysis methods** proposed to estimate the estimands are appropriate, including **handling of missing data and sensitivity and supplementary analyses**
  - Carefully consider which information needs to be **pre-specified in the protocol**
  - Adhere to **specific guidance** where applicable; where there is no guidance available, **consult regulators**



Going forward… learning in progress!

How we will react to strategies not covered in the ICH E9(R1)?

How to deal with the other (more complicated) strategies than composite and treatment policy?

Death is still a difficult IE to deal with

What is the future role of analysis populations, e.g. in equivalence trials?

More experience of application of the estimand framework to time-to-event endpoints is needed

Need to connect the estimand framework with innovative trial designs

Estimands are not (just) a statistical problem!

Thank you!

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Acknowledgments: MHRA colleagues, ICH E9(R1) Expert Working Group, EFSPI Scientific Committee, other contributors to the Estimand session