Estimands

EFPIA webinar

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Why estimands?

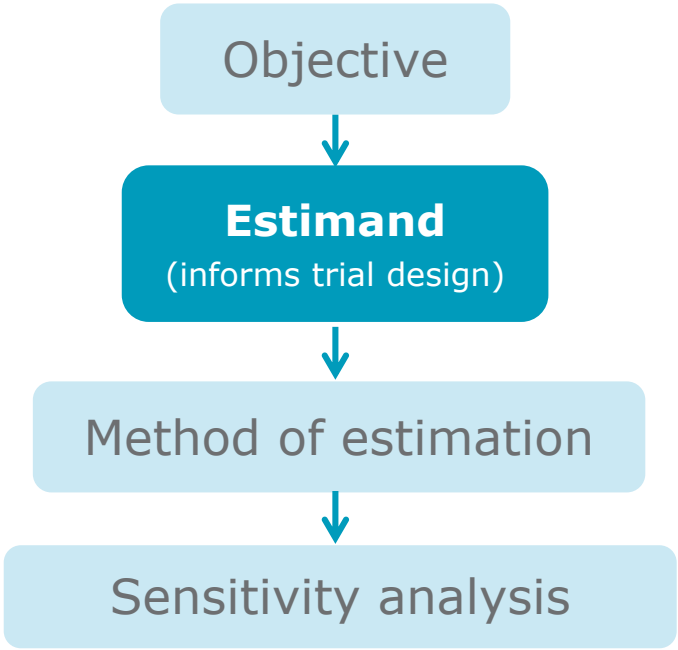
- To explain **which** treatment effect is described to prescribers and other stakeholders.
- To align objectives with (design and) analysis
- To improve conversations about current practice
- To enhance communication and understanding between disciplines
- Potentially, to describe treatment effects that are more relevant to prescribers and patients.

The ICH Expert Working Group

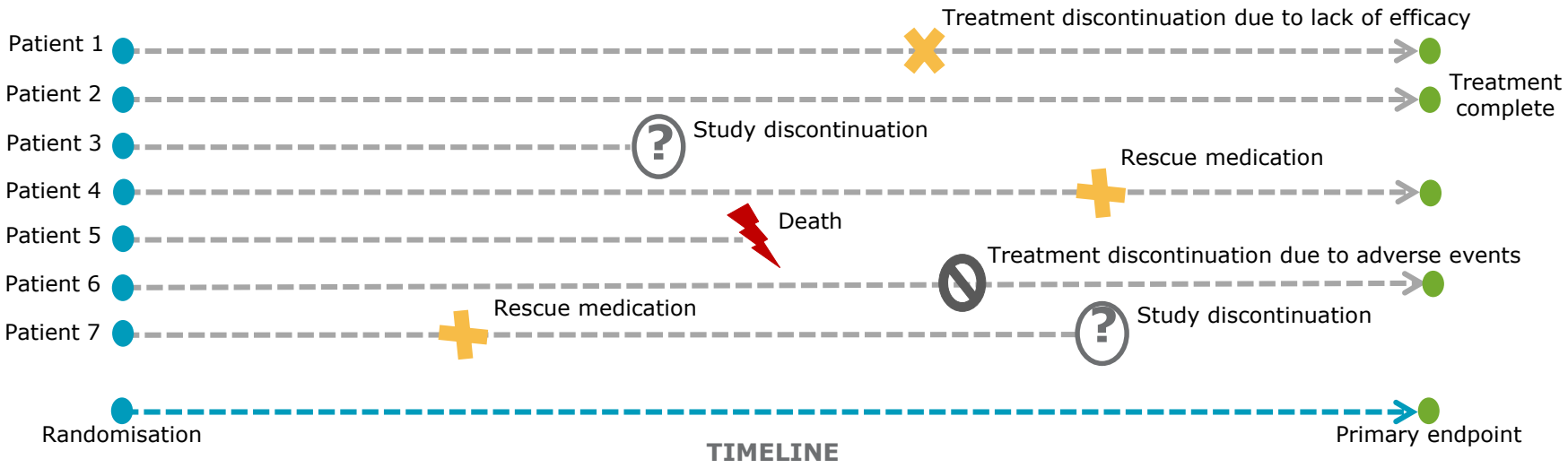
- Draft guideline addendum released for consultation
- Training materials in development
- Please use to ‘champion’ the topic

E9(R1) addendum - framework

- Description of estimand → selection of method of estimation.
  - Main estimator → estimate of treatment effect.
- Assumptions underpin main estimator
  - Deviations from assumptions → sensitivity analyses;
  - Sensitivity estimators still relate to the same estimand.



E9(R1) addendum – intercurrent events



- Challenges in defining and hence in estimating a treatment effect

E9(R1) addendum – intercurrent events

- Intercurrent events: Events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation.
- e.g. use of a rescue medication, a medication prohibited by the protocol or a subsequent line of therapy, discontinuation of treatment, treatment switching and terminal events such as, in some circumstances, death.

- NOT 'missing data'

E9(R1) addendum - strategies

- Strategies:
  - Treatment-policy
  - Composite
  - Hypothetical
  - Principal stratum
  - While on treatment

- One strategy for each type of intercurrent event

E9(R1) addendum - experience

- Increasing use at SAWP
- Evidence of ‘better’ conversations
- Regulatory policies not yet established
- Some interesting questions arise…

Real examples

- Example 1: Palliation in terminally ill cancer patients

  (based on work/slides by Rob Hemmings, MHRA)
- Example 2: Treatment of chronic pain

  (based on work/slides by Francesca Callegari, Novartis)
- Example 3: Using principal stratification

  (based on work/slides by Baldur Magnusson, Novartis)

Example 1 – Background (simplified)

- Consider a new Drug X for palliation in terminally ill cancer patients. Symptomatic treatment a priori not expected to beneficially or detrimentally effect mortality.
- Response on body weight and functioning are assessed after 12 weeks
- Scientific question of interest concerns the comparison in a randomized trial of Drug X to placebo.
- Some patients will die during the 12-week follow-up. This is the intercurrent event.
- Anti-cancer therapy used as background therapy in both treatment groups.

Example 1 – No intercurrent events

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval

B. **Variable**: change from baseline after 12 weeks

C. **Intercurrent events**: not expected to occur

D. **Summary measure**: difference in variable means

Unrealistic not to expect any deaths

Example 1 – Treatment policy

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval
B. **Variable**: change from baseline after 12 weeks
C. **Intercurrent events**: Regardless of death
D. **Summary measure**: difference in variable means

How to measure response on body weight and functioning after death?

Example 1 – Composite

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval

B. **Variable**: binary; alive and with maintenance of weight/functioning after 12 weeks

C. **Intercurrent events**: captured through the variable definition

D. **Summary measure**: difference in response proportions

Viable, but is it really a treatment failure if a patient lived reasonably well throughout 11 weeks and then dies?

Example 1 – Hypothetical

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval
B. **Variable**: change from baseline after 12 weeks
C. **Intercurrent events**: had the patient not died
D. **Summary measure**: difference in variable means

How would a hypothetical scenario look like: Would the patient have continued treatment? Or discontinued treatment?

Example 1 – Principal stratum

A. **Population**: defined through subjects alive after 12 weeks, within the targeted population defined by inclusion/exclusion criteria
B. **Variable**: change from baseline after 12 weeks
C. **Intercurrent events**: captured through the population definition
D. **Summary measure**: difference in variable means

Viable, but aren't we intrested in assessing the treatment effect even in those patients who died prior to week 12?

Example 1 – While on treatment

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval
B. **Variable**: area under the curve for weight/functioning while being on randomised treatment
C. **Intercurrent events**: captured through the variable definition
D. **Summary measure**: difference in variable means

Reasonable estimand?

Example 1 – Background (extended)

In reality, three relevant types of intercurrent events may occur:

- death
- change in background anti-cancer medicine;
- use of additional symptomatic medication.

The construction of an estimand should address each intercurrent event that may occur in the clinical trial and that will affect the interpretation of the results of the trial.

Example 2 – Background

- Consider a new Drug X for patients suffering from chronic pain.
  - Includes chronic pain from different etiologies, such as cancer pain, postsurgical or posttraumatic pain, neuropathic pain etc.
- Measured on an 11–point Numerical Rating Scale (NRS) for patient self-reporting of pain
- Scientific question of interest concerns the comparison in a randomized trial of Drug X to placebo
- Some patients will face intercurrent events not leading to study treatment discontinuation, but with potential confounding effects
  - E.g. changes in doses of allowed concomitant medications for pain
- Other patients will face intercurrent events leading to study treatment discontinuation
  - E.g. adverse events, lack of efficacy, use of other concomitant medications or due to other reasons

Example 2 – Scientific question of interest

- Scientific question of interest guiding the primary estimand:

  Estimate the treatment effect of Drug X against placebo for the target population on the primary variable. The treatment effect of interest shall

  - be unconfounded by events which are deemed non-informative, e.g. changes in doses of allowed concomitant medications for pain
  - account for the unfavorable outcome when patients are unable to continue taking the study drug due to an adverse event, lack of efficacy or use of other concomitant medications leading to study treatment discontinuation.

Example 2 – Primary estimand

Key attributes

A. **Population**: Patients suffering from the chronic pain condition at a moderate to severe disease stage. Patients may or may not be already on a concomitant medication for pain.

B. **Variable**: Change from baseline to last week of the study in weekly mean of the 24h average pain score measured by NRS

C. **Intercurrent events**: Events happening post-randomization, which can be an expression of how well the treatment works, but also of its safety and tolerability

D. **Summary measure**: Difference of variable means between Drug X and placebo

Example 2 – Primary estimand

Details on attribute C

We are interested in the treatment effect if patients:

- would not change dose of allowed concomitant medications for pain
- are allowed to take short-acting pain relief medication
- would continue to be treated for the entire study duration unless forced to discontinue treatment due to
  - adverse events (AEs)
  - lack of efficacy (LoE)
  - use of other concomitant medications leading to treatment discontinuation

Example 2 – Primary estimand

Justification

Desire to quantify the treatment effect of the study drug under the situation where:

- any potential confounders are removed, since these could lead to an attenuation or a dilution of the treatment effect of interest
- the drug is taken for the stipulated duration, however
- we cannot ignore the situations when a patient can no longer tolerate or benefit from the treatment (e.g. occurrence of AE, LoE etc), from whom a continuation of treatment would not be conceivable
- other patients who discontinued the drug due to other reasons could have theoretically continued to be treated without being put at undue risk

Example 2 – Further considerations

Statistical analysis

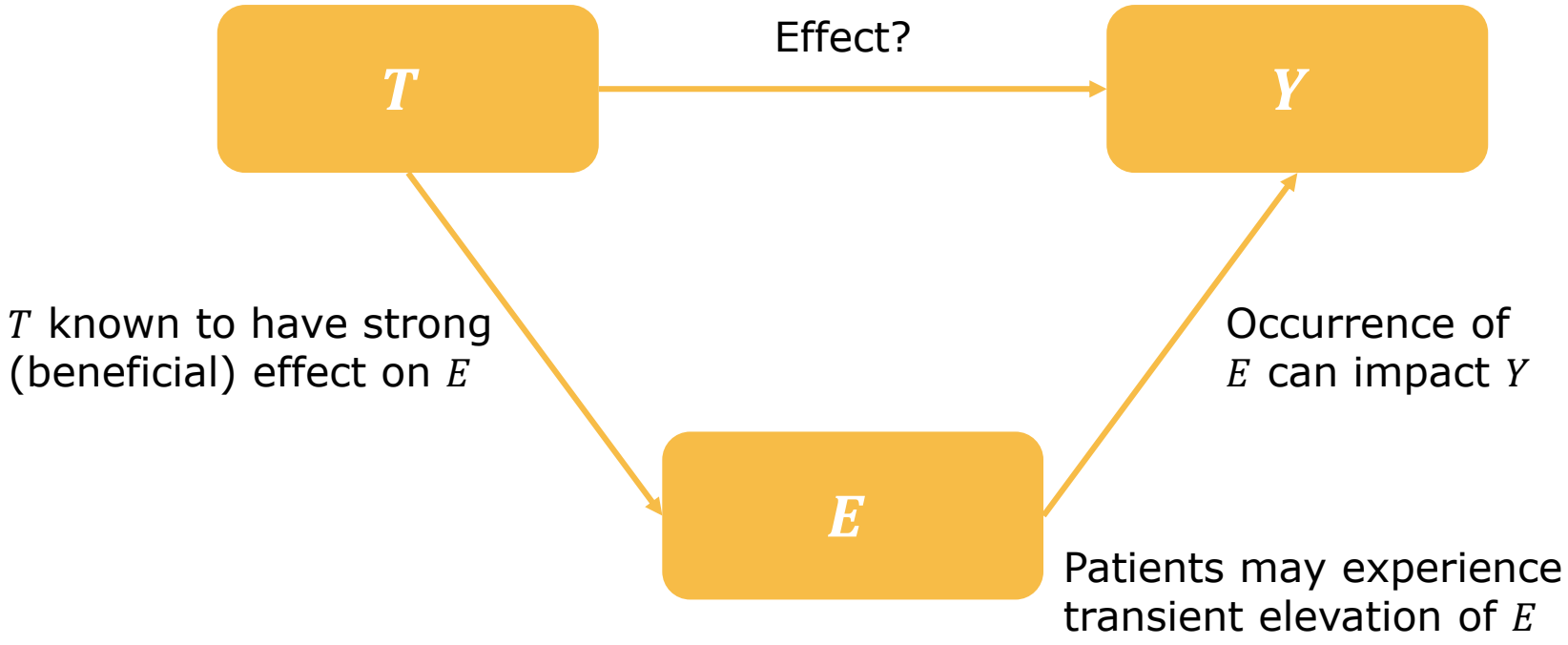
- Primary analysis approach is in line with the primary estimand, including handling of changes in doses of allowed concomitant medication for pain and handling of missing data due to study treatment discontinuation
- Sensitivity analysis targets the same estimand and is specified to assess the robustness of conclusions from the primary analysis
- Supplementary analysis for a broader understanding of the treatment effect

Necessary design features

- Information on changes in dose of allowed concomitant medications for pain
- Retrieved dropouts: data collected after study treatment discontinuation, if available

Example 3 – Background

- Phase III clinical trial where target population is difficult to identify at baseline
- Treatment T, with $T = 1$ for Drug X and $T = 0$ for placebo
- Outcome Y to assess progression of the disease
- Sporadic events E reflecting manifestations of the disease (the intercurrent event)



Example 3 – Scientific question of interest

- Scientific question of interest guiding the primary estimand:

  What is the risk ratio of experiencing Y in the population of patients that would not suffer from E regardless which treatment they receive?

- This is the principal stratum estimand:

  Focus on the treatment effect in the stratum (i.e. subgroup) of patients who would not experience E regardless of treatment assignment

Example 3 – Alternative estimands

As implied by common analyses

- Occurrence of E is irrelevant (treatment policy)
- Effect in the population of patients without pre-study E
  - Not useful if pre-study E is not predictive of on-study E
  - Does not acknowledge the treatment effect on E
- Effect in the population of patients without on-study E
  - Conditions on a post-randomization outcome affected by treatment
  - Estimate of treatment effect on Y would not have a causal interpretation
- Effect in a world where E would not occur
  - Hypothetical estimand since E cannot be intervened on

None of these estimands are appropriate for our situation

Example 3 – Principal stratification

Notation

- Let $E(T) = 1$ for patients who experience E if assigned to $T \in \{0,1\}$
  Likwise, $E(T) = 0$ for patients who do not experience E under T

- Let $Y(T) = 1$ for patients who experience Y if assigned to $T \in \{0,1\}$
  Likwise, $Y(T) = 0$ for patients who do not experience Y under T

- $E(T)$ and $Y(T)$ denote potential outcomes
  - Every patient has a potential outcome under both, $T = 0$ and $T = 1$
  - Only observe one potential outcome per patient

- E and Y denote observed outcomes

Example 3 – Principal stratification

Estimand of interest

- Stratify patients as belonging to one of four disjoint strata
  - E.g. S_{00} denotes the stratum of patients who do not experience E regardless of treatment

$E(0)$ \ $E(1)$	0	1
0	S_{00}	S_{01}
1	S_{10}	S_{11}

- Stratum membership not directly observable
- Observe outcome on actual treatment received
  - E.g. patient on $T = 1$ with $E = 0$ could either belong to S_{00} or S_{10}

- Estimand of interest is given by the risk ratio of Y in S_{00}:

$$\frac{P\left(Y(1) = 1 \middle| S_{00}\right)}{P\left(Y(0) = 1 \middle| S_{00}\right)}$$

Example 3 – Principal stratification

Identifying the estimand

- In practice, only observe the margins from this table
- Need identifying assumptions in order to link estimand to 'observables'

$E(0)$ \ $E(1)$	0	1	Sum
0	??		✓
1	??	??	✓
Sum	✓	✓	

- Monotonicity assumption:

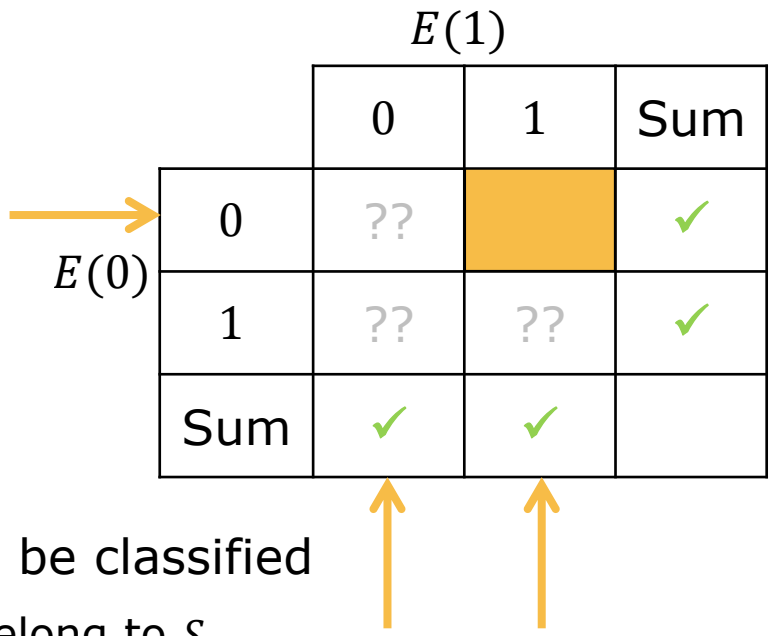
  No patients in S_{01}

  A patient not experiencing E on $T = 0$ (placebo) will not experience E on $T = 1$ (Drug X)

  - This is a substantive assumption that cannot in general be tested with the data, and hence needs strong clinical rationale

Example 3 – Principal stratification

Identifying the estimand



- Monotonicity allows some patients to be classified
  - Placebo patients with $E(0) = 0$ must belong to S_{00}
  - Treated patients with $E(1) = 1$ must belong to S_{11}
- Some patients remain not classifiable
  - Treated patients with $E(1) = 0$ can belong to S_{00} or S_{10}
- We can now estimate the strata proportions:
  - $P(S_{11}) = P(E = 1|T = 1)$, $P(S_{00}) = P(E = 0|T = 0)$, $P(S_{10}) = 1 - P(S_{00}) - P(S_{11})$

Example 3 – Principal stratification

Identifying the estimand

- Recall estimand of interest:

$$\frac{P\left(Y(1)=1\middle|S_{00}\right)}{P\left(Y(0)=1\middle|S_{00}\right)}$$

- Randomization and monotonicity allow us to identify the denominator as the proportion of responders among the placebo patients without E:

$$P\left(Y(0)=1\middle|S_{00}\right)=P(Y=1|T=0,E=0)$$

- Numerator remains not identifiable because $E(1)=0$ could imply S_{00} or S_{10}
- However, bounds on the numerator can be derived, possibly (but not necessarily) based on further assumptions, leading to range of feasible values for the estimand of interest

Example 3 – Principal stratification

Estimation and sensitivity analysis

Inference

- "Straightforward" to estimate parameters in a Bayesian or frequentist framework

Sensitivity analysis

- Partially relax monotonicity assumption
- Explore various (informative) priors if a Bayesian analysis was conducted