HOW TO IGNITE THE ESTIMAND DISCUSSION AND APPLY THE "ESTIMAND" LANGUAGE TO PROS IN CLINICAL TRIALS

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BACKGROUND - ESTIMANDS

> The draft ICH E9 (R1) addendum and its proposed estimands framework is becoming a well-known concept

> The ICH E9 Working Group has produced excellent training slides and extensive information on this topic

> Particularly welcome are examples in different contexts and settings

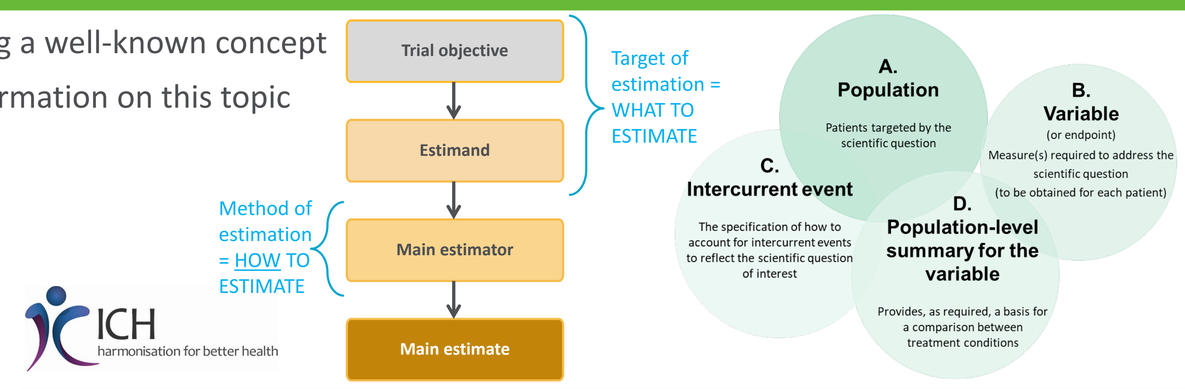
Potential Strategies for handling intercurrent events:

> **Treatment policy:** we are interested in the treatment effect on the variable regardless of the intercurrent event, i.e. the value for the variable is used regardless of whether or not the intercurrent event occurs

> **Composite:** occurrence of the intercurrent event provides relevant information about the treatment effect of interest and, hence, the intercurrent event is included in the endpoint definition

> **Hypothetical**: a scenario is envisaged in which the intercurrent event would not occur, e.g., if patients had not switched treatment or if death had not occurred

> **While on treatment**: we are interested in the response to treatment prior to the occurrence of the intercurrent event, e.g., prior to patient progression and starting new medication



Useful Definitions (as per ICH E9(R1) training)

> **Intercurrent event:** "Events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation" - Common examples of these events are death, treatment discontinuation – but don't confuse with missing data relating to lost to follow-up

> **Missing data** (e.g. lost to follow up) are NOT intercurrent events and are not reflected in the estimand, but instead represent limitations to the data

Taken from ICH E9 Training slides

"TYPICAL" PRO ANALYSIS & HOW TO APPROACH THE ESTIMANDS

> Patient-reported outcome (PRO) measures are commonly used in clinical trials to reflect the patients experience – or the "patient voice"

- They capture information about symptoms and associated impacts as well as more general reflections of overall health-related quality of life (HRQoL)
- Phase III clinical trials may include questionnaires focusing on different aspects of PROs and/or HRQoL

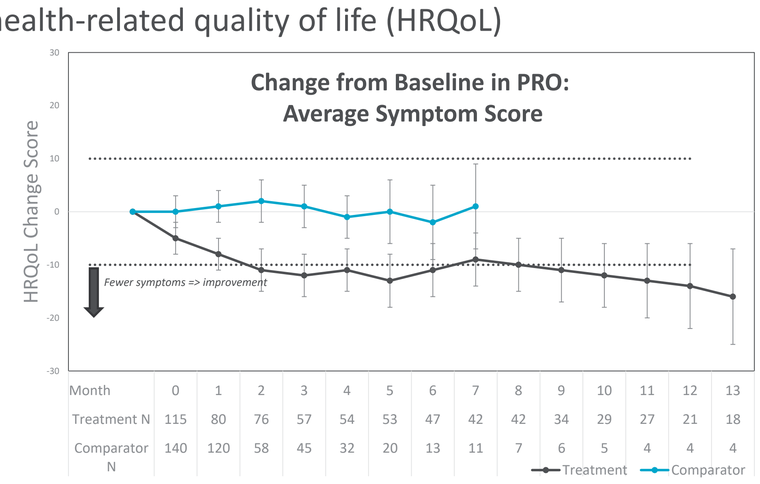
> The figure below illustrates thinking behind a "simple" question when considering longitudinal changes in PROs

> We have selected a timepoint of 6 months as an illustration and to demonstrate how we could potentially construct lots of potential estimands

> We found that this process highlights the thinking process we have applied and the consequences

> Initially we thought it was unlikely that an analysis by a fixed timepoint would be planned – however, in practice this is often what is currently estimated (data driven cut-offs may be used currently).

> The same process to define estimands could be repeated if the question was "while on treatment" or "until disease progression" and it would highlight the different estimands that would need to be considered



POTENTIAL ESTIMANDS FOR CHANGE FROM BASELINE IN PRO SCORE OVER TIME (TO 6 MONTHS)

Naive clinical question: What is between-group difference in PRO-based HRQoL after 6 months?

But what is meant by "after 6 months"?.... is it after 6 months of treatment or regardless of treatment discontinuation?

Treatment policy	Hypothetical	While on treatment
...after 6 months regardless of treatment discontinuation	...after 6 months in absence of treatment discontinuation	... after 6 months or at the time of treatment discontinuation

....and what if patient dies before 6m?

Hypothetical	While on treatment	Hypothetical	While on treatment	Hypothetical	While on treatment
...after 6 months regardless of discontinuation *and if deaths had not occurred*	...after 6 months regardless of discontinuation *or at the time of death*	...after 6 months in absence of discontinuations *and deaths*	...after 6 months in absence of discontinuations *or at the time of death*	... after 6 months or at the time of discontinuation *and if deaths hadn't occurred*	... after 6 months or at the time of discontinuation *or death*
Collect data until month 6 (continue beyond treatment discontinuation)		**Collect data until month 6 or treatment discontinuation, whichever comes first**			

Population: targeted disease population; Variable: PRO Score; Summary measure: difference in means at 6 months

Not all six questions may be clinically relevant - discussion is needed

General analysis considerations for appropriate estimator (mixed model) could be:

> **Treatment policy:** include all data in the analysis, even if after discontinuation
> **Hypothetical:** assume MAR data caused by deaths
> **While on treatment:** for patients with discontinuation before 6m, use all data collected while on treatment. Can carry forward their assessment at the time of discontinuation (although LOCF approaches are not necessarily advised) death

Once a question has been agreed, the process of ensuring the correct analysis method is applied (ie the estimator) needs consideration:

> Assess a single measurement at 6 months
- Simple mean comparison - but what about patients with no data at 6 months?

> Consider all measurements prior to 6 months
- Longitudinal MMRM is often a recommended approach;
- Allows for correlations within subjects over time,
- If saturated model, equal to univariate approach timepoint
- BUT assumes MAR – a hypothetical approach

ESTIMANDS FOR TIME TO EVENT

> For time to deterioration events key intercurrent events are death, progression, and starting new therapy

> Estimand needs to reflect clearly if PRO deterioration represents the only event of interest or a composite strategy should be applied (e.g. time to deterioration or death)

> Decisions for censoring rules need to reflect the estimand chosen (and the strategy for handling intercurrent event

> *One Example estimand: HR for difference in time to PRO-based HRQoL deterioration (first PRO score decrease > 10 points from baseline) or death, irrespective of disease progression*

CONCLUSION

> It is clear that the choice of estimands impacts the protocol and how data is collected – even secondary endpoints

> Statisticians can help others think through objectives and the precise estimand wording by considering timeframes of interest (e.g. fixed time, until disease progression) and possible intercurrent events, and then consider appropriate estimators

> It is important to consider the study question and objective relating to HRQoL, and what intercurrent events may occur and how to handle these in estimand framework, prior to defining an estimator and developing the protocol

Key Reference: ICH E9 Training Material: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1EWG_Modules1-3_Step2_COMPILATION_TrainingMaterial_2018_0703.pdf

Poster Presented at PSI Conference London, June 3rd 2019