EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
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Webinar 4: Proposing Estimands from Different Perspectives Patient, Clinician, Regulator, Health Technology Assessor and Statistician		
Answers to questions from the webinar		
#	**Question**	**Answer**
1	as after treatment initiation, how to intercurrent events compare/contrast to adverse events?	Regarding AEs, an intercurrent event may be treatment discontinuation due to tolerability. Other AEs may lead to taking rescue medication and taking rescue medication could be an intercurrent event. The team should discuss any expected AEs on a case by case basis and consider whether the scenario would affect the interpretation or the existence of the treatment outcome of interest per the research question.
2	How would you handle multiple ICEs occurring at different points in time, e.g patient first uses rescue medication, subsequently discontinues treatment at a later point in time. would you need to define priorities among ICEs?	live answered
3	When you decide on an estimand and strategy, do you use the same estimand and strategy for all endpoints or could they be different?	You may have several estimands for each trial objective and each estimand can use different strategies for handling different intercurrent events, e.g., for the same estimand you could use treatment policy for treatment discontinuation and composite variable strategy for use of rescue medication.
4	The treatment policy seems to be the most applied strategy in phase 3 registration trials. Hence, data should be collected after the ICE. But even with efforts to do that, one might end up with missing assessments after ICE. What are the strategies to handle these missing data? And should different strategies be used for different ICEs?	For a treatment policy approach with missing data after an ICE, methodology using multiple imputation methods such as 'jump to reference', 'copy reference' or 'pattern mixture models' may account for different missing data scenarios. These methods should be pre-specified and in addition sensitivity analyses such as a 'tipping point' analysis can be included to assess the impact of the missing data assumptions. See Reference: https://onlinelibrary.wiley.com/doi/10.1002/pst.2299 Regarding different strategies for handling different ICEs, for each ICE (and reason for the ICE) an evaluation should be made to decide which estimand strategy is most appropriate to address the clinical question of interest. It is possible to use different strategies for different ICEs.
5	will the presentation be available later, for a replay?	live answered
6	What are main concerns when deciding on estimands in Early phase vs Late phase? Oncology vs Biopharma?	The estimand framework can be used for any clinical situation both in early and late Phase and also in Oncology and non-oncology indications. I don't think there are concerns with the use of the estimand framework more opportunities. On saying that the earlier you are in the drug development process the less is known about the drug being studied, this affects the information available on likely intercurrent events.

		Also early studies are shorter and hence less likely to be the occurrences of intercurrent events.
7	Presumably one study can target more than one estimand. Does this create a multiplicity issue and how does one conclude 'trial success'?	Yes multiplicity issues may also arise from having multiple estimands, so you should clearly define your primary and key secondary estimands and make sure to control for type 1 error.
8	Why is treatment discontinuation considered an ICE but study discontinuation is not an ICE? Isn't' treatment discontinuation implied when a subject discontinues a study?	Treatment discontinuation is not necessarily implied when a subject discontinues from a study. For example, for a participant randomized to the standard of care arm if they withdraw from the study they could receive exactly the same standard of care outside of the study. It is also possible for a patient to discontinue treatment but remain in a study and agree to be followed up.
9	Any thoughts on using a hypothetical strategy to estimate ideal efficacy, and explicitly combining that information with e.g. tolerability issues using a utility function approach?	Firstly, note the hypothetical approach is an umbrella terms, there are many different types of possible hypothetical strategies that could be specified. One possible hypothetical strategy would be to evaluate the efficacy of drug A versus drug B in condition X for outcome Y using summary measure Z as though no treatment discontinuation for tolerability issues or lack of efficacy was possible. I would need more details to answer your question about using a utility function approach.
10	I am still confused about the topic at the very beginning that events leading to missing data are always NOT ICEs, since the E9 R1 literally states as first sentence when defining ICES "Intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest."	live answered
11	How do you suggest managing analysis of a trial where a disproportionate amount of pts on the control arm DC and continue in trial on an escalated therapy, eg one >= to IMP therapy	The design (whether it allows for rescue therapy, treatment switching or jumping to an open label extension) and resulting analysis should be aligned to the estimand which in turn is appropriate to the clinical setting. A composite strategy may be useful in considering the endpoint as treatment failure (if treatment is discontinued or switched either due to tolerability of lack of efficacy) and the higher proportion needing rescue and/or to discontinue in the

		control arm should not be a concern with this approach.
12	How can industry get FDA off the strong stance that TP is the only estimand to use for regulatory and labelling decision making?	live answered
13	'@David. Could a regulator be interested in the hypothetical "as if a new treatment was not started or not available" following on from a treatment discontinuation due to tolerability or worsening symptoms?	Yes, this may be of interest for certain indications. For example, the draft EMA Guideline on “clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus”, already appears to suggest an estimand which targets a treatment effect with treatment policy for treatment discontinuation due to tolerability but a hypothetical strategy for rescue medication. It states “the treatment effect can be estimated under the assumption that rescue medication, or use of other medications that will influence HbA1c values, was not introduced (hypothetical scenario), provided that a reliable estimate of that effect can be obtained.”
14	Are these different viewpoints applicable for superiority hypotheses, not necessarily say for non-inferiority? (referring to slide with coloured thumbs-up)	You are correct to highlight that the appropriate strategies are different if the goal is non-inferiority and indeed the treatment policy strategy may be considered to be anti-conservative.
15	So ideal situation for a phase 3 trial is in SAP the primary endpoint/methodology is aimed at regulatory approval (likely ITT population trying to cover full population with perhaps statistical adjustment if possible for ICE) and all other objectives (eg HTA, etc) are catered for in secondary analyses with predefined methods/sub-populations etc to deal with ICEs? Thus everything prespecified - but this placing great burden on SAP - likely not do-able?	live answered

16	Can you provide some examples about how to apply the composite strategy with the KCCQ Total Score at 1 year? Since the endpoint is a score, would you add a penalty for those subjects with tolerability issues?	A binary or ordinal score could be defined based on the level of improvement in KCCQ Total score with treatment discontinuation due to tolerability issues being penalised by assigning the treatment failure category (this is the simplest approach but does lose some information in the score). Alternatively, an unfavourable score should be assigned to patients after treatment discontinuation due to tolerability issues. Alternative ways of choosing unfavourable values are described in Darken et al. paper “The attributable estimand: A new approach to account for intercurrent events” Pharmaceutical Statistics. 2020;19:626–635.
17	From statistician's perspective, do we have all methodology to implement any strategy (e.g., hypothetical or principal stratum) for the not so uncommon ICEs?	Certainly standard methodology (such as MMRM) is a very easy way to estimate a hypothetical estimand. The principal stratum may be best estimated by using a different style of design (e.g. a run-in period or cross-over design); however, for parallel group designs, it is not possible to easily define the stratum (say of those able to tolerate IMP) as not every patient receives the test treatment. So appropriate unbiased analysis is difficult and may require use of multiple imputation approaches to define the stratum based on baseline characteristics.
18	I find it interesting that the *patient's* preferred strategy for handling different ICEs rarely seems to be aligned with the other parties (HTA, Stats, regulator, clinician) viewpoints. Shouldn't the patient's preference have more relevance in the estimand definition?	live answered
19	Can/how can the Principal Stratum strategy be applied in a one armed observational trial?	The principles for applying the principal stratum strategy to a single-arm trial would be expected to be the same as for a randomised controlled trial with a comparator arm. The principal stratum strategy reflects the case when we are interested in estimating the treatment effects in the stratum of patients who "would have a specific status with respect to the ICE (ICE would or would not occur) under one of more treatments in the study" (Mallinckrodt et al, 2020, Estimands, Estimators and Sensitivity Analysis in Clinical trials, CRC Press). In presence of a single arm trial, we may be interested in the treatment effects in the target population of interested, defined as patients who would not use or require rescue medication.
20	Does while on treatment strategy take into account the drug's	Generally this stops when the next treatment is due. However, you might decide to extend this approach for

	residual effect or stops data collection when treatment stops?	safety estimands to look over a period up to x days after the last dose.
20	Does while on treatment strategy take into account the drug's residual effect or stops data collection when treatment stops?	live answered
21	In the example you shared it was Phase III study designed using preliminary data from a Phase II study. Do we apply the estimands framework in Phase I/II studies?	live answered
22	what's the difference between intercurrent illnesses and treatment emergent AEs?	Any medical event occuring during a trial could lead to an intercurrent event, such as use of rescue therapy, dose modification, study treatment discontinuation etc. It is therefore important to understand how potential intercurrent illnessess or Aes may lead to ICEs and that strategies are established for handling these ICEs
23	Where can we find the recorded version?	The recording (and all the Estimand Academy for Trial Teams series) is now available online via the PSI website: https://www.psiweb.org/vod/item/psi-eiwg-webinar-proposing-estimands-from-different-perspectives---patient-clinician-regulator-health-technology-assessor-and-statistician. Recordings in the series are also available on the EFPIA youtube channel also. #1 (General introduction – diabetes) PIONEERing webinar: https://www.youtube.com/watch?v=7sV4Q_PrkIA #2 Oncology webinar: https://www.youtube.com/watch?v=20bviiufm2w #3 (General but with COPD case study) ETHOS webinar: https://www.youtube.com/watch?v=7LJ5RTROQh
23	Where can we find the recorded version?	https://www.psiweb.org/vod/Index/ If you filter the 'Collection' dropdown menu and select 'The Estimands Academy for Trial Teams' at the bottom of the list, that'll bring up the existing webinars.
24	Which is the best approach to be followed when defining the estimand strategy for an phase II CT?, given the main objective of a PII CT is to maximize the likelihood of detecting some efficacy in the molecule.	In this situation a hypothetical approach or while on treatment strategy may be useful to understand the proof of concept. In addition, you may wish to collect useful information to prepare for confirmatory Phase III where potentially you may envisage use of composite or treatment policy estimands.
25	Estimands can often be seen as a statistical topic. Any tips/experience on getting the whole study team engaged in the discussion?	you make a very good point, we have similar experience, we believe that awareness sessions as these seminars, workshops may help to ilustrate the importance of the cross-functional involvement, you could showcase how using different strategies for handling intercurrent events will affect the final

		estimate, and how cross-functional input is needed to define the research question
26	Would you please (one day) try to explore and summarize the topic of possible effects of the mathematized objective of a comparative study (I mean SUPeriority versus EQUivalence/NONINFeriority) on the ICE handling strategies to choose?	The EIWG has a sub-team looking into estimands in non-inferioirity trials
27	alway have difficult to understand why treatment policy is interested? if a patient took rescue meds, why efficacy data after taking rescue meds can be used for investigating the efficacy of the test drug?	The use of a treatment policy strategy is seen as understanding the efficacy and safety of a given technology in a real-world context, thus HTAs and regulators are keen to understand how the clinical and economic benefits of a new technology when it will be used in their respective health care systems. So this includes understanding the benefit and risks of treatment taken after original medicine is stopped or if other treatments are added, collectively this would define the consequence of being prescribed the original treatment.
28	Where there is no standard of care available (for a relatively healthy population and drug is for symptom relief), is it still appropriate to use treatment policy strategy? HTA always request for this strategy. What is the benefit of this strategy in such situations?	There are two distinct aspects to this question: 1) first, Health technologies assessments (HTAs) usually call for the comparative assessment of a new technology versus a given "standard of care" or "appropriate comparator", around a range of patient-relevant endpoints (see for example the internation definition of HTA in O'Rourke et al, 2020 - https://www.cambridge.org/core/journals/international-journal-of-technology-assessment-in-health-care/article/new-definition-of-health-technology-assessment-a-milestone-in-international-collaboration/8A3BA65D279F3FDAA83ADB3D08CF8C17). There are certainly cases (e.g., for orphan drugs) where there are no alternative treatment option available for patients. In these cases, the appropriate comparator for an HTA would be "no treatment". 2) Whether or not there is an established standard of care against which to compare the new health technology should not be seen as an obstacle to using the treatment policy strategy. This strategy calls for the collection of relevant data on a given endpoint irrespective of the occurrence of possible intercurrent events. The treatment policy strategy is seen as reflecting how patients will use a given treatment in a "real-world" context, which is what interests HTA Agencies.

29	For the hypothetical strategy, would it be acceptable to exclude patients having ICEs instead of imputing their missing values	In this particular situation you should rather consider a principal stratum strategy
30	If you have a single-arm observational trial, and your primary estimand uses the treatment policy strategy for IcE, and then as a secondary analysis you are doing a subgroup analysis by presense/absence of the IcE, is that the Principal Stratum strategy for that secondary analysis?	No
31	Is it mandatory to use Estimands in Protocol? How should it be implemented for Safety sections?	Estimands are required in confirmatory trials and highly recomended in other trials. How to apply estimands in safety is a topic of high interest and there are recent publications on the topic
32	In handling treatment discontinuation due to logistic issue with a hypothetical strategy, I believe the premise is that dose interruption will have a negative effect on the outcome therefore we no longer use the data after the ICE to avoid penalizing the endpoint unfairly. However, if a patient achieved positive outcome after the ICE despite of less doses administered, is there any way to factor that in, rather than completely discard the data?	The hypothetical strategy in an estimand leads us to an estimation approach that does not use any data (good or bad) after the ICE in order for us to estimate the effect as though that ICE had not occurred - imputation or prediction makes use of the profile of data so far on the patient and the other patients in their group. Of course, you may also decide to define another estimand which takes a treatment policy approach and thus uses all data collected after ICEs. However, often it is difficult to collect data after these logistical issues and thus estimation of treatment policy estimands may need to make assumptions in dealing with missing data.
33	just a comment re preference of treatment policy vs composite variable approach: both can be seen as allowing to follow the ITT principle; this could be an argument for accepting the composite approach, too.	- . -
34	For a trial that compares test drug to an active comparator and the objective is to show non-inferiority, if the test drug is not efficacious and most of the patients in the test arm would take rescue medication (say switch to the active comparator), will the treatment policy lead to high chance of success? so why	Note, (many) HTA assessors are not interested in non-inferiority, but rather they are looking for added value. Yes, you are correct to highlight that the estimated treatment effect using the treatment policy strategy may lead to a conclusion of “non-inferiority” in this scenario. For some stakeholders, the hypothetical strategy for dealing with rescue medication may be considered to be more relevant and indeed it may be sensible to define both these two estimands. However, in order to better understand and interpret your results, you need an overview of the intercurrent

	HTA is intested in the treatment policy?	events and if the scenario that you describe happens, decision-makers would most likely not approve your treatment.
35	do you have an example of what the estimand framework looks like in a protocol?	You can download the Transcelerate Clinical Protocol template to give you an idea of where to implement the estimand framework in a protocol. Many pharmaceutical companies have used this document to implement the estimand framework in their own templates: https://www.transceleratebiopharmainc.com/assets/clinical-content-reuse-solutions/