

BBS / EFSPi Webinar “Estimands addendum is final: Anything new for oncology?” 29th June 2020

Questions from the webinar chat addressed by the members of the organizing committee and panelists

The views expressed are the personal views of the panelists and members of the organizing committee and may not be understood or quoted as being made on behalf of or reflecting the position of the Agency or the company.

- 1) from Michael: Many sponsors might wonder if the estimand framework shall be used for ongoing studies, i.e. should trials be amended that have not used the estimand framework when they were started to reflect estimand thinking.

Anja Schiel: I don't think we ever advise amendments to ongoing trials unless absolutely necessary. This is probably also true for the Estimand framework. Trials for which we reasonably can argue that they could not have been planned with the Estimand in mind and therefore might have for example still terminated data collection on treatment discontinuation changing the trial mid-way is not a good idea. Can trials that were planned before the Estimand era be discussed from and Estimand viewpoint, absolutely. I doubt that it would be considered acceptable to substantially change an ongoing trial just to make it fit the Estimand framework, equal to the regulators position to change trials for any other reason. And if such a need would be identified then changes should be agreed on with the regulators and not be presented at the time of the submission. It needs to be clear that it is still possible to design and run successful trials even if one hasn't spent a second thinking about the Estimand!

- 2) from Nilani Liyanage: How do you handle an intercurrent event such as a rescue medication which is allowed later in the trial with a protocol amendment?

Addressed in the webinar

- 3) from Michael Tribanek: The hazard ratio was mentioned in both talks as summary measure of the estimand. According to the ICH E9 addendum, the summary measure is the "basis for comparison between treatment conditions". Isn't the HR already the result of the comparison? Should we define the hazard rate in each treatment group as population-level summary?

Kaspar Rufibach: The addendum says "Finally, a population-level summary for the variable should be specified, providing a basis for comparison between treatment conditions." So, a measure that directly makes the comparison appears fine in our opinion, it must not necessarily be based on group-specific effect estimates. Estimating hazards in each treatment group first answers a different question, as it does not (immediately) relate to a comparison between treatment conditions.

- 4) from Armin Schüler: You seems to use all death dates (in case of no intercurrent events), independent when occurring - did you reflect on this during the estimands discussion?

Addressed in the webinar

5) from Dirk Lehnick: For the panel discussion (could be a provocative question):

In the circle of webinar participants, we are certainly many people who tend to support the Estimands Framework. However, are we still open enough to the idea that a silent majority in the drug development community (and even more so in the clinical research community beyond drug development) might not be willing to accept or apply the Estimands Framework? And, if so, might we still be prepared to accept a failure of the idea of establishing the Estimands Framework?

Addressed in the webinar

6) from David Wright: Great slides Ingolf. Clearly shows why effect attributable to investigational drug is not shown in a treatment policy approach should not be used for licensing (or reimbursement purposes). Sounds like a good topic for the panel discussion. Sorry too many notes I think in my question! The effect that can be attributed to the investigational drug is clearly of key importance. Given this shouldn't an approach other than treatment policy be used when a significant amount of cross-over and switching takes place (or is expected)?

Evgeny Degtyarev: In principle, as highlighted in the talks and in ["Question and answer on adjustment for cross-over in estimating effects in oncology trials"](#) released by EMA, the scientific question of interest should guide the choice of the analysis. Therefore, the choice of the analysis depends less on the amount of cross-over and more on whether such cross-over reflects clinical practice. For example, if the investigational drug is approved and widely used in 3L and it is studied in 2L vs SOC, treatment policy strategy for cross-over from SOC to investigational drug appears reasonable. Hypothetical strategy would target the question "What would be OS if patients had not cross-over" which does not seem to be clinically relevant considering that cross-over reflects clinical practice.

7) from Hong:

What about add-on treatments? Should we also consider them as a scenario of treatment switching, e.g., switching from monotherapy to combination therapy from different drug class? And can the same estimand be applied to this scenario??

Hannes Buchner: Switching from monotherapy to combination therapy can potentially be treatment switching, yes. What you consider as treatment switching can vary from trial to trial so there is no general answer. Therefore the same estimands may apply.

8) from Emmanuel Zuber to everyone: Alternatively (to David's proposal): could we develop ways to really design our studies with an inclusive definition of the Treatment Attribute in mind: could we find ways to ensure that the treatment journey of patients beyond investigational drug really reflects an expected SoC?

Addressed in the webinar

- 9) from nguyea37: How can the "treatment cond. of interest" for the 4th case be the same as that for the 3rd case?

Hannes Buchner: You have a point here but I believe it is a bit a matter of taste. You have two places within the Estimand to define this: a) the treatment condition of interest and b) the intercurrent event section. We discussed this when we developed this table and we believe that you have to define it under intercurrent events and you see that the two scenarios differ here. However, the treatment condition is anyway already very long and complex, so we believe it is not a must to put the "disease related time point" in here too but you could add it if you prefer this.

- 10) from Tina Nielsen: Are the treatment switching methods generally accepted by regulatory agencies?

Addressed in the webinar

- 11) from Renaud Capdeville: Another aspect: as trial progress, some investigators may have start to use to new, not yet standard assays/tests to make a decisio to take a patient out of a trial to receive another therapy in absence of protocol-defined progression. Could be the case for MRD assessment in heme malignancies, or PET scan in some lymphomas. How to handle these?

Addressed in the webinar

- 12) from Leo Liang: Same questions as Tina's. Are the IPCW and RPSFT accepted by regulatory agencies, given they rely on assumptions that are hard to justify?

Addressed in the webinar

- 13) from Rossella Belleli: Should not focus on the effects of covid-19 which can be differential with respect to treatment arm, taking into account the blinding of the study?

Stefan Englert: It is recommended that the sponsor assesses the impact of COVID-19, clearly defines the risk due to this impact and, if deemed necessary, defines mitigation methods in a blinded review. An initial risk assessment would require a clear understanding of study participants who are directly affected by COVID-19, an assessment of missed visits and specific reasons for those missing visits, an understanding of COVID-19 related deviations from the protocol, as well as a potential enrollment change or shift in population. All these aspects can be reviewed by the sponsor in a blinded fashion. This is also reflected in the EMA Points to Consider (EMA/158330/2020 Rev. 1), which highlights that "risk assessment [...] should primarily be performed by the Sponsor on aggregate and blinded data with the intent to inform the likelihood of the trial to deliver interpretable results" and that "A more thorough analysis based on blinded review may be warranted, but the use of unblinded data is not recommended."

14) from Nelson Kinnersley: Kudos to organisers & speakers for hosting this webinar to share case studies wider and enhance education of these important concepts. To help adoption of estimands framework do the panel know of any efforts to require Sponsors to include Estimands in their entries for EudraCT or ClinicalTrials.gov? I just did quick search on EudraCT and only 8 (of 37449) results included the word "estimand"

Lorenzo Guizarro: EMA is currently working on the successor to EudraCT, an EU portal and database, as mandated by the EU No. 536/2014 clinical trial regulation. I will make sure the colleagues working on it receive your suggestion. It is understood that the database will initially be based on the same structure as EudraCT, and that future iterations might include estimand concepts and terminology. This exercise will be in line with other initiatives implementing estimands in trial documents, such as ICH M11 on this type of data collection. Please be aware that the ICH M11 is planned to be put to public consultation in June 2022, so you will also have the possibility to submit such suggestions for inclusion internationally: https://database.ich.org/sites/default/files/Revised_M11_EWG_WorkPlan_2020_0504.pdf

15) from Stefan Driessen: The FDA has recently issued their guidance " Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency" but does not talk about estimands and also does not really propose something like Hypothetical Strategy as Stefan Englert mentioned. Can the panel comment on this?

Kaspar Rufibach: Let me start with the updated EMA "points to consider document" on COVID-19: [Implications of coronavirus disease \(COVID-19\) on methodological aspects of ongoing clinical trials](#) It is great to see that they now acknowledge the usefulness of the estimand framework: The estimand framework provides a comprehensive approach to articulate this impact analysis. This is in line with the Stefan's conclusion, and also the one of Degtyarev et al ([paper](#)).

The following comment on the recent FDA guidance is a result of discussions within the EFSPi regulatory statistics working group, which I'd like to acknowledge. FDA did chose not to even mention "estimand" or "treatment effect" in their [guidance](#). And where there is reference to sensitivity analyses, it appears it is in the context to the pre-addendum definition. Furthermore, it is surprising to see FDA's focus on excluding subjects under the MCAR assumption (see 5 (a, b)) given

(1) FDA's caution with making unverifiable assumptions (e.g. in the discussion around principal stratification) and

*(2) where the estimand discussion has focused on the importance of including *all* patients and addressing intercurrent events.*

General exclusion of all patients who have had some impact caused by the pandemic seems a quite rough approach. Rather, assessing this in the estimand framework as "indirect" impact (as in Degtyarev et al) and proposing a suitable estimand strategy seems an alternative option, or even preferable.

16) from Hong: Should both interval censoring and right censoring intercurrent events be considered during COVID19 pandemic? E.g., patient died during pandemic and patients survived post pandemic.

Stefan: For tumour endpoints that rely on imaging technology, potential complications can arise from the pandemic mitigation measures. An example would be delay of imaging assessments, meaning that the interval between tumour assessments could become (much) larger than specified in the protocol assessment schedule. Although in theory indicated even pre-pandemic but rarely used for such type of data, methods that appropriately deal with interval-censoring may indeed become more appropriate.

17) from Khadija Rantell: Is there any flexibility in trial endpoints as a consequence of the impact of COVID-19. • For example where RECIST reporting of endpoint is required could clinical progression be used instead if RECIST unavailable? • What would be the options for a biomarker endpoint if a sample couldn't be taken, or for studies requiring a QoL questionnaire where this was not completed?

Anja Schiel: I think we cover this in the Points to consider. (<https://www.ema.europa.eu/en/implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical-trials>). The update was released almost during the webinar.

We advise to record and report, so it means that once you have realised you have a problem with the original endpoint you should first try to understand the potential impact (in terms of numbers of events, would it be possible to collect the endpoint as planned later or at a next visit etc). If the conclusion is that the trial might be compromised we would not immediately advice any protocol amendments but rather keep collecting all variables that might help to understand the impact and come for SA before you take action. It might be acceptable to replace a measurement as proposed by Khadija but this depends on the actual endpoint.

QoL questionnaires might be done by phone depending on the type of questionnaire. Replacing a scan is possibly more complicated but it could be discussed if and how a delayed scan could be used (and how f.e PD should then be handled; or how exclusion due to missing observations needs to be handled).

Some variables might be difficult to rescue, biomarker measurements come to mind or possibly also treatment decisions that are affected.

In a nutshell, don't change anything in a rush, rather come and discuss with the regulators and in the meantime make sure you collect all the info you can get related to the reasons for the inability to observe the variable of interest.

18) from Johannes Huesing: What kind of estimand strategies would result in the suggestion of basket or umbrella trials?

Evgeny Degtyarev: Woodcock and LaVange (2017) defined the objective of umbrella studies as studying multiple targeted therapies trials in the context of a single disease and the objective of basket trial as studying a single targeted therapy in the context of multiple diseases or disease subtypes. The estimand framework further helps to clarify this general objective ensuring that all elements are appropriately considered in the study design. For example, there may be a need to use different estimand strategies for the same intercurrent event in cohorts with different diseases in a basket trial.

19) from Rachael Lawrance: Thank you to all the speakers today. Does the panel have any experience or suggestions about considering estimands for secondary endpoints in the trial (e.g. PRO endpoint) - how consistent should strategies be and how best to present any differing approaches to all stakeholders?

Rob Hemmings: Articulating an estimand for secondary endpoints is worthwhile and, as implied in the question, is important since a different clinical question of interest might be relevant. In particular PRO / It is not at all necessary to be consistent in respect of identification of intercurrent events or choice of strategies when reflecting different clinical questions of interest. QoL data might be used to address different types of questions, for example on the impact adverse events, or the treatment effect on a specific symptom. Strategies that are appropriate for quantification of efficacy on the primary variable might not address the clinical question of interest in these different domains. In addition, the variable might dictate that other intercurrent events need to be considered. Say the PRO is a secondary endpoint focussed on pain in a trial with OS as the primary endpoint. Use of analgesics might not affect the interpretation of OS times and hence might not be considered as an intercurrent event. However, changes in analgesia would be important as an intercurrent event for that PRO. It can be good to start the discussion with different stakeholders with the clinical question of interest and have that agreed, before translating that into more technical estimand language.