EFSPI regulatory statistics conference webinar "Estimands – emerging questions now that we are using the framework", 13th October 2020

Questions from the webinar chat addressed by the 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.

General questions:

Estelle Russek-Cohen: Many drug approvals require more than one trial. How should one be comparing trials in the same indication if the trials are impacted differently?

Emmanuel Zuber: Wouldn't that support the use of hypothetical strategy, giving a common estimand approach ?

Answer: [Armin] Yes, this is the right approach if your pre-covid 19 clinical question, and as a consequence your pre-covid 19 estimand, is still applicable. This would be the most likely scenario. However, as indicated in the talk of Finbarr, there are situations where a modified estimand might be more appropriate (see also answer to question from Finbarr below).

[Finbarr] The ability to compare trials conducted in different periods of the pandemic may also provide useful information on the overall impact of the pandemic in that indication.

[David]The question also raises an interesting point if one trial is conducted before the pandemic and another is conducted during it and for example imagine a situation where both studies pre-specified a treatment policy approach for all/most intercurrent events. The pre-defined primary analyses in this situation could give quite different answers due to the second study being impacted by COVID. This shows why a hypothetical approach will be important in evaluating the overall effect of the product in a post COVID setting (here being needed for the 2nd study).

What are top two priorities?

Finbarr: In the context of the Covid-19 pandemic, flexibility and pragmatism while maintaining scientific rigour.

Vivian Lanius: In general (not only related to covid-19): awareness, training, and case studies across all disciplines such that estimands (or the need to specify the relevant clinical question in more detail) are truly considered a relevant multidisciplinary topic.

Bharani Bharani-Dharan: For trials starting in the midst of pandemic assuming pandemic's lasting effect to last for 1-2 years, what is the panel's opinion on the relevant question of interest for such trials - should it still be treatment effect had the pandemic not occurred based on hypothetical strategy?

Answer: See answer given above on the question from Estelle Russek-Cohen. It depends. You should ask yourself the question: Will the life after the pandemic (if there is an after) the same like before or would the pandemic lead to a general change of patient behavior (e.g. continue to avoiding to go to a hospital) or a change of medical standard.

Arunava Chakravartty: Has there been any discussion around what estimands regulators care about vs the estimands that may be more important from reimbursement perspective? Does the panel have any thoughts?

Answer: [Vivian] My understanding is that this question is about the likely or preferred strategies chosen for certain types of intercurrent events. (Personally, I would avoid speaking of, e.g., "a hypothetical estimand" or a "treatment policy estimand".) From the examples that have been shared in the EIWG, in Phase 3 the "default" strategy expected by regulators and/or chosen by teams for most intercurrent events is very often 'treatment policy'. However, the framework allows for more thorough thinking, which is both an opportunity but also a new responsibility for all parties involved. Giving a rationale for choosing a specific intercurrent event strategy – as also mentioned by Finbarr – may help.

[Finbarr] My sense is that the relevance of a particular estimand to the decision making processes of regulators and payers can differ but that both groups value the ability to compare and contrast results from alternative estimands.

[David] Yes there has been lots of discussion about this. One clear difference is regulators are interested in evidence that a drug is superior to placebo (and has a clinically relevant treatment effect that outweighs any safety concern (i.e. has a positive benefit risk). Payers are interested in whether a drug is better than standard therapy (with the addition of being cost effective). These are 2 different objectives and clearly a placebo controlled trial as an example does not provide Payers with direct evidence of a relative effect that they are interested in.

Paul Terrill: 'ITT' has been pushed for years. Not a surprise that treatment policy is now pushed?

Answer: We have to keep in mind that in several cases the treatment policy estimand is an appropriate one. Especially, if you are interested in the additional effect of a new drug acknowledging for the existing treatment options.

Leacy

Mouna Akacha: Based on slide 13: In which settings would a hypothetical strategy for pandemic-related reasons be not appropriate? Any examples/additional considerations you could share with us? Thank you.

Answer: There is still uncertainty about the ultimate course of the pandemic. It might be a risk to focus solely on a setting of "a world without COVID". Of course, the setting of "a world with an acute COVID-19 pandemic" may also not be particularly generalizable. Patient factors may impact the relative frequency of some types of intercurrent events (e.g. treatment interruption where study site remains open but some patients choose not to attend) during the pandemic and this has implications for estimation.

Where a particular intercurrent event can occur pre-, post- and during the pandemic, use of different strategies in the different period could be plausible. In particular, proposals to also change handling of intercurrent events in the pre-pandemic period are unlikely to be acceptable.

There is also concern that blanket use of hypothetical strategy could lead to reduced or less detailed data collection.

Yongming Qu @Finbarr: I agree on your comment on COVID-19. Therefore, we may need 2 estimands to handle COVID-19 related ICEs differently.

Paul Terrill: Finbarr said that they don't see (enough) justification/rationale of the strategies used for ICEs and that treatment policy is often used for all ICEs without justification. To discuss: Should we have a 'default' strategy that doesn't need full rationale (like we used to have 'default' analyses based on 'ITT') or do we always need to describe the rationale for the handling of all ICEs? Also, does all of this belong in the protocol or elsewhere?

Answer: [Yongming] This is an interesting idea. In my opinion, it might be difficult to have ONE default strategy for all ICEs; however, it is possible to have a default strategy for each type of ICEs. For example, the default to handle ICEs due to administrative reasons can be the hypothetical strategy (assuming patients would adhere to the study medication).

[Vivian] I agree with this view. However, in some cases this is so far still a discussion between the statisticians. We need to work together to ensure that other disciplines get more experience with the estimand framework such that also for regulatory consultation it is truly considered a multidisciplinary topic.

[Finbarr] It may also be possible to provide general guidance by therapeutic area, but there will almost always be subtleties to a particular trial design that require additional consideration.

Wessiepe: Are there plans to harmonize these guidelines across regions?

Answer: Harmonization within EMA. Potential for differences between regions. Expected that authorities may reach agreement for specific cases.

Khadija Rantell: Introducing a post-hoc interim analysis because of issues relating to recruitment into the trial and sample size re-estimation. How frequent are these requests?

Answer: Proposals have been submitted. Variety of justifications, and quality of these justifications has varied among applications. Key is to propose a scientific justification for all changes proposed because of the pandemic.

Khadija Rantell: Request for amendments overall is poorly justified. There is always a concern about the trial integrity when introducing post-hoc interim analyses triggered by pandemic.

Alison Balfour: When would revision of other Guidelines such as Non-inferiority margin been considered? Also will there be any guidance considering appropriate use of FAS and PPS analysis sets?

Answer: Yes, the potential need to revise the non-inferiority guideline has been identified. I would expect a revision to address analysis sets as part of the estimand discussion.

David J: How to deal with Estimands for early phases (FIH, phI)?

Alison Balfour: Can the Estimand Framework be used for PK bioequivalence studies considering PK concentrations in healthy volunteers?

Answer: No reason why the estimand framework could/should not be applied here. Avoid that estimand framework is perceived as "only" belonging to registrational trials – it is about the scientific question, and that is relevant for all study phases and study types.

Hans Ulrich Burger: To Finbarr: Do we see a take up of the estimand framework for handling Covid-19 related ICE?

Answer: Few Covid-19 related proposals so far. Not more details in PtC document because everyone involved first needs more experience with Covid-19. Estimand framework is clearly a good concept to talk about Covid-19 and its impact on trials. The PtC is a living document and further revisions are likely with growing experience of Covid-19 pandemic.

Amel Besseghir: Would the topic of estimands choice be a point that can be considered as part of the consultancy discussions (trial design with regulatory authorities)

Answer: [Yongming Qu]: Yes, in my experience, estimands are an important topic for regulatory consultation on study design in multiple occasions.

[Finbarr]: Yes, and is encouraged! Regulators can provide more tailored advice when concrete, well-reasoned estimand proposals are presented.

Emmanuel Zuber: What are the possible avenues for industry to collaborate with EMA on approaches to the identified areas of application of the framework: therapeutic area guidelines revisions, use of RWE, implications on labeling...?

Answer: After the move to Amsterdam and Covid-19 will be digested EMA will become more active in these areas.

Emmanuel Zuber: Can you elaborate on your statement regarding the lower engagement on the Oncology side? Is it in applicants, at EMA or both?

Answer: I would say this is across both regulators and applicants. It is more that we do not see explicit use of estimand framework in SA oncology requests but this may be addressed implicitly, e.g. through specification of censoring rules.

Lanius, Schüler, Wright

Egbert Biesheuvel: any feedback from and/or training for Ethical Committess?

Answer: We would like to include all relevant stakeholders in training, so ethics committees is another important one (we don't want them turning down estimand language as part of their review for example, but building an understanding of the estimand framework and its uses would definitely be useful for ethics committees).

Juergen Loeffler: Do we need a rationale for the estimand or a rationale for the research question?

Answer: see the work James Bell has done on Detailed Clinical Objectives. So in my view you first need a rationale for the research question/detailed clinical objective - this then informs the choice of estimand.

Emmanuel Zuber: Can you share your perspective on how to engage further the Clinical Academic world into estimand thinking on the impact on the different therapeutic areas?

Answer: I think we need to give them clear examples where there are different questions of interest for different stakeholders and where we see quite a large difference in effect size on analyses based on these different questions of interest. I think this is of importance in the meta-analysis space where without full details on the estimand strategies used and the analysis done there is a danger of doing a meta-analysis on studies that have used widely differing approaches and this could end up with misleading conclusions.

There is potentially a disconnect between clinicians involved in pharma trials and practicing clinicians. We see the need for papers in major clinical journals where we can drive home the importance of the estimand framework.

Mouna Akacha: David, you concluded that it is too simplistic to think about just two potential questions (i.e. with/without pandemic). While I agree, I guess we need to start the discussion somewhere. Could we get some agreement for the question of interest for ongoing studies that are impacted due to the ongoing pandemic? Most (if not all) ongoing studies probably started out being interested in a question in the absence of a pandemic - moving into the future, hopefully the pandemic impact will be very much limited (while the disease itself will of course still be around)... Some harmonization would be useful. Even if we look at several estimands for the same trial, we still will need to decide on: what is the primary estimand? Which estimates play a key role in the label, etc.?

Sigrid Klaar: You have to win over the clinicians within your own organisations (companies, agencies) first, and through them win over the academic clinicians.
In a 2nd step the concept short crisp reflections on detailed clinical objectives at clinical conferences might possible after having convinced clinicians within the organisations

Paul Terrill: The presented examples from protocols seemed to always split objective from estimand, but a lot of the objective includes estimand attributes (as can be described using DCOs) so does it make sense to do it this way?

Finbarr: There is a need to reflect some of the discussions around the estimand in the corresponding protocol section(s).

Vivian: I think that there is an understanding that the current approaches on how to implement estimands in study protocols can still be improved and we are learning from our shared experiences. This is one of the points where the EIWG sub-team on protocol templates would like to provide recommendations or at least food for thought.

Evgeny Degtyarev: is it truly possible to define research question/DCO without discussing estimand attributes? I think without such discussion it's very difficult to formulate your question of interest as a first step. DCO appears to be rather a consequence of estimand discussion.

Vivian Lanius @Evgeny: Yes, the discussion of the research question/DCO would involve a discussion of the estimand attributes. It's just that it may be easier to engage a clinical colleague by inviting to a "detailed discussion of the research question" as compared to "the construction of the estimand" - i.e. the discussion is the same/similar but the wording used may increase the engagement.

Marian @Vivian: I think the fewer names for the same thing will decrease the risk for ambiguity and would be totally honest with the clinician colleagues and explain upfront that estimand ~ reflection of the clinical question. Rather than "sugar-coating" the estimand.

Answer: Using detailed clinical objectives is not about "sugar-coating" or not being totally honest. The same discussion about details is needed. I understand the point about using too many different names for the same thing. I've made the experience that some clinicians prefer (for that reason) to "discuss estimands" but others where more comfortable when they understood the need to be very specific and detailed discussing the clinical question(s) using the estimand attributes. In my view, teams may flexibly vary the approach for having the discussion as long as the result is the same. I agree with what Sigrid and Melanie mentioned in the chat: (1) the need to "bring the estimands down to earth and make them less abstract and more understandable" and (2) phrasing "the estimand as a relevant clinical question, it will become less abstract and more accessable to clinical colleagues".

Sigrid Klaar: There is a need for education of regulatory assessors on the estimand framework. For example, there are no/very few oncology training examples available. Clinical assessors are interested to learn but the available training examples are not suitable for all therapeutic areas.

The addendum highlights the multi-disciplinary characteristics of estimands and the need for collaboration between clinicians, statisticians and other disciplines in the construction of an estimands. Still it appears that the ongoing estimand discussion and development of the framework occurs mainly between statisticians, without the involvement of clinicians. I believe that clinical assessors should be more involved in this development of new practice.

Kaspar Rufibach: I can speak for the oncology estimand working group (www.oncoestimand.org, an EFSPI and ASA biopharmaceutical scientific working group) is regularly meeting with regulators globally to share examples, findings from its research activities, and open questions. While these interactions so far focus on statisticians on both sides we start to include the clinical side as well. The WG is also just starting a task force "clinical engagement" where the focus is precisely on engaging partner functions beyond statistics. So the need is clearly identified - thanks for the input!

We'd be interested to hear how we can support regulators in involving clinicians more / better? Should that happen through statisticians at the agencies? Or through events as today, with a more applied / clinical focus? Any suggestions very much welcome!

Sigrid Klaar: @Kaspar: I believe that there is a need to bring the estimands down to earth and make them less abstract and more understandable. To do this, examples are needed to illustrate e.g. different handling of ICE affect the interpretation of the results. I would be happy to collaborate around this.

Evgeny Degtyarev: thanks for your comment, education of clinicians remains an important and difficult topic within the industry as well. Maybe just to add to Kaspar's reply - the oncology estimand WG recently organized a webinar together with clinical speakers presenting case studies, recording/slides available here and may be helpful: http://bbs.ceb-institute.org/?p=1453

Melanie Wright: Perhaps the more we can phrase the estimand as a relevant clinical question, it will become less abstract and more accessable to clinical colleagues. In addition, it helps to have estimands discussed as part of the therapy area guidelines and related to real examples. Hence the idea to run the EIWG training based on case studies!

Qu

Elena: The Addendum defines the hypothetical strategy "as if the intercurrent event would not have occured". How do you see proposing NTH wrt this aspect?

[Yongming Qu]: The hypothetical strategy in the addendum is more like CDH strategy; I suggest we should have other hypothetical strategies.

Müller-Velten

Egbert Biseheuvel: EU Health mentioned Estimand Framework explicitly, what about response from FDA?

Estelle Russek-Cohen: Guidance is not binding at FDA. FDA started an internal working group on estimands in early 2020. Prior to that several divisions were already moving along in formulating possible estimands for various indications. The discussions are ongoing and clinicians are included.

Hans Ulrich Burger: Do we have done any evaluations of the impact of choosing different estimands on the power? For example censoring versus taking all information? Can we combine the statistical significance from the most powerful analysis with the point estimate from the most unbiased one, i.e. the censoring one?

Answer: The estimand should depend on the study objective and be defined prior to estimation. Given an estimand, generally the estimation method that provides the most power (and not inflating the type-1 error) should be used. Of course, given the sample sizes, certain estimation/estimand combination may provide high power. If sponsors can find an estimand that is clinically meaningful and accepted by regulatory agencies, and provides high statistical power with certain estimation procedures, it is plausible to choose such an estimand.

If the question refers to the PARADISE-MI example, censoring the analysis at the start of COVID-19 impact (estimand in a world without COVID-19) would lead to a loss of power due to basing the analysis on approx. 80% of the information for which the study was powered. The analysis based on all data (including 20% affected by COVID-19) will be more powerful as long as the observed treatment effect dilution during the pandemic does not exceed a certain threshold (which can be quantified), but the estimated overall treatment effect may underestimate the true treatment effect in a world without COVID-19.

Oliver Keene: You referred to "increased noise" as a problem with using data collected after the start of the pandemic. How will this affect the estimation of the treatment effect given that the summary measure is a hazard ratio? Appreciate there may be fewer events. Would you expect the treatment effect to be diminished? If events are postponed as a result of the pandemic, would it be reasonable to assume the treatment effect (hazard ratio) will be the same?

Answer: There is a theoretical concern (uncertainty) about the impact of COVID-19 on the treatment effect during the COVID-19 impacted phase. Hospitalizations for HF that would have occurred in the absence of the pandemic may not happen during lock-down periods due to impaired health care systems and patients' fear of infection. These "unrealized hospitalizations for HF" could lead to a potential change in the composition of the primary endpoint, in that CV death (a less disease-specific endpoint) might become proportionally more prevalent in the composite endpoint. In addition, important concomitant treatments (e.g., IV diuretics) may change during this time and there may be direct impact on the treatment effect in case of an increased number of treatment interruptions or discontinuations. Having said this, the actual impact depends on various factors, including how well the COVID-19 impact is managed (e.g., ensuring continuous drug supply) and the treatment effects on the components of the primary endpoint.