MOST FREQUENTLY ASKED QUESTIONS DURING THE WEBINAR "PIONERING ESTIMANDS IN CLINICAL RESEARCH"

Disclaimer: *The most frequently asked questions during the pioneering estimands webinar are summarized below. The answers represent the views of the presenters and organizers from EIWG (Estimands Industry Working Group). They do not represent official guidance or policy of industry or authorities.*

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PIONEER RELATED

QUESTION	ANSWER
How much missing data did you end up with and how did you handle missing data for Estimand 1? Please comment on missing values due to handling intercurrent events.	Overall, the retention was approximately 95%. A few more patients had missing assessment of changes from baseline in HbA1c to week 26 in both groups for estimation of estimand 1. Missing data for estimation of estimand 1 was imputed according to McEvoy approach (McEvoy BW. Missing data in clinical trials for weight management, Journal of Biopharmaceutical Statistics 2016;26(1):30-6): within each randomised arm according to treatment discontinuation or initiation of rescue medication. We do not in general have missing data due to intercurrent events, but if you are asking with respect to estimand 2 where we leave out data collected after the first ICE, estimand 2 was estimated by an MMRM. That is, missing data was predicted from the MMRM.
Did you have discussions with commercial on the different level of response, compared to historical data from competitors?	Yes, we clearly communicated the interpretation of the two estimands and that we expected to see differences in results. This was also part of the reason why estimand 2 was included, so the results could more easily be compared with previous results
In the PIONEER study, did the choice of two estimands affect sample size calculations, e.g., different effect sizes depending on treatment policy or hypothetical strategy? What estimand was used in the sample size calculations?	Estimand 1 was used as basis for the sample size calculation. We adjusted the effect size and the SD according to expected frequency of the intercurrent events
Can the speakers comment on how the PIONEER study handled events that precluded future data collection (e.g., death or study withdrawal)? Are these considered intercurrent events and, if so, how were they handled?	Study withdrawal (and lost to follow up) is not considered to be an intercurrent event, but it rather poses a missing data problem. Death was not considered an intercurrent event in the PIONEER studies, since they all are standard diabetes studies where you would not expect an excess of deaths. Therefore, death was handled as a missing data problem
Did you seek regulatory advice on your choice of primary estimand?	Yes, we talked to various agencies, including FDA, EMA, Health Canada and PMDA. It was also a learning process for the health authorities.
Did the development process of the ICH E9 R1 (concept paper -> draft guideline -> final guideline) impact protocol/stat. Analysis?	The concept paper was part of the reason why we included estimands in the protocol. The final guidance from November 2019 was not available to influence protocol or SAP. When the draft guidance came out in 2017, we aligned the terminology with that from the guidance for clarification, but we did not change the essence of the estimands, analyses etc.

QUESTION	ANSWER
Hearing if they have had "buy up" of estimand thinking outside of the statistics organization and if so, how much? Has this brought different information or discussion for teams?	There are still many stakeholders that perceive the estimand framework as being a statistical topic, but stakeholders are now beginning to acknowledge that this is an important topic that needs to be addressed. The estimand is the "backbone" of the study in the sense it impacts the design, conduct, statistical analyses, and the reporting of the results. Trial teams are now discussing intercurrent events and especially in "non-standard" studies there are good discussions and today we define many estimands with different strategies for handling different intercurrent events. Also, the implications of using different strategies are discussed. We clarify upfront which stakeholders we are addressing with a given study, since this will often have an impact on which strategies are relevant.
In that specific example, we had two estimands for one primary objective. How are the two different estimands implemented in the protocol - primary and secondary endpoint? How are they handled in the testing hierarchy? With 3 active IMP arms versus placebo, and 2 estimands, what was the type 1 error control strategy? Would the study have been successful if only one of them would have be statistically significant?	Formally, estimand 1 was used for getting the claim, but as in all cases it really depends on the context. Is it the first approval, is it a line extension, is it a drug targeting an unmet medical need or is it yet another drug in a crowded market, etc? Estimand 1 was the primary estimand and that was clearly specified in the protocol. The trial was a success if we could demonstrate superiority with respect to that estimand. Estimand 2 was not included to get any claims, but rather to give more information on different treatment effects of oral semaglutide and to be able to compare to the effects of other competitor drugs and no multiplicity controlled was applied to estimand 2. Regarding the dose levels, multiplicity was controlled, but only within estimand 1. We had a confirmatory secondary objective defined regarding change in body weight. An estimand like estimand 1 with only the endpoint substituted with change from baseline to week 26 in body weight was defined. That is, we had six hypotheses to be tested. Multiplicity was controlled according to Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. Biometrical Journal. 2011;53(6):894-913. Estimand 1 was primary estimand for the primary objective and estimand 2 was an additional estimand for primary objective. Results from estimand 1 were reflected in the US label and the EMA SmPC for both HbA1c and body weight.
Which result is reflected in the labelling?	Formally, estimand 1 was used for getting the claim, as estimand 1 was the primary estimand and that was clearly specified in the protocol.

QUESTION	ANSWER
	Results from estimand 1 were reflected in the US label and the EMA SmPC.
In terms of presenting results derived from estimands in a CSR (such as the PIONEER example of 2 different results based on 2 different estimands), is there a suggested/preferred approach for describing and discussing these in conclusion and discussion text in the CSR?	Having two estimands defined provides more information on your treatment, but of course in all communications it needs to be clear what is the confirmatory part. No doubt that having two estimands complicates communication – not only for the CSR and we are still trying to improve on that. As was also indicated in the presentation, the results need to be interpreted and concluded on in the light of the frequency of the different intercurrent events per treatment group. In the case of PIONEER 1, both set of results were presented and discussed.
What can you interpret from the different estimates in PIONEER - that the 'true' treatment effect lies somewhere between the treatment policy and the hypothetical estimates, or can you not think that way?	Not really. What you can say is that you have addressed two different questions regarding the treatment effect. You may argue/claim that estimand 2 asks (or aims at asking) the question "What is the pharmacological effect of your treatment?". Whether you end up answering this question satisfactorily/reliably or not, depends on your method of estimation
Can you explain a little more the differentiation between Estimand 2 for Pioneer and the LOCF strategy?	Estimand 2 was estimated by a mixed model for repeated measurements, where missing data are predicted by the model (MAR assumption) and not imputed by Last Observation Carried Forward (LOCF). LOCF and other single imputation approaches do not allow for the uncertainty in the imputation, and in the case of LOCF there is a n assumption that the underlying condition is stable had they stayed on treatment. EMA Guideline on Missing Data in Confirmatory Clinical Trials "The risk of **underestimating the variance** of treatment effect when imputing can be reduced by proper implementation of techniques such as multiple imputation" The Prevention and Treatment of Missing Data in Clinical Trials: "Single imputation methods like last observation carried forward and baseline observation carried forward **should not be used as the primary approach** to the treatment of missing data unless the assumptions that underlie them are scientifically justified" ICH E9 (R1): "In case of missing measurements, data need to be predicted based on plausible assumptions **while accounting for the added uncertainty** due to missing data"
Would you please share experience of communicating estimand with investigators? any challenges?	Like all other stakeholders, they in general perceive this as a difficult new task. The project statistician gave presentations of the topic that focused on the patient journeys at investigator meetings. Some of the investigators even engaged in preparing a manuscript:

QUESTION	ANSWER
	Wiley Review Article (2019): Aroda et al, Incorporating and interpreting regulatory guidance on estimands in diabetes clinical trials: The PIONEER 1 randomized clinical trial as an example https://dom-pubs.onlinelibrary.wiley.com/doi/full/10.1111/dom.13804 They even prepared a small video (https://www.youtube.com/watch?v=oeoTOOlx37c – note different labels for the two estimands), so it was a very positive experience to learn that they were interested in the topic.
Can you clarify that in the example where you say "as though they continued the medicine" do you use the data after the intercurrent event, or do you exclude this, or do you impute it based on the trend or best available evidence?	The MMRM used in PIONEER or alternatively a multiple imputation both assume missing data are missing at random (MAR) and use the information about the individual subject as well as trends in the data. So, we can say yes, it is "based on the trend" and evidence within the data set.
If the patient still withdraws early, will the data be imputed for primary endpoint and will the approach be the same as that used for hypothetical strategy?	Yes, primary endpoint for early withdrawals were also predicted and in case of estimand 2 the same approach was used as for the two intercurrent events, i.e., treatment discontinuation and initiation of rescue medication
in one word, a single estimand, as described in the presentation, would result in different results and interpretations.	Not exactly, in the case presented in the webinar there were 2 estimands, each resulting in different results and interpretations, as answering different clinical questions.
Could an estimand be defined as an evaluation strategy? If no, could you provide a dictionary like definition of what is an estimand?	ICH E9 definition: An estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Rather than an evaluation strategy, it can be defined as the detailed clinical question that we want to answer, and by detailed we mean that all attributes, i.e. population, treatment condition, endpoint, population level summary measure (difference between treatments) and strategies for handling intercurrent events, of the estimand are defined.

ESTIMAND DEFINITION

QUESTION	ANSWER
Is the estimand a new statistical general principle or an old one recently incorporated in CT methodology?	The estimand framework is a general principle for designing, conducting and reporting clinical trials, a cross-functional task, where all relevant players need to be involved, it is not a statistical principle, although in some cases it will modify our estimator (approach to analyses), not because of the framework, but because "the what" we want to estimate becomes clear. It is old wine in new barrels!! It does not change the way we analyse the trials; it just brings transparency and consistency on THE WHAT are we analysing Mitroiu, M., Oude Rengerink, K., Teerenstra, S. *et al.* A narrative review of estimands in drug development and regulatory evaluation: old wine in new barrels?. *Trials* **21,** 671 (2020). https://doi.org/10.1186/s13063-020-04546-1
How does this differ from sensitivity analyses that censor data according to various criteria?	The main analytical approach should be aligned with the estimand, that is, the methodology is a consequence of the estimand. The sensitivity analyses address the same estimand but evaluate the underlying assumptions of the main analysis, i.e., missing data mechanism. For example, if estimand 1 is your primary estimand that you estimate, a sensitivity analysis is not an estimation of estimand 2.
From your perspective, what is the most difficult for clinicians in the concepts of estimands framework and how can statisticians facilitate the process of getting familiar and comfortable with those concepts?	Key is to understand that an estimand and working within the framework is not a statistical principle and not solely a statistical task. This is also why I find it a shame that the 'Addendum on estimands and sensitivity analysis in clinical trials' is an addendum to the guideline on statistical principles for clinical trials and not a general addendum for clinical trials engendering responsibility across stakeholder managements. Working within the estimand framework is a cross-functional task where the estimand is key or the backbone in both planning, conduct, statistical analyses, and reporting. Through the clinical question of interest, the estimand precisely describes under what conditions, i.e., precise specification of the ingredients or attributes, that we are to interpret the treatment effect or the estimate, i.e. the numerical result. Understanding these key elements of the framework and accepting the cross-functionality case, in my opinion, working with estimands. The addendum is not an easy read; therefore a close collaboration with the statistician allowing the medical specialist or any other non-stat stakeholder to ask all the questions needed for her or him to understand the key elements of the framework will facilitate the comfortability with the concept.

QUESTION	ANSWER
Are these principles reasonably applicable to actively controlled trials?	Yes. The principle is about how to clearly define the question we want to answer whatever the treatment conditions being compared, i.e., estimands apply regardless of whether a study treatment is compared to placebo or active treatment or even to a historical control.
Hi, I'm surprised to see estimator is not mentioned as an ingredient of estimand definition/ in the example of difference of HbA1C means, estimators could be unadjusted difference of means (mean changes from baseline), adjusted mean change from baseline, as estimated by an ANCOVA; adjusted mean change from baseline as estimated via MMRM...	The estimator is not part of the estimand definition (WHAT) but addressing HOW we will estimate the estimand. It is not part of the estimand definition, but definitively needs to be aligned with the WHAT and defined in the protocol in the stats section.
How would you define and illustrate the difference between ICEs and Protocol Deviations?	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. Intercurrent events would occur in clinical practice outside of the study and will depend on the clinical setting (i.e., taking rescue or additional medication, dose titrations, discontinuation of treatment, other medical procedures such as transplants/surgery, death). A Protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol, a subset of them, called major protocol deviations, are those that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject´s rights, safety or well-being. Study designs will generally allow for someone who is not achieving efficacy to take an additional or rescue medication and will also allow for someone who has an AE to discontinue treatment. Thus, the intercurrent events we anticipate (like receiving rescue medication) are handled within the study design and framing of our questions (estimands) and are not considered deviations from the protocol.

INTERCURRENT EVENTS

QUESTION	ANSWER
How important is it to distinguish between intercurrent evens related or not related to the drug and the condition? What is the process you follow to distinguish between them to avoid bias?	There is usually an expected imbalance of intercurrent events across different treatment groups which is why these need careful thought upfront. This question seems to be most applicable in PIONEER for considering discontinuation or interruption of treatment. In other situations, we may need to distinguish deaths due to related and unrelated causes. In the case of discontinuation or interruption of study treatment, it is important to distinguish if this is related to a) Tolerability issue b) Worsening of underlying condition (i.e., lack of efficacy) c) Unrelated (logistical issues/circumstantial) It may be of interest to understand the treatment effect irrespective of discontinuation for a RELATED reason, but we may be happy to consider this AS THOUGH the logistical issues did not arise. Similarly, we may wish to use a composite strategy which assumes "failure" for related reasons but not for logistical issues where a hypothetical strategy seems more appropriate. RECOMMENDED PROCESS: consider each of the above as separate intercurrent events and think through the appropriate strategy and then you can see if that leads to handling them in different ways. Agree that often the related reasons (a and b) should be handled in a different way to unrelated reasons. A useful tool is to discuss patient journeys and try to evaluate how often you would expect the identified events and if they are likely to be related to treatment/condition. Extremely rare events may not be needed to be defined as intercurrent events, but their impact on the estimands could be considered later in a protocol amendment if they become relevant.
Can you address strategies of how you can try to "predict"/impute the effect of initiating rescue treatment?	Not sure why you would do that. Instead of doing that, you should define an estimand where initiation of rescue medication is handled by the treatment policy strategy and another that aims at estimating the pure effect. In case the question relates to sample size calculation, you need to state the expected frequency and the impact on effect size and precision. For that purpose, you may use reference trials to inform your sample sizes. In some therapeutic areas such as diabetes, new drugs are frequently introduced in the market and this makes prediction of the effect difficult.

	QUESTION	ANSWER
	Slide 29 - If we only consider the duration until the first intercurrent event, would it necessarily be comparable among participants who would have different durations until the first intercurrent events, or will the results in general be meaningful?	You use the patient's data up until the first intercurrent event. The data after that point in time are predicted or imputed according to the estimator you have chosen. The more data you have to impute/predict, the more uncertainty is introduced in the estimated treatment effect.
	Could COVID19 time be defined as an intercurrent event? In many trials, because of COVID19, many functional assessments have been administered remotely.	Yes. See R. Daniel Meyer et al. "Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic". Statistics in Biopharmaceutical Research, vol 12, 2020: https://doi.org/10.1080/19466315.2020.1779122
	How would a projection for the drug effect in the Pure scenario be made if the intercurrent event happens before first effect measurement? Example: oncology, discontinuation due to toxicity on week 2, MRI scan not done until week 8.	That depends on how you estimate the estimand. In the PIONEER example it would be predicted by the MMRM model, but another approach could be to impute it using other measurements taken more easily in a multiple imputation model that are correlated with the outcome (i.e., use of biomarker data). We are planning our 3rd Estimands Academy in oncology
	How many concomitant medications required and at what duration, does that have impact on the conclusion? such as paracetamol which will only impact pain scores for 4 hours. In this situation, pain assessments beyond the duration of action of the rescue are still valid. Would it then be feasible to apply a hypothetical estimand for the time period when the rescue med is active? And then continue to collect and use the observed pain scores once the rescue med is no longer having an effect?	This depends on the clinical setting and what question you intend to ask and that will ultimately have an impact on your conclusion. You are correct that the handling of rescue medications that are short term (i.e., paracetamol in pain) is different to the PIONEER study where rescue medication is added for the remainder of the study. You can do that, but it is important that you formulate the question you want to answer and justify that this question is relevant to the stakeholders you want to address (i.e., regulators, payers, prescribing physicians). You also need to consider if the question/estimand can be reliably estimated.

POPULATIONS/ANALYSES DATA SETS

QUESTION	ANSWER
Could we consider Intention to treat and Per protocol analyses as some kind of estimands? **I think the estimand approach perhaps removes the need to specifically define ITT and PP analysis populations, as each of these populations would be addressing different questions. Is that correct? There is a danger that "Population" in the estimand definition is misinterpreted as analysis population. Any suggestions as to how to approach this?**	Intention to treat principle is reflected by an estimand where intercurrent events are handled by the treatment policy strategy. Per protocol can be a mix of everything, there is not really an equivalent causal estimand to it, in fact it is very unclear what is the clinical question that an analysis based on the per-protocol population would answer. If we could identify upfront which patients would adhere "perfectly" to treatment regardless of which treatment they received, the principal stratum strategy could be relevant. However, the problem is that such an estimand would be difficult to estimate and many strong assumptions had to be made. The intention of the estimand framework is to replace phrases such as 'Intent to treat analysis' and 'Per-protocol analysis', and instead replace with the estimand definitions which will determine the analysis to be performed.

ESTIMANDS IMPLEMENTATION

QUESTION	ANSWER
I understand that it should be addressed in the protocol (as much as possible). Where (which section) should we include all the wording related to estimand (Objectives and/or Stats Methodology)?	Our recommendation is that the estimands, which reflect the clinical questions we want to answer, are defined in the objectives and endpoints section, as this is not a statistical topic, but a cross-functional topic that affects design, conduct and analysis. (A proposal on how to write them is provided in the TransCelerate Protocol template - link- and the EIWG will soon provide recommendations for how to implement estimands in protocols)
How to deal with randomized patients who did not receive any dose of study drug? Which strategy do you suggest in the estimand framework?	The analysis set is not part of the estimand definition. This is described in the statistical considerations section. The section on Analysis Sets will define the patient data to be used for estimating each estimand defined.
IS it correct that a simple loss to follow-up (i.e., patient just does not return) would be handled as pure missing data if it can be shown to be unrelated to the study IMP in any way?	Yes.
How do you model the selection bias when there is attrition?	Attrition will likely introduce bias. In general, we do not model the bias, but we try to impute data in alignment with the estimand. For example, for estimand 1 we identify patients that are as similar as possible to those with missing data, by treatment status and use of rescue medication, and imputed from those groups.

QUESTION	ANSWER
I am not a statistician, but I guess you need to define how to "use" the estimands for a specific trial in the submission before DBL? I mean, do you need to pick your story before DBL?	Definitively!!! The estimands need to be defined in the protocol, way before DBL and first patient visit. For confirmatory clinical trials, it is also advisable to discuss the proposed estimands with regulatory authorities before running the trials.
Would you recommend using estimands for the primary endpoint only, or also for key secondary endpoints? **Do you need to define estimands for all secondary endpoints as well as the primary endpoint?**	Estimands for the primary and key/confirmatory objectives are mandatory. Estimands can also be used for the remaining objectives, but it may suffice with a less detailed description in case they are similar to one of the confirmatory ones. If they are very different it is recommended to specify it in detail. Estimands are about transparency.
Considering an estimand of a "pure" outcome as if rescue medication was not available, would it be ok from a regulatory perspective to include data from patients with rescue medication until the end of follow-up, including the post-medication data? I'm thinking of for example estimate the outcome using a regression approach where we assume that the rescue medication has an additive effect, and adjusting for this effect to recover the underlying trend without medication?	Not being regulators, we would not know for sure! What is acceptable for regulators vary to a great extent. It would also depend on the type of study – is it a confirmatory phase 3a study or an exploratory phase 2 study. You should be able to justify not only your estimand, but also your estimation approach and to plan for relevant sensitivity analyses that address the underlying assumptions in your main analysis, and thus evaluate the robustness of your results. As stated in E9(R1) you should discuss with regulators upfront.
Each time I try and recommend complete follow-up of all patients I meet resistance (i.e., cost, unwillingness of patients etc): any tips for how to address this? I like the suggestion of prioritising visits	In our experience there are three main factors impacting patient compliance and retention: • there are protocol factors, i.e., frequency and number of visits and length of trial, • patient factors, i.e., time conflicts with work schedules and family and perceived lack of benefit, • trial product related factors, i.e., AEs. The more we are aware of these factors, the more likely we are to address them. The key to success when it comes to compliance and retention is to build strong relationship between the study site staff and the patient. A strong relationship includes setting patient expectations, encouragement, making procedures easy and include reminders. The patients need to understand the importance of staying in the study to be assessed for the primary outcome assessments, both on and off treatment drug, so keeping track of patients who prematurely discontinue treatment is important to understand the motivations and adjust accordingly. Prioritising visits is not a recommend initial to approach, but in cases where the patient would otherwise withdraw consent of be lost to FU key assessments are, of course, preferred.

	QUESTION	ANSWER
	Would you use standard censoring in this case when estimating PFS?	We are planning our 3rd Estimands Academy in oncology. A hypothetical strategy in Progression Free Survival is aligned with censoring and so this may be an option for 2nd lines for therapy.
	If we are interested in clear data, then should there be a clause of subject exclusion from trial the moment he requires a rescue medication?	It depends on the study and what the study protocol allows, as in many cases the use of rescue medication is allowed, thus cannot be a cause of subject exclusion. In the PIONEER 1 case, we also had estimand 1 that includes any effect of rescue medication, so therefore, we should keep the patients who take rescue medication in the study and keep collecting data on these. However, in case an estimand not using the treatment policy strategy to handle an intercurrent event is not included in the study, there may not be a need to let such patients continue in the study. Note, it requires careful considerations, since it may be that these data would have been needed for other purposes (addressing other stakeholders with other needs with the same study).
	In the stratum IE strategy, doesn't it raise a concern of loss of benefit of randomization, i.e., if you plan an analysis in patients who took rescue medications, you have no guarantee the trt arms would remain balanced in terms of patient's characteristics at baseline?	The principal stratum strategy seeks to establish a treatment effect in those who *would* tolerate active treatment (probably not interesting to look at this strategy for those who would use rescue medication if on placebo). It is very complex to identify principal stratums in a parallel group design by looking at who tolerates study treatment (as we don't know if the placebo patients would have tolerated active). Sometimes a different type of design is required with run-in or as cross-over.
	Sometimes the timelines for writing the protocol are very short. What is your experience regarding finding the right estimand and the time it takes? I assume a lot of discussions and alignments are needed before it is in place?	No doubt that we are on a steep learning curve. In the beginning it takes a longer time, but once you discover how the framework helps you, it becomes a useful tool that if used will help you avoid errors due to non-alignment. It helps guide the discussions and should save time over the lifetime of the study in avoiding protocol amendments and guiding SAP development later.
	What is the maximum number of estimands that you would recommend using for a given trial (phase 3)?	Cannot really provide a number. Define your primary and key secondary estimand(s)/scientific question(s) of interest and, if possible, evaluate if other relevant questions can be addressed with the same trial design.
	in the hypothetical strategy, doesn't prediction model fitting the predicted value of the endpoint already requires assuming about IMP efficacy? i.e., we'd try to estimate trt effect that already assumes that the IMP works properly? I'm not clear here...	First, it is important to make a distinction between the estimand and the statistical method used to estimate it. The hypothetical strategy as such does not assume IMP efficacy. In the method used for estimating estimand 2, we assume "missing at random". That is, that the distribution of the unobserved data is the same as the observed given the model, covariate and observed data. No assumption of IMP efficacy.
	Are there any disadvantages of using estimands?	We cannot think of any!!! If anything, you need to spend more time upfront in the planning stage, but this cannot be a

QUESTION	ANSWER
	disadvantage as it will save time in interpretation of results and any subsequent discussions with regulatory agencies. Estimands are recommended for primary and important secondary objectives. However, to allow flexibility for exploratory or tertiary objectives, these do not require estimand definitions but they may still be helpful.

REGULATORY EXPERIENCE

QUESTION	ANSWER
Can it be assumed that the pure strategy results in the biggest treatment effect - are regulators open to reflect it in the label in addition to the primary (reality) estimand/endpoint?	The expected treatment difference should not drive your choice of estimand – it should be the relevance of the estimand in the given setting. Currently, in general, it would be difficult to get results from more than one estimand in the label. For example, in the US the legislation says that what goes into the label is the basis for approval.
Can you elaborate a bit on experiences with Health Authorities besides FDA/EMA (i.e., NMPA) and their view on estimands? Do they appear to favour one strategy/estimand over another?	It depends rather on the therapeutic area than on the regulators. In other therapeutic areas also "composite" and "while-on-treatment" strategies are used. Again, discuss in your trial teams, justify your choice, and talk to regulators.