Estimands—What Do They Mean for Health Technology Assessment?

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KEY POINTS

An estimand aims to clarify whether a clinical trial is actually measuring what we think/hope it is measuring.

While the ICH E9 revision focuses mainly on pre-approval activities and stakeholders, estimands will also play an important role in late phase.

Despite the current lack of clarity surrounding implementation, the HEOR community should welcome the revision.

Estimands are coming! The upcoming revision of the International Conference on Harmonisation (ICH)'s E9 "Statistical Principles for Clinical Trials" places greater emphasis on the thorny issue of whether what is actually being estimated in a clinical trial reflects what was intended when the trial was designed. This increased emphasis is framed around the concept of the "estimand"—a term that this ICH revision introduces. Estimands will have a considerable impact upon the design, conduct, and analysis of clinical trials, especially those destined for regulatory submission. This as a very good thing—more thought is definitely needed to ensure that clinical trials do a better job of answering the scientific questions they seek to address.

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This brings us to our first, albeit somewhat pedantic criticism. Although we applaud the effort, we are less convinced by the confusing attempt at branding. Could the E9(R1) authors really not have thought of a better name than "estimands?" Or at least one that sounds a little less like other related and commonly used terms, such as "estimator" and "estimate?"

Putting any naming criticisms aside, it's entirely conceivable that estimands will play an even greater role in the later phases of clinical development. Indeed, the role of the estimand has not escaped ISPOR's attention. A formal response to EMA's request for comments on the addendum has been made by ISPOR this year, following a recent survey of their members. While the ISPOR reviewers gave generally positive feedback, they quite rightly highlighted the limited coverage of the impact of estimands upon post-regulatory approval activities and related stakeholders. Clearly, observational studies and pragmatic trials suffer more acutely from the types of problems that this ICH revision seeks to address. The occurrence of intercurrent events (such as patient dropout, treatment switching, and rescue medication) complicate the estimation of treatment differences in most clinical trials, and especially in low-interventional and real-world studies. These issues convolute, in often subtle and unquantifiable ways, the interpretation of the treatment difference being estimated. The need for a solution that the estimand aims to provide is arguably even more urgent in the health technology assessment (HTA) environment than that in the pre-approval setting.

HTA professionals have a certain luxury in relation to this revision—they will probably be able to observe how the use of estimands evolves in early development before being forced to consider it in their plans. Indeed, they might be well-advised not to rush their adoption. Embedding estimands as part of an addendum to ICH E9 was probably the one way to ensure that it won't make any 2018 readers' choice shortlist. Containing this very critical, cross-functional issue within a statistically focused ICH guidance document could well lead to a slow and tortuous adoption. Given its isolated positioning with the overall guidance, non-statisticians will no doubt interpret estimands as a "problem" that the study statistician alone needs to solve.

How will the practicalities surrounding the implementation of ICH E9 be addressed? And, more importantly, who's going to do it? If estimands end up being discussed in just the statistical sections of a study protocol, then there are no prizes for guessing who's going to end up writing them. Non-statisticians won't exactly be eager to start tackling the subtleties between study objectives, endpoints, outcomes, variables, estimates, estimators, and [deep breath] estimands. In this we see a danger of the ICH revision not being properly addressed in many relevant sections of a study protocol, but rather abandoned in the "statistical section." Guidance on these sorts of protocol-development issues is urgently required.

It is perhaps easy to be overly critical here, and there are already plans afoot to revise other ICH guidance (E8 springs to mind) in line with E9, such that awareness spreads to functions other than statistics. Updates of other ICH guidance should make the process of incorporating estimands throughout a protocol clearer. We therefore advise patience; the understanding, appreciation, and use of estimands will surely improve.

HTA professionals need not necessarily fear the rise of the estimand. There is considerable overlap between this and other concepts often employed by the post-regulatory approval, real-world data environment. PICOT springs to mind, which specifically aims to address important issues such as the population and outcome of interest, among other estimand-related topics. The PICOT "branding" is arguably better too.

In some respects, it's a shame this E9 revision is even needed. Indeed, one might be forgiven for assuming that treatment estimation challenges would already have been given their due attention, but sadly ICH must feel (quite rightly) that the industry needs a considerable push in the right direction.

Estimands are coming and with a potentially huge impact in both pre- and post-approval settings. Those of you with a penchant for wordplay might have recognized that an anagram of "ESTIMAND" is "A MINDSET" — something which we'll soon all need to adopt.

Additional Information:

For more information on the ISPOR Health Technology Assessment Special Interest Group, go to https://www.ispor.org/sigs/HTA.asp