Statistics in Biopharmaceutical Research

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/usbr20

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To cite this article: Alexei C. Ionan, Miya Paterniti, Devan V. Mehrotra, John Scott, Bohdana Ratitch, Sylva Collins, Shanti Gomatam, Lei Nie, Kaspar Rufibach & Frank Bretz (2023) Clinical and Statistical Perspectives on the ICH E9(R1) Estimand Framework Implementation, Statistics in Biopharmaceutical Research, 15:3, 554-559, DOI: 10.1080/19466315.2022.2081601

To link to this article: https://doi.org/10.1080/19466315.2022.2081601

Published online: 06 Jul 2022.

STATISTICS IN BIOPHARMACEUTICAL RESEARCH
2023, VOL. 15, NO. 3, 554–559
https://doi.org/10.1080/19466315.2022.2081601

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Clinical and Statistical Perspectives on the ICH E9(R1) Estimand Framework Implementation

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ABSTRACT

The ICH E9 (R1) Addendum on "Estimands and Sensitivity Analysis in Clinical Trials (Step 4)" was finalized in November 2019 and subsequently implemented by many regulatory agencies, including FDA (May 2021). This article is based on a session organized to cover experience implementing the estimand framework, including its use, impact on drug/biologic development, common challenges and ways to address them, as well as keys to productive interdisciplinary collaboration.

ARTICLE HISTORY
Received January 2022
Accepted May 2022

KEYWORDS
Clinical trials; Intercurrent event; Missing data; Sensitivity analysis; Treatment policy

1. Introduction

In 1998, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) issued an ICH Harmonized Guideline, ICH E9 Statistical Principles for Clinical Trials (1998), that has served as the bedrock regulatory guidance on the fundamentals of design and analysis of clinical trials. The guideline clarified foundational principles of drug development, such as the intention-to-treat principle, randomization, blinding, choice of control, multiplicity adjustment, and interim analysis.

In light of perceived outstanding issues in the handling of missing data in clinical trials, a panel on the subject was convened by the U.S. National Academy of Sciences in 2010 at the request of the US Food and Drug Administration (FDA). The release of the panel's report on the prevention and handling of missing data in clinical trials increased awareness that, in many trial protocols and associated discussions, the specific scientific question often remained implicit (National Research Council, Committee on National Statistics, Division of Behavioral and Social Sciences and Education 2010). This led to discrepancies in interpretation between sponsors and regulators, often late in the drug development process; in particular, often only at the stage of regulatory submission for drug approval. As a reaction, an ICH expert working group was initiated in 2014 with the mandate to develop an addendum to the original ICH E9 guideline. It released a Step 2 draft version of the addendum to ICH E9 in the third quarter of 2017 (International Council for Harmonization 2017) for public consultation and published its final Step 4 version in the last quarter of 2019 (International Council for Harmonization 2019). Since then, the addendum, "E9(R1) Estimands and Sensitivity Analyses in Clinical Trials," has been officially adopted by several health authorities globally, including, in May 2021, the U.S. FDA (U.S. Food and Drug Administration 2021a).

ICH E9(R1) introduces the estimand framework for clinical trials to obtain precisely defined treatment effects corresponding to the clinical questions of interest. An estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population level what the outcomes would be in the same patients under different treatment conditions being compared. ICH E9(R1) introduces five attributes that are used to define an estimand: (1) the population of patients targeted by the clinical question of interest, (2) a precise definition of the treatment conditions to be compared, (3) the clinical outcome variable (or endpoint), (4) the population summary measure, and (5) intercurrent events. In addition, it includes strategies that specify how the treatment effect will be interpreted in presence of these events. Intercurrent events are events occurring after treatment initiation that may affect either the interpretation or the existence of measurements associated with the clinical question of interest. Depending on circumstances, these might include, among others, administration of rescue medication, treatment discontinuation due to lack of efficacy or adverse events, and death. The addendum also identifies five general strategies to address intercurrent events: (1) treatment policy, (2) composite, (3) hypothetical, (4) principal stratum, and (5) while-on-treatment. ICH E9(R1) also focuses on sensitivity analyses to investigate the robustness of a trial's conclusions to deviations from the modeling assumptions underlying a given

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estimator. The goal is that the proposed estimand framework improves alignment between clinical questions of interest, trial objectives, target of estimation, design, method of estimation, and sensitivity analyses. These inform data collection and facilitate clearer interpretation and reporting of clinical trials in regulatory submissions, product labels, and publications.

Prior to FDA's formal adoption of the ICH E9(R1) guidance in May 2021, some divisions of the Office of Biostatistics and the Office of New Drugs in the U.S. FDA had been using the estimand framework for some years. Permutt (2015a), Permutt (2015b), and LaVange and Permutt (2016) collectively describe the problem of choosing an appropriate estimand during the planning stage of a study. They make a case for sensitivity analyses that are designed to evaluate the impact that the handling of missing data and associated assumptions have on a trial's results. They discuss the importance of prevention and prevention strategies for missing data that include selection of appropriate study design, planning for discontinuations and data collection post-discontinuation. This thinking contributed to the subsequent ICH E9(R1) discussions.

The estimand framework is intended to strengthen and facilitate the dialogue on drug/biologic development among review disciplines, as well as between sponsor and regulator. Additionally, the estimand framework is also intended to provide clarity to physicians, patients, and Health Technology assessments. ICH E9(R1) has generated substantial interest and invigorating discussions, mostly within the statistical community. However, productive collaboration and extensive input from members of cross-disciplinary teams are essential for successful implementation of the estimand framework. Statistical and clinical colleagues typically collaborate closely during the FDA review of regulatory submissions. Use of the estimand framework can improve the efficiency and quality of this collaboration. Collaborative discussions are sometimes especially challenging due to multiple complex trial design and analysis issues. The estimand framework provides a structure to facilitate such discussions.

In this article, clinicians and statisticians from the pharmaceutical industry and the FDA, including three members of the ICH E9(R1) Expert Working Group [Frank Bretz, Devan V. Mehrotra, John Scott], highlight the following: impact and benefits of using the estimand framework in drug/biologic development; challenges in using the estimand framework and ways to address these challenges; and keys to productive interdisciplinary communication. Perspectives of other stakeholders (e.g., patients, providers, and Health Technology assessors) are important as well, but are beyond the scope of this article.

2. Impact and Benefits of Using the Estimand Framework in Drug/Biologic Development

The release of ICH E9(R1) has led to an increased use and reporting of estimands in clinical trials, including the reporting of estimands for randomized controlled trials (RCTs) in leading medical journals. Some of these articles discuss clinical trials in specific indications, including diabetes, obesity, and chronic obstructive pulmonary disease, among others (e.g., Rabe et al. 2020; Ludvik et al. 2021; Rubino et al. 2021). A variety of terms have been used to describe the treatment effect of interest, including "treatment policy estimand", "efficacy estimand", "trial product estimand" and "attributable estimand". Drug developers may not yet have consistently adopted the exact terminology suggested in ICH E9(R1). We caution that merely using the term "estimand" does not necessarily lead to a precise description of the treatment effect of interest. For example, "The efficacy estimand is the treatment effect between trizepatide and insulin degludec among all randomized participants who continued to receive the study drug without rescue medication" (Ludvik et al. 2021) remains ambiguous in many respects. Furthermore, continuous endpoints were often analyzed in these studies using mixed model repeated measures (MMRM) with an implicit and hard-to-justify missing at random (MAR) assumption, and a sensitivity analysis, as defined in ICH E9(R1), was rarely reported.

The concept of intercurrent events in the estimand framework is one of the key aspects that makes it different from the pre-addendum practice of clinical trials. It helps both regulator and sponsor clinicians and statisticians to align on how to interpret treatment effects in the presence of post-randomization events that may disturb the clear causal inference associated with randomization, yet accurately reflect heterogeneous journeys of participants throughout the trial. Clarity can be provided around what the treatment effect is, how it can be estimated, and the assumptions—implicit or explicit—under which estimation is possible. This facilitates a dialogue between statistical and non-statistical members of trial and review teams because the focus is less on the technical analytic methods, but rather on the treatment effect of interest and the underlying clinical and statistical assumptions, which can often be best assessed and discussed in the clinical context.

Timing of the discussions regarding the above-mentioned aspects has started to shift as well. In the past, some of these issues were discussed relatively late, for example, as protocol deviations during the blinded data review, or even as late as the submission discussions when raised by regulators. Shifting these discussions to the study design stage helps identify risks and complexities proactively and promotes clarity and preparedness for dealing with estimand considerations in advance. Early alignment of clinical questions of interest, study objectives, study design, data collection, and analysis, as well as precise definition, estimation, and interpretation of a treatment effect, avoids ambiguous data interpretation at later stages. While some study outcomes and their analyses may be interpretable in isolation, it is their alignment with all other aspects of the study that is most important. Precise specification of clinical questions of interest and the alignment of estimand elements with the clinical question of interest helps in obtaining relevant and clearly interpretable treatment effects. Early alignment on estimand specification between sponsors and regulators can substantially facilitate drug and biologic development in terms of quality and speed. This can potentially lead to bringing new safe and effective therapies to patients faster.

Some of the barriers to the implementation of the estimand framework include lack of standardization, lack of familiarity with the estimand framework, and the need to specify estimands appropriate for the intended use under consideration. Multiple international estimand framework implementation

standardization efforts are ongoing, including ICH M11 Clinical electronic Structured Harmonized Protocol. At the Center for Drug Evaluation and Research at the FDA, the protocol review templates have been updated to include estimand considerations, and educational activities focused on the estimand framework are ongoing for staff. While the precision of the estimand specification varies substantially among the submissions now, we hope that the estimand framework educational activities and efforts to implement standardization within the FDA and other regulatory agencies, as well as in the industry, will clarify the estimand considerations and streamline drug/biologic development. With increasing experience, regulatory agencies and sponsors may recommend disease-specific strategies to address specific intercurrent events for regulatory approval and labeling purposes, for example, in a recently published draft guidance for "Chronic Rhinosinusitis with Nasal Polyps: Developing Drugs for Treatment" (U.S. Food and Drug Administration 2021b).

As for the estimand framework impact on design and reporting of clinical trials by industry sponsors, as implemented in trial protocols, statistical analysis plans (SAP), electronic case report forms (eCRF), clinical study reports (CSR), submissions and product labels, we consider the current situation to be very heterogeneous. Some, primarily large, sponsors have rolled out the addendum concept broadly in their organizations and embedded it in their processes, for example, by making it part of the internal protocol and SAP template. Some sponsors advise study teams to include a phase 3 estimand proposal in the Briefing Book as early as possible for a discussion with regulators. For phase 2 studies, it is increasingly embraced as well, as study teams gain experience with defining estimands. Additionally, primary estimands may be somewhat different in phase 2 and 3 and they allow study teams to be clear on why that may be the case and the related implications. It helps to keep in mind that the results from phase 2 need to inform the design of phase 3 and it may be helpful to produce estimates, at least in supplementary analyses of phase 2 data, that will support planning for estimands used in phase 3. However, caution is warranted in interpreting phase 2 estimates for phase 3 planning purposes because clinical questions of interest, study design and conduct, and estimand attributes may differ between phase 2 and 3 studies.

One of the key factors for successful implementation of the estimand framework and translation of the estimands to well-aligned estimators is to collect the information relevant to all estimand elements. Clear pre-specification of intercurrent events that need to be ascertained and the types of clinical events on which information needs to be actively collected during the trial may reduce potential issues with interpretation of results. A key consideration is to strike a new balance between standardization and allowing for trial-specific flexibility in eCRFs, such as capturing reasons for treatment discontinuation. This balance may allow proper capture and classification of intercurrent events and collection of the necessary data to estimate the estimand of interest. When enumerating potential intercurrent events, there are a number of features to consider, including: reason for the events; nature of the event's disruption of endpoint interpretation; and the circumstances for the trial subject after the event has occurred.

Another positive impact of ICH E9(R1) is that it has helped to differentiate whether observations subsequent to an intercurrent event should be construed as missing data. Prior to the adoption of the estimand framework, post-event data from participants who experienced intercurrent events, such as treatment discontinuation due to adverse events or initiation of rescue medications, may or may not have been collected. For example, including plans in a protocol to continue to follow and ascertain outcomes in patients who discontinue treatment, when there is an interest in an estimand with a treatment policy strategy for treatment discontinuation, ensures that relevant data will be available. When we have missing or unobservable data, it is clearer now that not all unavailable data are alike, and we need to handle them in alignment with the estimand. Perspectives in handling of intercurrent events may differ between different stakeholders (e.g., regulatory authorities, Health Technology assessors, patient advocates, physicians). An early dialogue with all stakeholders is critical.

The addendum has also initiated research into statistical methodology on a variety of topics, including analysis of continuous longitudinal data (specifically, estimation of estimands associated with the hypothetical, composite, and treatment policy strategies), causal inference methods, methods for estimand-aligned covariate adjustment, effect quantification for time-to-event endpoints and methods for informative censoring and handling of missing data.

The estimand framework also has utility in simply structuring and formulating the scientific objective in complex situations. It also allows greater clarity on methods that have been routinely used and encouraged in health authority guidelines in the past. An interesting example is addressing subsequent treatment prior to disease progression. Multiple options for this situation exist, including: envisioning a scenario where the subsequent therapy did not occur; or, considering such treatment as part of the overall regimen consistent with the clinical practice; or, considering such treatment initiation to be an endpoint event. We now have nomenclature to talk about these situations: hypothetical, treatment policy, and composite strategy, respectively.

ICH E9(R1) has also had a notable impact on the statistical and broader clinical trial community. It has led to closer collaborations between clinical trial statisticians and specialists in epidemiology and causal inference, to the benefit of all fields. In addition, several working groups (defined by therapeutic areas with examples in oncology and neuroscience, or the European Federation of Pharmaceutical Industries and Associations (EFPIA) estimands implementation working group) have been formed that by now serve as global networks of like-minded statisticians working together across companies with academics and regulators to bridge the gap between the high-level principles put forward in the addendum and the actual implementation in clinical trials.

3. Challenges and Opportunities of Implementing the Estimand Framework

While the addendum has sparked many activities and progress has been made, we see areas where more work needs to be done.

This is primarily in terms of being more careful when describing the estimand so that it aligns with the clearly formulated clinical question of interest and in delivering estimand-aligned analyses.

Lack of training to familiarize both clinicians and statisticians with the new terminology and to facilitate their collaboration may hinder implementation of the framework introduced in ICH E9(R1). To support collaboration between statisticians and clinicians, statisticians need to decode estimand terminology using plain language and provide clear explanations and definitions for common terms used within estimand discussions. Terms that may need elaboration include the differences among intercurrent event strategies, differences between sensitivity and supplementary analyses, and distinctions between missing data and data that are not relevant in the context of the intercurrent event and associated strategies. Defining and understanding estimand terminology is a collaborative and iterative process requiring both statistician and clinician engagement to fully support estimand framework discussions. Training on estimand framework using real examples with illustration of discussions between clinical and statistical disciplines can be especially effective in solidifying understanding of the estimand framework concepts.

Precise definitions of and distinctions between different types of intercurrent events occurring in a trial may be challenging. Determination of treatment discontinuation may become complicated if the experimental treatment is administered in combination with other treatments in a complex treatment regimen. The discontinuation could be of the experimental treatment only or of any other agent(s) in the combination. In addition, trial participants may experience multiple intercurrent events. For example, trial participants who discontinue treatment due to adverse events may take additional or alternative medications. Trial participants may take rescue medication before treatment discontinuation due to lack of efficacy. Addressing these complex issues needs careful forethought and collaborative discussions across multiple disciplines and between sponsors and regulators.

Parties may disagree with the choices of the estimand strategies to address certain intercurrent events. When considered of clinical interest, some strategies (e.g., principal stratum and hypothetical strategies) to address intercurrent events may require use of traditionally less-used statistical methods.

Determining whether strategies to address intercurrent events are appropriate also relies on two critical factors:

1. whether the strategies address questions of clinical and regulatory importance or interest;
2. whether a reliable estimator of the corresponding estimand can be provided, with appropriate sensitivity analyses.

Cross-disciplinary collaboration is vital to answer these questions. Identifying intercurrent events and choosing strategies to address them for different therapeutic areas requires careful thinking to answer the clinical question(s). Choosing appropriate intercurrent event strategies is complex as it requires an individualized approach for each intercurrent event within the context of the identified clinical question. Even before this process begins, clinicians, statisticians, and other stakeholders must identify and agree upon the clinical question the trial is aiming to answer as well as identify the intercurrent events. Both tasks can be challenging as they must be individualized for each trial. Once the clinical question and intercurrent events are identified and agreed upon, discussions can begin on the most appropriate strategy to handle each intercurrent event. There may be more than one strategy that can be used for an intercurrent event. Discussions of which strategy to use as the primary versus supplementary approach is often complex and can vary depending on the clinical context and the intercurrent event. Because each estimand must be tailored to the clinical context, clinicians, statisticians, and other stakeholders must engage in discussions to ensure that the appropriate estimand is defined precisely to answer the clinical question of interest.

Specification, implementation, and result interpretation of some strategies to address intercurrent events is especially challenging. Results obtained based on strategies used to address intercurrent events should inform the clinical questions of interest. For example, in the case of a hypothetical strategy, it is necessary to describe precisely the nature of the hypothetical scenario under which estimation of treatment effect is of interest and why the actual scenario in which the intercurrent event occurs is problematic for the interpretation of the treatment effect. It is important to justify the relevance of the corresponding treatment effect to be estimated, and the statistical model that accurately captures the specific chosen hypothetical scenario. Per ICH E9(R1), "For example, for a subject that will suffer an adverse event and discontinue treatment, it might be considered whether the same subject would not have the adverse event or could continue treatment in spite of the adverse event. The clinical and regulatory interest of such hypotheticals is limited and would usually depend on a clear understanding of why and how the intercurrent event, or its consequences, would be expected to be different in clinical practice than in the clinical trial." For example, a treatment discontinuation due to investigational drug supply chain issues in a trial held during the COVID-19 pandemic would presumably not occur with similar patients in clinical practice in the future. It is therefore conceivably relevant to estimate what would have happened in a population in which this intercurrent event did not occur, even though it did occur in the trial (Akacha et al. 2020; Meyer et al. 2020; Qu and Lipkovich 2021). However, it is necessary to specify an aligned method of analysis that is able to provide an estimate on which reliable interpretation can be based. Key assumptions should be stated explicitly together with the hypothetical estimand and accompanying main and sensitivity analyses. Assumptions should be clinically justifiable and implausible assumptions should be avoided. As ICH E9(R1) notes, lack of a reliable estimation strategy can itself be reason for not considering an otherwise interesting estimand. In contrast to the pandemic-as-intercurrent-event example, treatment discontinuation due to lack of efficacy, due to adverse events, due to pursuit of alternative therapies, due to administrative reasons (personal scheduling conflict, etc.) or many other causes, would be expected to occur in similar patients in clinical practice in the future. Therefore, the clinical relevance of a hypothetical scenario in which these events do not occur is questionable. Furthermore, the problem of estimation for a hypothetical strategy is inherently even thornier when the statistical models are meant to capture not only a scenario that did not occur in the trial, but a scenario that is not believed

to hold in any way in the population, present or future. The hypothetical scenario being envisaged must be plausible in real life and thoroughly justified. Additionally, a patient's perspective should be considered. Causal inference may facilitate definition and implementation of strategies to address intercurrent events (Lipkovich, Ratitch, and Mallinckrodt 2020). Early cross-disciplinary discussions within teams and among stakeholders are critical when assessing whether a certain hypothetical scenario is relevant. ICH E9(R1) provides one potential example of such a scenario: "For example, it may be of clinical or regulatory importance to consider the effect of a treatment under different conditions from those of the trial that can be carried out. Specifically, when additional medication must be made available for ethical reasons, a treatment effect of interest might concern the outcomes if the additional medication was not available." The clinical question of interest, in addition to availability and likelihood of use of the rescue intervention in future clinical practice, would determine the relevance of this kind of hypothetical no-rescue scenario.

The principal stratum is another challenging strategy to address an intercurrent event. Here, the scientific question of interest involves a definable but generally nonidentifiable subpopulation of patients. Bornkamp et al. (2021) provide various motivating examples. In one of their examples, they describe an application involving the severity of prostate cancer diagnosed in a prevention setting. Specifically, Thompson et al. (2003) reported results from the Prostate Cancer Prevention Trial (PCPT) showing that finasteride significantly reduced the risk of prostate cancer relative to placebo. However, they noted that among patients who developed prostate cancer after randomization, those randomized to finasteride had a higher prevalence of high-grade prostate cancer compared to those randomized to placebo. This "naïve" comparison did not account for potential post-randomization selection bias due to differences among treatment arms in patient characteristics of cancer cases or differential biopsy grading associated with finasteride-induced reductions in prostate volume. A subsequent principal stratification analysis (Shepherd, Redman, and Ankerst 2008) accounting for these two potential sources of selection bias cast doubt on results from the aforementioned naïve analysis. Indeed, a more recent report based on long-term follow-up of PCPT patients (Goodman, Tangen, and Thompson 2019) concluded that "The early concerns regarding an association between finasteride and an increased risk of high-grade prostate cancer have not been borne out." This example serves as a reminder that if the clinical question of interest is restricted to a subpopulation that can be defined but not necessarily identified at the randomization stage, a thoughtful use of the principal stratum strategy, as outlined in the ICH E9(R1) addendum, may help with both an estimand definition and subsequent analysis. However, whether such an approach may yield clearly interpretable and clinically relevant results would need to be discussed early with key stakeholders to ensure alignment. Additionally, application of the principal stratum strategy relies on strong and unverifiable assumptions. Identification of a reliable estimator may be challenging. Early engagement with relevant stakeholders is imperative to discuss considerations of using the principal stratum.

Other strategies to address intercurrent events have their own challenges as well. While the composite strategy is appealing, its implementation is sometimes not obvious, especially with continuous endpoints. Implementation of the treatment policy strategy requires efforts for trial participant retention and prevention of missing data. There remain methodological challenges in dealing with missing data even under this strategy. Additionally, per ICH E9(R1), "treatment policy strategy cannot be implemented for intercurrent events that are terminal events, since values for the variable after the intercurrent event do not exist". The while-on-treatment strategy appears to be misunderstood often and, per ICH E9(R1), requires particular care "if the occurrence of the intercurrent event differs between the treatments being compared". Increased reporting of the proper use of the estimand-defining strategies, ideally through well-documented case studies, will further strengthen the implementation of the addendum.

In addition to ensuring that the strategies to address intercurrent events of interests are relevant from clinical and regulatory perspective, a reliable estimator of the corresponding estimand needs to be specified. Such an estimator needs to be clearly interpretable and must align with the clinical question of interest. The process of identifying a relevant estimator starts with the clinical question. There may be occasions where a suitable estimator may not yet have been developed. It may be tempting to start with a familiar estimator and adjust the clinical question of interest accordingly—this is one of the actions the estimand framework is aiming to avoid. Precise specification of the clinical question must precede, rather than follow, identification of a relevant estimator. This specification must be done either before trial design or early in the design stage.

4. Concluding Remarks

In conclusion, ICH E9(R1) has introduced the estimand framework into drug development. The Addendum has emphasized clear formulation of the treatment effect of interest—the estimand—and the use of estimation methods with transparent assumptions and associated sensitivity analyses. This framework has already proved very useful, not only in tackling new questions but also in better understanding "old" problems. Our subjective experience has been that estimand thinking has been well-accepted so far and that uptake is good. Notably, it has also sparked collaborations among various quantitative disciplines and among statisticians in companies, regulatory agencies, and academia globally. That said, more work needs to be done, as illustrated by the challenges discussed above.

Acknowledgment

The authors would like to thank Gregory Levin, PhD for his valuable comments and suggestions.

Disclaimer

This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

Disclosure Statement

Frank Bretz owns stocks of and is employed at Novartis Pharma AG. The rest of the authors report there are no competing interests to declare.

Funding

The authors reported there is no funding associated with the work featured in this article.

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