

Title: Eliminating ambiguous treatment effects using estimands

Authors: Brennan C. Kahan*, Suzie Cro, Fan Li, Michael O. Harhay

Correspondence Address: *Correspondence to Brennan C. Kahan, PhD, MRC Clinical Trials Unit at UCL, 90 High Holborn, London, WC1V 6LJ, UK (email: b.kahan@ucl.ac.uk)

Affiliations: MRC Clinical Trials Unit at UCL, London, United Kingdom (Brennan C. Kahan); Imperial Clinical Trials Unit, Imperial College London, London, United Kingdom (Suzie Cro); Department of Biostatistics, Yale School of Public Health, New Haven, Connecticut, United States (Fan Li); Center for Methods in Implementation and Prevention Science, Yale School of Public Health, New Haven, Connecticut, United States (Fan Li); Clinical Trials Methods and Outcomes Lab, Palliative and Advanced Illness Research (PAIR) Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States (Michael O. Harhay); Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States (Michael O. Harhay).

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Abstract

Most reported treatment effects in medical research studies are ambiguously defined, which can lead to misinterpretation of study results. This is because most studies do not attempt to describe what the treatment effect represents, and instead require readers to deduce this based on the reported statistical methods. However, this approach is fraught, as many methods provide counterintuitive results. For example, some methods include data from all patients, yet the resulting treatment effect applies only to a subset of patients, whereas other methods will exclude certain patients while results will apply to everyone. Additionally, some analyses provide estimates pertaining to hypothetical settings where patients never die or discontinue treatment. Herein we introduce *estimands* as a solution to the aforementioned problem. An estimand is a clear description of what the treatment effect represents, thus saving readers the necessity of trying to infer this from study methods and potentially getting it wrong. We provide examples of how estimands can remove ambiguity from reported treatment effects and describe their current use in practice. The crux of our argument is that readers should not have to infer what investigators are estimating; they should be told explicitly.

Introduction

Results from randomized trials and observational studies are used to inform policy decisions about which interventions to use. However, reported treatment effects in these studies are often ambiguously defined, which can lead to misinterpretation of study results [1, 2]. This is because most studies do not attempt to describe what the treatment effect represents, and instead require readers to deduce this based on the reported statistical methods [1, 2]. However, this approach is challenging, as many methods provide counterintuitive results (Table 1).

For example, a recent trial reported that baricitinib significantly reduced impairment in daily activities for patients with atopic dermatitis [3]. All randomized participants were included in the analysis in their randomized group, so readers may expect the treatment effect to correspond to the intervention's effect if introduced as part of routine practice. However, the reported effect actually corresponds to the hypothetical setting where participants who stopped treatment had instead continued and rescue therapy was denied [1]. This interpretation is due to the statistical methods employed, where outcome data recorded after patients used rescue therapy or stopped taking treatment were set to missing, and then a mixed model for repeated measures was used to implicitly impute what outcomes would have been had participant's not discontinued treatment or received rescue therapy.

Regardless of one's preference for a treatment effect corresponding to usual practice vs. one corresponding to a hypothetical situation, it is clear that the treatment effect's interpretation should be reported so that readers can understand the exact question being addressed in the trial. However, the interpretation for the baricitinib trial was not given in the published manuscript, and instead readers were left to sift through and interpret complex statistical methods to understand what exactly was being estimated.

Ambiguity in reported treatment effects

The problems described above are not unique [1, 2]. A recent review of randomized trials published in 2020 found that 98% of trial reports did not attempt to describe what their reported treatment effect represented [1]. Instead, readers were left to deduce these interpretations based on the reported study methods.

However, this approach is fraught. In 54% of trials, it was impossible to deduce what exactly was being estimated from the reported methods [1]. There are several reasons for this. First, statistical methods are often insufficiently described [4-6]. In around 15% of trial reports it is impossible to ascertain exactly what statistical analyses were performed [4].

Second, the statistical methods (even when reported in precise detail) are not always sufficient to uniquely identify which treatment effect is being estimated [2, 7]. For instance, consider a trial where the analysis population is restricted to those who complied with their allocated treatment (often referred to as a per-protocol analysis). Does this analysis estimate the treatment effect in the entire trial population, had all patients complied with their allocated treatment? Or does it estimate the treatment effect in the subset of trial participants who would have complied with their allocated treatment? In fact, investigators may use this analysis approach to estimate either treatment effect depending on which assumptions they make, and so readers are unable to deduce what investigators have intended unless they are told explicitly [8].

Finally, it is often difficult to understand what is being estimated from advanced statistical procedures, unless readers are proficient in the particular method. This is particularly the case when certain aspects of the estimator do not match that of the estimand, for instance when statistical methods use data from an analysis population which is not the same as the population for which the treatment effect applies. For example, complier average causal effects (CACE) analysis [9] uses data from the full trial population but the resulting treatment effect only applies to the subpopulation of participants who would have complied with the intervention [9]. Conversely, some statistical methods exclude participants who did not comply with treatment, yet estimate the treatment effect in the entire study population, under hypothetical compliance [10].

Unraveling ambiguous treatment effects

In 14% of trials published in 2020 that were included in a recent systematic review [1] and 74% of those submitted for regulatory approval between 1996 and 2017, hypothetical “what if?” treatment effects were used [11]. Hypothetical “what if?” treatment effects describe what would have happened in hypothetical settings, for instance, if patients who forgot to take their daily medication had instead remembered to. However, only two of the published trials explained that their reported treatment effect related to a hypothetical scenario. For the other trials, correct interpretation of results required readers to infer from study methods that the treatment effects pertained to a hypothetical scenario, provided they had sufficient expertise to do so [1].

“What if?” treatment effects can be useful to inform clinical practice. For instance, patients who forget to take medication can be sent a reminder, or sometimes the reason treatment was discontinued won’t apply in the future (for example, treatment interruptions due to COVID [12-14]). However, many trials use “what if?” situations where the clinical relevance is less clear. For instance, in a recent review, 24% of “what if?” scenarios related to the setting where patients who were forced to stop taking treatment due to adverse effects had instead continued to take medication

despite the adverse effects, and in 79% of trials where deaths occurred but were not considered part of the outcome measure, investigators estimated what the treatment effect would have been in the hypothetical setting where those patients who died had lived instead [1].

None of these trials gave any indication of how patients might continue taking the assigned treatment despite the adverse effects, or how mortality might be completely eliminated in their “what if?” scenario [1]. For instance, would patients be forced to continue taking treatment despite toxicities? Or were investigators imagining a setting where the treatment had somehow become less toxic? These scenarios address fundamentally different questions, and the validity of each may depend on the plausibility of the assumptions around *how* the hypothetical setting envisaged may occur [15].

Limitations of current reporting guidelines

Readers need to understand *what* is being estimated to make informed decisions about the evidence. Yet, this information is rarely reported in study manuscripts or protocols [1, 2]. This may be partly due to current reporting guidelines, which do not mandate this information [16-19]. Instead, reporting guidelines typically require precise descriptions of the study methods, such as the eligibility criteria, analysis populations, treatment arms, and statistical methods; however, as described above, telling us *what* was done does not necessarily tell us what the treatment effect *means*. For instance, providing the study's eligible population or analysis population does not necessarily tell us the population the treatment effect corresponds to, and similar issues exist with trying to identify the treatments being compared or even the outcome measure being used in the estimation of the treatment effect (Table 2).

The crux of the issue comes down to this. Readers should not have to infer what investigators are estimating; they should be told explicitly [20].

Estimands as a solution

Estimands present a solution to the aforementioned issue [2, 7, 11, 15, 21-25]. An estimand is a clear description of what the treatment effect represents, thus saving readers the necessity of trying to infer this from study methods (and potentially getting it wrong). Estimands describe what happens to the same set of patients under different treatment conditions (i.e. they define a causal comparison between treatments based on a common target population [26]).

The concept of an estimand (the target of estimation) is not inherently new, but its use in trials has only been recently formalized with the publication of the ICH-E9(R1) addendum [15]. Estimands can be defined using a structured approach and are typically comprised of five attributes

(Table 2): the population of patients the treatment effect applies to, the treatment conditions being compared, the endpoint, a summary measure of how endpoints will be compared between treatment conditions (e.g., through a risk ratio or risk difference), and how intercurrent events (post-baseline events which affect interpretation or occurrence of outcomes, such as treatment discontinuation or treatment switching) are handled in the treatment effect definition (Table 3). In some settings, additional attributes may also be required [27-30].

An example of how estimands remove ambiguity from treatment effects is provided in Table 4. In the atopic dermatitis trial introduced earlier, inferring the treatment effect's interpretation based on the reported methods requires knowledge of how mixed effects models can implicitly impute missing outcome data under hypothetical "what if?" scenarios. Conversely, the fact that the treatment effect pertains to a hypothetical scenario is explicitly described in the estimand, ensuring readers understand the treatment effect even in the absence of detailed statistical knowledge. Examples of how estimands can be reported are available in Web Appendices 1 and 2, and Web Tables 1-3 [31].

At its heart, an estimand provides readers with a clear sense of what reported treatment effects represent.

Use of estimands in practice

Though the concept of estimands is not new, estimands have only recently started to gain widespread attention. Since the publication of the estimand framework in the ICH-E9(R1) addendum November 2019, medicine regulators in Europe, US, Canada, Singapore, China, Switzerland, and Chinese Taipei have changed their policies to require companies submitting applications to include estimands, and currently regulators in Brazil, the Republic of Korea, and Japan are in the process of implementing this [32].

Notably, most reporting guidelines were written before the release of the ICH-E9(R1) addendum, which may in part explain why estimands are not featured. However, at least one recent reporting guideline has included specification of the target estimand as a required item [33].

Furthermore, some published trial reports and protocols have begun using estimands to clarify reported treatment effects [34-37].

Use of estimands in non-experimental research

Because the primary goal of estimands is to increase the clarity of what reported treatment effects represent, they are just as important for observational studies as for randomized trials. All of

the same principles discussed thus far still apply, however there may be additional considerations for observational research [30].

For example, when using propensity score balancing weights to address measured confounding, different methods of doing so can target different populations, thus changing the “population” attribute of the estimand [38, 39]. Specifically, the average treatment effect among the observed population is estimated by inverse probability of treatment weights (IPTW); the average treatment effect among the treated is estimated by multiplying the IPTW with the propensity score; and the average treatment effect among the overlap population (a population emphasizing clinical equipoise with highest uncertainty in receiving both treatments) is estimated by the overlap weights [40]. Thus, a clear description of not only what weighting scheme has been used but also what population it has targeted is essential to proper interpretation of study results.

Furthermore, different types of intercurrent events may occur in observational studies compared to randomized trials. For instance, the protocol of a randomized trial may mandate that participants reduce their treatment dose in a specific manner when adverse events occur, while in observational studies, where treatment decisions are left to the treating physicians, some participants may stay on the same dose while others may stop treatment entirely or switch to an alternative. Additionally, many routinely collected data sources, such as registries, may not collect information on which participants experience certain intercurrent events. Thus, studies using these data sources may not be able to choose which strategy to apply for these events.

What should change going forward

Despite the increased focus on estimands, their use in practice is still rare [1, 2]. We believe the inclusion of estimands as a mandatory reporting item in reporting guidelines (including each of the five aspects encompassing the estimand) would have an enormous positive impact on increasing clarity around the interpretation of reported treatment effects in research studies.

Conclusion

Estimands offer a simple way of clarifying the interpretation of reported treatment effects so as to avoid misinterpretations of study results.

References

1. Cro S, Kahan BC, Rehal S, Chis Ster A, Carpenter JR, White IR, et al. Evaluating how clear the questions being investigated in randomised trials are: systematic review of estimands. *BMJ*. 2022;378:e070146.
2. Kahan BC, Morris TP, White IR, Carpenter J, Cro S. Estimands in published protocols of randomised trials: urgent improvement needed. *Trials*. 2021;22(1):686.
3. Wollenberg A, Nakahara T, Maari C, Peris K, Lio P, Augustin M, et al. Impact of baricitinib in combination with topical steroids on atopic dermatitis symptoms, quality of life and functioning in adult patients with moderate-to-severe atopic dermatitis from the BREEZE-AD7 Phase 3 randomized trial. *J Eur Acad Dermatol Venereol*. 2021;35(7):1543-52.
4. Cro S, Forbes G, Johnson NA, Kahan BC. Evidence of unexplained discrepancies between planned and conducted statistical analyses: a review of randomised trials. *BMC Med*. 2020;18(1):137.
5. Greenberg L, Jairath V, Pearse R, Kahan BC. Pre-specification of statistical analysis approaches in published clinical trial protocols was inadequate. *J Clin Epidemiol*. 2018;101:53-60.
6. Kahan BC, Ahmad T, Forbes G, Cro S. Public availability and adherence to prespecified statistical analysis approaches was low in published randomized trials. *J Clin Epidemiol*. 2020;128:29-34.
7. Mitroiu M, Teerenstra S, Oude Rengerink K, Pétavy F, Roes KCB. Estimation of treatment effects in short-term depression studies. An evaluation based on the ICH E9(R1) estimands framework. *Pharmaceutical Statistics*. n/a(n/a).
8. Kahan BC, White IR, Edwards M, Harhay MO. Using modified intention-to-treat as a principal stratum estimator for failure to initiate treatment [preprint]. *ArXiv*. 2022. (doi:10.48550/arXiv.2206.10453). Accessed February 1, 2023.
9. Angrist JD, Imbens GW, Rubin DB. Identification of Causal Effects Using Instrumental Variables. *Journal of the American Statistical Association*. 1996;91(434):444-55.

10. Hernán MA, Robins JM. Causal Inference: What If. Boca Raton, Florida: Chapman & Hall/CRC; 2020.
11. Mitroiu M, Oude Rengerink K, Teerenstra S, Petavy F, Roes KCB. A narrative review of estimands in drug development and regulatory evaluation: old wine in new barrels? *Trials*. 2020;21(1):671.
12. Cro S, Morris TP, Kahan BC, Cornelius VR, Carpenter JR. A four-step strategy for handling missing outcome data in randomised trials affected by a pandemic. *BMC Med Res Methodol*. 2020;20(1):208.
13. Kahan BC, Morris TP, White IR, Tweed CD, Cro S, Dahly D, et al. Treatment estimands in clinical trials of patients hospitalised for COVID-19: ensuring trials ask the right questions. *BMC Med*. 2020;18(1):286.
14. Van Lancker K, Tarima S, Bartlett J, Bauer M, Bharani-Dharan B, Bretz F, et al. Estimands and their Estimators for Clinical Trials Impacted by the COVID-19 Pandemic: A Report from the NISS Ingram Olkin Forum Series on Unplanned Clinical Trial Disruptions. *Statistics in Biopharmaceutical Research*. 2022:1-38.
15. ICH E9 working group. *ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials*. Amsterdam, The Netherlands: European Medicines Agency; 2020. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf. Accessed September 1, 2022
16. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332.
17. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-7.

18. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453-7.
19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
20. Altman DG. Better reporting of randomised controlled trials: the CONSORT statement. *BMJ*. 1996;313(7057):570-1.
21. Clark TP, Kahan BC, Phillips A, White I, Carpenter JR. Estimands: bringing clarity and focus to research questions in clinical trials. *BMJ Open*. 2022;12(1):e052953.
22. Fiero MH, Pe M, Weinstock C, King-Kallimanis BL, Komo S, Klepin HD, et al. Demystifying the estimand framework: a case study using patient-reported outcomes in oncology. *Lancet Oncol*. 2020;21(10):e488-e94.
23. Lawrance R, Degtyarev E, Griffiths P, Trask P, Lau H, D'Alessio D, et al. What is an estimand & how does it relate to quantifying the effect of treatment on patient-reported quality of life outcomes in clinical trials? *J Patient Rep Outcomes*. 2020;4(1):68.
24. Rufibach K. Treatment effect quantification for time-to-event endpoints-Estimands, analysis strategies, and beyond. *Pharm Stat*. 2019;18(2):145-65.
25. Sun S, Weber HJ, Butler E, Rufibach K, Roychoudhury S. Estimands in hematologic oncology trials. *Pharm Stat*. 2021;20(4):793-805.
26. Frangakis CE, Rubin DB. Principal stratification in causal inference. *Biometrics*. 2002;58(1):21-9.
27. Kahan BC, Li F, Copas AJ, Harhay MO. Estimands in cluster-randomized trials: choosing analyses that answer the right question. *International Journal of Epidemiology*. 2022.
28. Kahan BC, White IR, Eldridge S, Hooper R. Independence estimators for re-randomisation trials in multi-episode settings: a simulation study. *BMC Med Res Methodol*. 2021;21(1):235.

29. Kahan BC, White IR, Hooper R, Eldridge S. Re-randomisation trials in multi-episode settings: Estimands and independence estimators. *Stat Methods Med Res.* 2022;9622802221094140.
30. Li H, Wang C, Chen W-C, Lu N, Song C, Tiwari R, et al. Estimands in observational studies: Some considerations beyond ICH E9 (R1). *Pharmaceutical Statistics.*n/a(n/a).
31. Cro S, Cornelius VR, Pink AE, Wilson R, Pushpa-Rajah A, Patel P, et al. Anakinra for palmoplantar pustulosis: results from a randomized, double-blind, multicentre, two-staged, adaptive placebo-controlled trial (APRICOT)*. *British Journal of Dermatology.* 2022;186(2):245-56.
32. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Guideline Implementation [Available from: <https://www.ich.org/page/ich-guideline-implementation>. Accessed September 1, 2022.
33. Homer V, Yap C, Bond S, Holmes J, Stocken D, Walker K, et al. Early phase clinical trials extension to guidelines for the content of statistical analysis plans. *BMJ.* 2022;376:e068177.
34. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *New England Journal of Medicine.* 2021;384(11):989-1002.
35. Frias JP, Bonora E, Nevarez Ruiz L, Li YG, Yu Z, Milicevic Z, et al. Efficacy and Safety of Dulaglutide 3.0 mg and 4.5 mg Versus Dulaglutide 1.5 mg in Metformin-Treated Patients With Type 2 Diabetes in a Randomized Controlled Trial (AWARD-11). *Diabetes Care.* 2021;44(3):765-73.
36. Aroda VR, Rosenstock J, Terauchi Y, Altuntas Y, Lalic NM, Morales Villegas EC, et al. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes. *Diabetes Care.* 2019;42(9):1724-32.
37. Goodwin GM, Aaronson ST, Alvarez O, Arden PC, Baker A, Bennett JC, et al. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. *New England Journal of Medicine.* 2022;387(18):1637-48.
38. Li F, Li F. Propensity score weighting for causal inference with multiple treatments. *The Annals of Applied Statistics.* 2019;13(4):2389-415, 27.

39. Li F, Morgan KL, Zaslavsky AM. Balancing Covariates via Propensity Score Weighting. *Journal of the American Statistical Association*. 2018;113(521):390-400.
40. Li F, Thomas LE, Li F. Addressing Extreme Propensity Scores via the Overlap Weights. *Am J Epidemiol*. 2019;188(1):250-7.

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Table 1 – Standard statistical estimators which can lead to unexpected estimands

Estimator	Estimand being estimated
Cox model for a non-fatal outcome (e.g. hospital admission), where participants who die are censored at point of death (where death is the intercurrent event)	<p><i>Hypothetical strategy</i> (i.e. the hazard ratio in the hypothetical setting where participants do not die).</p> <p>This is because the Cox model makes the implicit assumption that censored participants are still alive and at risk of the outcome (hospital admission). This model assumes (i) the hypothetical setting is well defined (i.e. we can describe how participants would no longer die); and (ii) no unmeasured confounding between occurrence of the intercurrent event and outcomes.</p>
Mixed-models for repeated measures, where outcome data is not collected after participants die (where death is the intercurrent event)	<p><i>Hypothetical strategy</i> (i.e. the treatment effect in the hypothetical setting where participants do not die).</p> <p>This is because outcome data will be missing after death (as it does not exist, and so cannot be measured), and the mixed-model for repeated measures implicitly imputes what the missing data would have been had participants been alive. This model assumes (i) the hypothetical setting is well defined (i.e. we can describe how participants would no longer die); and (ii) no unmeasured confounding between the occurrence of the intercurrent event and outcomes.</p>
Inverse probability weighting (where outcome data post-intercurrent event is excluded, and the remaining data is weighted according to their inverse probability of not experiencing the intercurrent event)	<p><i>Hypothetical strategy</i> (i.e. the treatment effect in the hypothetical setting where participants did not experience the intercurrent event).</p> <p>This is because data after the intercurrent event occurs is implicitly replaced using data from participants who did not experience the intercurrent event. This model assumes (i) the hypothetical setting is well defined (i.e. we can describe how participants would no longer die); and (ii) no unmeasured confounding between occurrence of the intercurrent event and outcomes.</p>
Complier-average causal effects using all randomised patients	<p><i>Principal stratum strategy</i> (i.e. the treatment effect in the subpopulation of participants who would always adhere to treatment regardless of the assignment).</p> <p>This is because although complier-average causal effects analysis is performed using the entire trial population, the results only apply to the subset of participants who would have adhered to treatment. Common complier-average causal effects estimators, such as those based on instrumental variables, assume the absence of “defiers”, i.e. participants who would receive the intervention if assigned to usual care, but would not receive the intervention if assigned to the active intervention group.</p>
Modified intention-to-treat analysis where participants who do not begin	<p><i>Principal stratum strategy</i>^a (i.e. the treatment effect in the subpopulation of participants who would begin</p>

treatment are excluded

either treatment).

By excluding participants who do not begin treatment, this approach estimates the effect in those who *do* begin treatment. This estimator assumes that the intercurrent event (treatment initiation) is not affected by randomised treatment arm (i.e. those who begin treatment in one treatment group would also do so in the other group, and vice versa) [8]

^aThis analysis can also estimate a *hypothetical* strategy under an alternative (stronger) set of assumptions.

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Table 2: Core elements of an estimand

Attribute of estimand	Description	Limitations of current reporting requirements
Population	The population of patients we want to estimate the treatment effect for	Reporting guidelines require authors to report the patient eligibility criteria and the analysis population, however neither of these tell us <i>who</i> the treatment effect applies to. For instance, certain statistical methods use data from all randomized patients but estimate the treatment effect for a subpopulation of patients. Other methods that exclude certain patients (e.g., those with treatment deviations) estimate a treatment effect that applies to <i>all</i> participants under hypothetical compliance.
Treatment conditions	The treatment conditions being compared for the treatment effect	Though most reporting guidelines require a description of the treatments patients are assigned to, these are not necessarily the same as the versions of treatment being compared for the treatment effect. For example, some protocols may allow patients to discontinue treatments or receive rescue medication, but use statistical methods which estimate the treatment effect for a version of treatment where patients did not discontinue or receive rescue medication.
Endpoint	The outcome measure collected for each patient that the treatment effect is based on	The outcome measure collected for each patient is a key component of all reporting guidelines, however this is not always the outcome measure used for the treatment effect. This mismatch can occur when there are intercurrent events (see row below), particularly death (if death is not inherently part of the outcome measure). For example, for the outcome “disease recurrence up to 12 weeks” it is not entirely clear what outcome should be used in the treatment effect if a patient dies at week 7 without recurrence. The outcome used in the treatment effect could either be “recurrence up to 12 weeks or death, whichever is sooner” or “recurrence or death up to 12

		weeks” (both of which would lead to a different outcome for this patient).
Summary measure	The summary measure used to compare endpoints between treatment conditions for the treatment effect (e.g. mean difference, risk ratio, odds ratio, etc.)	The summary measure can typically be inferred from the statistical model used (e.g. a difference in means from a linear regression model, or odds ratio from a logistic regression model), though this is not always the case. Sometimes advanced statistical models are used to compute risk ratios or risk differences from logistic models (whose regression parameters correspond to odds ratios).
Handling of intercurrent events ^a	How post-baseline events, which affect the interpretation or occurrence of the endpoint (e.g. treatment discontinuation, treatment switching, use of rescue medication, or death if not defined as part of the outcome) are handled in the definition of the treatment effect	Reporting guidelines do not typically require handling of intercurrent events to be reported, however the handling of such events are critically important to the interpretation of the treatment effect. For instance, how we handle “treatment discontinuation” can lead to drastically different treatment effects, ranging from “the effect regardless of discontinuation”, “the effect in the subset of patients who would not discontinue”, or “the effect in the hypothetical setting where patients would not discontinue”.

^a Standard strategies for handling intercurrent events are (a) treatment policy (we are interested in the treatment effect regardless of the intercurrent event); (b) hypothetical (a hypothetical scenario is envisaged where the intercurrent event does not (or does) occur; we are interested in the treatment effect if participants did not (or did) experience the intercurrent event); (c) composite (the intercurrent event is used as part of the endpoint definition); (d) principal stratum (we are interested in the treatment effect in the subpopulation of patients who would (or would not) experience the intercurrent event); and (e) while-on-treatment (the endpoint measured up until the occurrence of the intercurrent event is of interest; this is referred to as “while alive” when the intercurrent event is death).

Table 3 – Definitions of different strategies to handle intercurrent events in the estimand definition^a

Strategy to handle intercurrent events in estimand definition	Description	Definition using potential outcomes
Treatment policy	The outcome regardless of the occurrence of the intercurrent event is of interest (i.e. the intercurrent event is considered part of the treatment strategy). Cannot be used for truncating events which preclude occurrence of the outcome.	$E \left(I \{ T_Y^{(Z=1)} \leq F \} - I \{ T_Y^{(Z=0)} \leq F \} \right)$
Composite	The intercurrent event is included in the endpoint definition, e.g. by assigning a particular value of the endpoint to patients who experience the intercurrent event. Different composite estimands could be defined based on the particular value assigned to the endpoint.	$E \left(I \{ \min(T_Y^{(Z=1)}, T_R^{(Z=1)}) \leq F \} - I \{ \min(T_Y^{(Z=0)}, T_R^{(Z=0)}) \leq F \} \right)^b$
While on treatment/while alive	The endpoint prior to the occurrence of the intercurrent event is of interest.	$E \left(I \{ T_Y^{(Z=1)} \leq \min(F, T_R^{(Z=1)}) \} - I \{ T_Y^{(Z=0)} \leq \min(F, T_R^{(Z=0)}) \} \right)$
Hypothetical	The effect of treatment in a hypothetical scenario where the intercurrent event would not occur is of interest. There can be multiple hypothetical settings that would apply to any particular intercurrent event, so it is necessary to describe the precise hypothetical setting envisaged.	$E \left(I \{ T_Y^{(Z=1, R^{(Z=1)=0})} \leq F \} - I \{ T_Y^{(Z=0, R^{(Z=0)=0})} \leq F \} \right)^{b,c}$
Principal stratum	The treatment effect in the subset of participants who would (or would not) experience the intercurrent event is of interest.	$E \left(I \{ T_Y^{(Z=1)} \leq F \} - I \{ T_Y^{(Z=0)} \leq F \} \mid R^{(Z=1)} = R^{(Z=0)} = 0 \right)^b$

	Different principal stratum could be defined (e.g. the set of participants who would not discontinue treatment under either treatment vs. the set who would not discontinue if assigned to the intervention)	
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^a Z denotes treatment allocation (0=control, 1=intervention), and Y denotes a binary outcome, defined as 1 if an event occurred within over a defined follow-up F , and 0 if an event did not occur by time F . Equivalently, Y can be written as $I\{T_Y^{(Z=Z)} \leq F\}$, where T_Y denotes the time the outcome Y occurred, $T_Y^{(Z=0)}$ and $T_Y^{(Z=1)}$ denote the potential outcomes for the time of Y under intervention and control respectively, and $I\{\cdot\}$ is an indicator variable (defined as 1 if the expression inside the brackets occurred, and 0 otherwise). R denotes an intercurrent event (1=occurred, 0=did not occur), with $R^{(Z=1)}$ and $R^{(Z=0)}$ representing the potential occurrences of the intercurrent event under intervention and control, and $T_R^{(Z=1)}$ and $T_R^{(Z=0)}$ denoting the potential times of the intercurrent event under intervention and control.

^b For composite, hypothetical, and principal stratum strategies, different versions of the estimand could be defined than those considered here (e.g. based on different values assigned to the outcome, different hypothetical settings, or different principal stratum populations). For instance, an alternative principal stratum estimand, where the population is defined as participants who would adhere to the intervention, is: $E\left(I\{T_Y^{(Z=1)} \leq F\} - I\{T_Y^{(Z=0)} \leq F\} \mid R^{(Z=1)} = 0\right)$

^c In order for the hypothetical estimand to be well-defined, the specific setting under which the intercurrent event would not occur (i.e. under which $R = 0$) needs to be precisely defined alongside, as the potential outcomes may differ depending on the exact setting imagined where $R = 0$. This implies that impossible hypothetical scenarios, for which there is no possible setting in which $R = 0$ for all patients, are in general not well-defined.

Table 4: Understanding what treatment effects represent based on reported statistical methods vs. estimands in a trial of baricitinib for atopic dermatitis

Statistical methods	Estimand
<p>“The analysis population comprised all randomized patients, regardless of whether they received the correct treatment. Mean change from baseline for continuous measures (PROMIS and WPAI-AD) was evaluated using a restricted maximum likelihood-based mixed model repeated measures (MMRM), where the model includes treatment, region, baseline disease severity [validated Investigator Global Assessment for AD (vIGA-AD)], visit and treatment-by-visit-interactions as fixed categorical effects and baseline and baseline-by-visit-interaction as fixed continuous effects.”</p> <p>“Data collected after first rescue therapy or permanent study drug discontinuation were considered missing. No explicit imputations were conducted for continuous measures; MMRM analysis was performed to mitigate the impact of missing data because it yields valid inferences assuming that missing observations are missing-at-random.”</p>	<p>The treatment effect is the difference in means in the WPAI-AD change from baseline score at 16 weeks between baricitinib 4-mg or 2-mg vs. placebo daily plus topical corticosteroids for adults with atopic dermatitis (meeting the trial eligibility criteria), regardless of whether participants received the correct treatment, in the hypothetical scenario where treatment discontinuation did not occur regardless of side effects or other adverse effects, and rescue therapy was not provided, even if medically indicated.</p>

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