Comments on ‘Estimands in clinical trials – broadening the perspective’

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The paper by Akacha, *et al.* [1] is an excellent addition to the literature on this emerging ICH topic [2] [3] prompted by the NRC missing data report [4] and also identified as a gap in the original ICH document [5] [6]. I thank the editors for allowing me to comment on this work.

The ‘tripartite approach’ proposed by the authors appropriately highlights the need to think about the outcomes of trials more comprehensively. Many have shown why ‘last observation carried forward’ can be misleading for many reasons, and while in some cases, even the trusted intention to treat (ITT) can lead us astray. Thus, having more windows into the results from multiple perspectives should broaden our ability to interpret trials. In fact, this paper and the estimands discussion in general point out the need for better connection between each estimand and its associated clinical hypothesis. Clinician scientists may not be best positioned to select the ‘best’ estimand, but they can surely help determine where the estimand/estimate is actually describing something of clinical value or meaning to healthcare practitioners and patients. My assumption in this review is that the treatment has been shown to be efficacious based on a primary endpoint that is randomization and design-based (dare I say ITT?), as I do not think estimands that stray from that will be readily accepted by the scientific community as the sole basis for establishing the ‘benefit’ part of benefit to risk of a new medicine.

While all stakeholders do indeed want improved health for patients, I do not completely agree that patients, payers, and regulators always have all the same motivations and objectives, thus the need for drug and device regulations requiring special targeted patient input [7–9]. It is well understood that benefit-to-risk considerations can be very different for patients than for public health officials. While I do agree that all three parts of the tripartite approach have their place in the debate and a part in the complete benefit to risk picture, I am not as certain as the authors that all would be given equal weight by all parties. The paper mentions benefit–risk later but not in this context and perhaps that could be an extension of this work to give this approach even more useful. I realize it is a journey, and the authors have taken an important first step; perhaps what I suggest is a next generation refinement.

Some of the key premises of the paper are discussed in section 2.2, although stated reasons to discontinue a treatment are rarely as crisp as implied in this section. If a treatment is ‘working’, the safety issues a patient is willing to tolerate are very different than if it is not; that is, each patient and their investigator/healthcare practitioner make their own benefit–risk decision. For prevention (vaccines, secondary MI prevention, etc.) the level of tolerance is much less because the individual patient sees little discernable benefit (patients do not know their event that did not happen was the one prevented) and the ‘treatment policy’ is actually the primary objective in this situation as they point out later in the paper.

The authors set up the tripartite discussion by reviewing current practice in section 3. They discuss the differing approaches to accounting for patients who do not complete the trial and/or have substantial missing data from the original intended design collection. They also review the shortcomings of any individual approach such as last observation carried forward or per-protocol (completers or adherers). They point out correctly that intention to treat [10] approaches, while retaining the power and value of randomization, also have some limitations, thus the need for a broader approach to evaluating the endpoints in clinical trials. This applies mostly to trials of repeated measurements of a disease state in response to intervention of a treatment, active control, or placebo. The same issues of missing data can emerge in a prevention trial of a vaccine or pharmaceutical and exhibits itself as ‘loss to

follow-up'. This paper is really focused on the former and, as noted earlier and by the authors, their approach does not necessarily apply in the same manner for the latter cases.

I wonder about the assumption of the generalizability of adherence estimates in the real world. Data indicate that a third of prescriptions are never filled in the first place [11] and we know that label instructions are not always followed, [12–15] so it is hard to imagine the 'perfect adherers' are the 'largest population of patients' in the real world. How then does that change the way the adherence estimate from a trial relates to the real world? While it is true, there are those patients who 'can' or 'cannot' follow the label; among those who can, they are further divided into those who 'will' and 'will not'. Furthermore, while ITT can have its issues, it is a well-established and trusted scientific concept used to convey results to the scientific and medical community. Physicians prescribe medications to patients and inform them in some manner that they work better if you take them; a theory that also applies to people who are more compliant with placebo in clinical trials [16,17]. If ITT is so unclear to the medical community, then consideration needs to be given to how to interpret and communicate that and the newer, more complex approaches to practicing physicians and patients.

I agree with the argument that providing all three estimands would, at a minimum, force a discussion with regulators and payers about appropriate messaging to patients, even if all three do not end up in the label. If they do all appear, then the wording in patient information brochures needs to be considered as the conditional nature of these arguments will need some careful language.

There is indeed a good practical example of the application of the adherence estimate in the label or patient package insert. For example, even if one cannot predict which patients will 'adhere', would knowing what happens if they do perhaps influence a patient or healthcare practitioners to encourage the patient to 'tolerate' adverse effects long enough and modify their personal benefit–risk decision if they knew benefit was likely to come at the other end?

The tripartite approach proposed by the authors is a well-thought-out discussion and a step forward in the evolving debate around estimands. The authors effectively get across the point about the need to think about the outcomes of trials more comprehensively and from multiple points of view. This paper, and estimands discussion in general, points out the need for better connection with each estimand and the associated clinical hypothesis. I do think the robustness of the link between the proposed estimands calculated from trials and the way they be implemented in practice needs to be considered further as the real world may not behave as intended. Finally, a follow-up piece of work around evaluation of safety and benefit to risk would be another valuable addition to the estimands story.

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