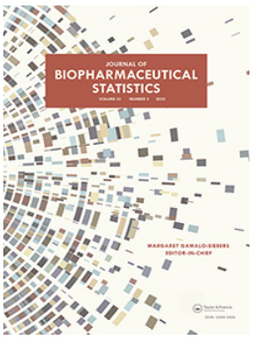

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Response to Comment on "Emerging insights and commentaries – MMRM vs LOCF by Naitee Ting"

David Wright[a], Daniel J. Bratton[b], Thomas Drury[b], Oliver N. Keene[c], Sunita Rehal[b], and Ian R. White[d]

[a]Statistical Innovation, Data Science & Artificial Intelligence, Biopharmaceuticals R&D, AstraZeneca, Cambridge, UK; [b]Statistics and Data Science Innovation Hub, GSK, London, UK; [c]KeeneONStatistics; [d]MRC Clinical Trials Unit at UCL, University College London

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In a recent article, Ting (2023) discusses use of MMRM and LOCF analysis strategies in the context of the ICH E9 (R1) estimands framework (ICH E9R1 2020). While the author has presented an interesting argument for the broad adoption of LO (last observation) analysis, we have serious concerns regarding the justification provided and the conclusions drawn by the author.

Developing an estimand for a trial starts by determining the objective and the related clinical question of interest. Once these have been agreed and clearly described, an estimand that is aligned with the clinical question of interest can be defined, which will in turn drive the choice of study design. A method of estimation that is in line with the chosen estimand under plausible assumptions can then be specified. It is crucial that the chosen estimation method should not drive the choice of estimand. In our opinion, Ting ignores the need to identify plausible assumptions and conflates choice of estimand with choice of estimation method. As an example, the choice to focus on outcomes at the last observed time point, or a specific time point, should be a clinical decision at the estimand level and not a statistical choice as Ting suggests.

The author makes a universal recommendation that "for longitudinal data analysis, while on treatment strategy and treatment policy strategy are more appropriate than hypothetical strategy". This ignores the clinical setting and the consequences the intercurrent event(s) (IEs) could have for a particular study. All strategies defined in the ICH E9 (R1) Guideline (ICH E9R1 2020) may be appropriate depending on the clinical question. The author's perspective on the hypothetical strategy appears to be based on the view that this approach does not reflect reality. However, use of the hypothetical strategy can answer important clinical questions in medicine, for example in diabetes trials where rescue medication will affect the endpoint and use may be imbalanced between treatment arms (Keene et al. 2021). The hypothetical strategy has close links to the causal inference literature, and the importance of estimating causal effects in clinical trials has been emphasised by Hernán and Robins (Hernán and Robins 2017).

Ting asserts that LO can be an implementation of the treatment policy or while on treatment strategies. In the context of a treatment policy strategy, the author claims that an LO analysis represents an appropriate estimator and does not require any carrying forward of data. ICH E9 (R1) states that the treatment policy strategy requires follow-up of participants to the end of the trial (Ratitch et al. 2020) and so any uncollected data following a participant's last observation is considered missing data. Therefore, LO analysis without any further imputation of data is not an appropriate estimation method for a treatment policy strategy approach. A "while on treatment" strategy might be a valid option to handle IEs in cases where the timing of the IE or the duration of treatment does not matter. However, the time aspect of a treatment effect is important for many diseases because it clarifies whether the effects are short term or long term and how the effects evolve (instant, gradual,

CONTACT David Wright david.wright1@astrazeneca.com

delayed, etc.). Using an LO outcomes analysis disregards the time aspect and does not offer the same level of granularity about the effects of an intervention.

A composite handling strategy is not addressed in the article in a repeated measures setting, but it can still be relevant, for example, when a poor outcome is to be assigned to participants discontinuing due to lack of efficacy. In the simple situation where the only IE is discontinuation of investigational product and participants are not followed up after this, one justification for LO is that it reflects a poor outcome for participants with the IE. Even in this case, better approaches are available for the composite strategy (Darken et al. 2020; Keene 2019).

Ting asserts a concept of "one patient one vote". The idea that patients are equal is important, but the concept needs to be clearly defined. Ting applies equality of patients to the statistical analysis, but we argue that it should instead apply to the *estimand*. For example, an average treatment effect for a treatment policy estimand handles different patients' outcomes equally, regardless of whether the outcomes follow an IE, and regardless of whether the outcomes are observed or not. It does not follow that all patients should be weighted equally in *estimation*. For example, consider a patient who is lost to follow-up at an early stage in the trial before their main outcome is observed. The estimand relates to their unobserved main outcome value, which may be better informed by the observed outcome values of *other comparable patients at the correct time* than by the values of *the same patient at earlier times*. The choice between these should depend on what assumptions are plausible in the clinical context.

In terms of MMRM, Ting states that "it is not clear what MMRM attempts to estimate". Depending on the structure of the model, MMRM can provide an appropriate estimation method for either the treatment policy or the hypothetical strategy. For a treatment policy approach, an MMRM for estimating the treatment effect at specific visits would include outcome measures observed after the IE. Estimating the outcome measures in this way targets the treatment effect including the IE as part of the treatment policy. Problems with IE induced missingness can be resolved by accounting for its occurrence in the MMRM, for example by first estimating separate treatment effects prior to and following the IE. If on the other hand MMRM is used as the estimator where outcome measures are only included pre-IE, missing-at-random (MAR) is implicitly assumed and the estimates are targeting the effect in the absence of the IE, which is well-aligned with the hypothetical strategy.

One of Ting's main reasons for favouring LO over MMRM is that "LO has established excellent tracking records in approving life-changing drugs". This reasoning stems from the author's comment that LO was "the main method for drug development and drug approval over four decades between 1962 and 2008", during which "approved drugs have extended human life expectancy and improved patients' quality of life successfully". To us, it is incorrect to attribute the discovery of new medicines to a particular method of analysis. There are a multitude of reasons why many effective medicines were discovered during this period, most notably because of scientific advances. Furthermore, trials of drugs which primarily assessed survival would not have used LO for such an outcome measure and so the "prolonging of human life expectancy" cannot be attributed at all to LO which is applied to repeated measures data.

Finally, we also question the assertion that LO analysis is superior because "this estimator is well understood – by physicians and statisticians". Even though it has been used in some historical settings, what an LO analysis actually estimates is not obvious and prone to misunderstandings.

In summary, we disagree with Ting's attempt to choose estimation methods from purely statistical considerations. The choice of estimation methods should be driven by the choice of estimands, which in turn should be based on clinical rationale. A principle of holding all patients equally important applies in the estimand, not in the estimation method. What an MMRM estimates in a repeated measures setting is clear, well defined and can provide an appropriate estimation method for both a treatment policy and hypothetical approach. Finally, LO analysis without any further imputation of data is not an appropriate estimation method for a treatment policy strategy approach.

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References

Darken, P., J. Nyberg, S. Ballal, and D. Wright. 2020, Sep. The attributable estimand: A new approach to account for intercurrent events. *Pharmaceutical Statistics* 19(5):626–635. doi:10.1002/pst.2019.

Hernán, M. A., and J. M. Robins. 2017 Oct 5. Per-protocol analyses of pragmatic trials. *The New England Journal of Medicine* 377(14):1391–1398. doi:10.1056/NEJMsm1605385.

ICH E9(R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. (Effective in EMA 30 July 2020)

Keene, O. N. 2019, Jan. Strategies for composite estimands in confirmatory clinical trials: Examples from trials in nasal polyps and steroid reduction. *Pharmaceutical Statistics* 18(1):78–84. doi:10.1002/pst.1909.

Keene, O. N., D. Wright, A. Phillips, and M. Wright. 2021. Why ITT analysis is not always the answer for estimating treatment effects in clinical trials. *Contemporary Clinical Trials* 108:106494. doi:10.1016/j.cct.2021.106494.

Ratitch, B., J. Bell, C. Mallinckrodt, J. W. Bartlett, N. Goel, G. Molenberghs, M. O'Kelly, P. Singh, and I. Lipkovich. 2020, Mar. Choosing estimands in clinical trials: Putting the ICH E9 (R1) into practice. *Therapeutic Innovation & Regulatory Science* 54(2):324–341. doi:10.1007/s43441-019-00061-x.

Ting, N. 2023. Emerging insights and commentaries – MMRM vs LOCF. *Journal of Biopharmaceutical Statistics* 33 (2):253–255. doi:10.1080/10543406.2023.2184828.