Two estimands in a clinical trial

Same old same old or double trouble?

Michael O'Kelly, Centre for Statistics in Drug Development, Decision Sciences, IQVIA

Summary

- Multiple objectives
- Multiple estimands
- Multiplicity
- Discussion

Example objectives from protocols close to hand

- “To demonstrate the efficacy of <treatment> in <efficacy measure> in patients with <syndrome>.”
- “To evaluate the efficacy of <treatment> in the reduction of <efficacy measure> in adult female subjects at <time point>.”
- “To assess the efficacy of <treatment>”

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Multiple latent objectives

Multiple estimands should be expected

- Ratitch et al. (2019): “In designing clinical trials, it is important to consider the decisions to be made by various stakeholders”
- The ICH E9 (R1) multiple estimands, even for a single stakeholder.
- Akacha et al. (2017): All stakeholders have two interests:
  - (a) lack of adherence to treatment due to different reasons and
  - (b) efficacy and safety profiles when patients, in fact, are able to adhere.
- Bell et al. (2021): idea of *detailed clinical objectives.*
  - Paper allows for multiple (more-focussed) objectives=>multiple estimands

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Ratitch et al. (2019): multiple stakeholders

- Estimands will differ to suit the kind of decision to be made
  - Regulators and payers: population-level decisions.
  - Prescribers: patient-level decisions.
- Safety vs efficacy: populations of interest may differ.
- Safety: multiple summary measures of interest:
  - For example: counts and % of AEs.

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ICH E9 (R1) envisages potential need for >1 estimand, for a single stakeholder – the regulator

- Section A.3.4: “[Where a treatment policy approach is not of main clinical interest, an] estimand based on the treatment policy strategy might offer the possibility to obtain a reliable estimate of a treatment effect that is still relevant. In this situation, it is recommended to also include those estimands that are considered to be of greater clinical relevance and to present the resulting estimates along with a discussion of the limitations, in terms of trial design or statistical analysis, for that specific approach.”

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Bell et al. (2021): encourages detailed *clinical* objectives (DCOs)

- DCOs involve clinicians
  - DCO includes clinical perspective on intercurrent events. Two protocol examples:
    - “The treatment effect of primary interest is while on treatment, excluding the effects of discontinuation or switching to maintenance therapies.”
    - “The treatment effect of interest is for randomized and treated patients regardless of the extent of treatment adherence or discontinuation but excluding the effects of any subsequent anti-cancer therapy.”
  - More focussed objectives=>multiple objectives=>multiple estimands

Multiple estimands: impact, interpretation…and multiplicity

- One per stakeholder, agreed beforehand with that stakeholder.

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- One per stakeholder, agreed beforehand with that stakeholder.
  - Multiple results, each with equivalent status
    - › From the perspective of those not named as stakeholders, potential hidden multiplicity
      - »Non-stakeholder can publish “best” of multiple pre-planned estimand results.
  - Ratitch et al. (2019): may be “expedient” to name a primary objective and estimand.

/Multiple estimands: impact, interpretation…and multiplicity

- >1 estimand per stakeholder
  - Decision-making becomes complex
    - › Example: good treatment-policy result but clinical effect not strong
    - › Example: good efficacy in adherers but dropouts with AEs

Multiple estimands for payers

- Payers may need to deal with multiple estimands for efficacy
  - External and internal rubrics needed for fair comparison across treatments and across time.

Same old same old or double trouble: what's primary?

- Double trouble
  - Estimand terminology may smudge the barrier between primary and secondary estimates of efficacy
- Same old same old
  - Before estimands were a thing, publications and even clinicaltrials.gov results were often unclear about whether a featured estimate of treatment effect was the primary one.

Same old same old or double trouble: decision-making affected?

- Double trouble
  - Double or tripartite estimands could make regulatory decisions difficult.
- Same old same old
  - For some trials, ICH E9 (R1) specifically envisages >1 estimand as helpful for regulatory decisions, so perhaps double or triple estimands are not such a problem for regulatory decision makers?
  - Including formal safety estimands in a trial could usefully highlight safety issues.

Same old same old or double trouble: multiplicity problems?

- Double trouble
  - Multiple estimates of efficacy could facilitate cherry-picking for submissions to payers, and submissions to journals.
- Same old same old
  - Payers are likely to be careful to compare like with like estimates when negotiating.

Some real issues?

- New possibilities for cherry-picking in publications
- ICH E9 (R1) envisages multiple estimands for the regulatory stakeholder
  - Interpretation by pressure groups;
  - Impact via media.

References

- Ratitch B et al. (2019) Choosing Estimands in Clinical Trials: Putting the ICH E9(R1) Into Practice. *Therapeutic Innovation and Regulatory Science.*
- European Medicines Agency (2020) *ICH E9 (R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.* EMA/CHMP/ICH/436221/2017 Committee for Medicinal Products for Human Use.
- Bell J et al. (2021) The detailed clinical objectives approach to designing clinical trials and choosing estimands *Pharmaceutical Statistics.*
- Akacha et al. (2017) Estimands in clinical trials - broadening the perspective *Statistics in Medicine.*

Questions?