ICH E9(R1): terminology, taxonomy, systematic approach. Reflections on trimmed means and undilution

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General comments

- ICH E9 is an important document, but light on handling of missing data and intercurrent events.
- The NRC report on missing data expanded greatly on missing data and on the concept of estimands, but had emphasis on outcome trials with meaningful missing data and is light on trials in which intercurrent events render missing data either irrelevant (eg, switch to effective rescue) or non-existent (eg, death where endpoint is creatinine clearance).
- ICH E9(R1) draft (and Devan's discussion) provide defined terminology, taxonomy, a structured framework, and related strategies that likely will:
  - Sharpen thinking about objectives, issues, and approaches
  - Enhance communication between sponsors, FDA, trialists, data consumers.
  - Improve design of trials and their ability to address key questions
  - Spur development and adoption of innovative approaches
- Thomas' discussion of cross-country scoring* and undilution open the door to useful approaches to a common and important problem.

* Actual cross-country scoring is not exactly as Thomas describes.

Therapeutic Trials: the Setting
(I do not mean clinical trials)

A common clinical setting

- A patient has a chronic condition or illness.
- Several therapeutic options exist.
- A short trial of one therapy is begun, but soon switched if not tolerated or if the response seems inadequate.

This approach is taken both in symptomatic therapy (eg, back pain, migraine) or in disease modifying therapy if there is an early indicator of response:

- A surrogate such at BP, cholesterol, HbA1c
- A lesser clinical response such as signs and symptoms improvement in rheumatoid arthritis treated with immunomodulators which address joint destruction and disability.

Therapeutic Trials Setting

- In a substantial numbers of patients, a therapeutic trial of one or more drugs may fail due to inadequate response or inability to tolerate.
  - The incidence of such events is relatively straightforward to measure;
  - the benefit in those who did not switch (or would not have switched in a non-trial setting) due to poor efficacy or tolerability is more difficult to quantitate due to difficulty identifying a comparator group (those on control arm who would not have switched had they received the experimental agent).
- Despite difficulties, an estimate of how well the therapy works in those who tolerate it and appear to respond to it (ie, those who are kept on it) is of substantial value for clinical decision making – this is the population likely to stay on the drug.
  - A therapy with outstanding efficacy, albeit limited to a relatively small subset who tolerate and respond, could be of great value and well worth a short trial.
  - Most tradition approaches incorporate untestable assumptions to identify a comparator group and/or dilute estimates of efficacy by including efficacy data from non-responders.
  - In many settings with short therapeutic trial settings, the clinical implications of needing to switch are modest (e.g., non-serious reversible AEs, minor delays in initiation of effective therapy). Thus, the interpretability of measures of efficacy in completers is especially clear and relevant.

Addressing the Information Needs

- Some design features can help focus estimates on those who tolerate and appear to respond
  - Run-in, randomized withdrawal, enrichment designs
  - But they have limitations.
- Unilaterally trimmed mean approaches* can . . .
  - Randomize and analyze the relevant population (those who might receive a therapeutic trial),
  - Manage patients as if in a therapeutic trial
    - If not tolerated, switch to rescue
    - If inadequate response, switch to rescue or trim from analysis those who with responses likely to lead to switching in clinical practice.
  - Both estimate the frequency of tolerator/responders and provide a conservative (ie, if biased, biased against the experimental agent) estimate of the magnitude of benefit of in tolerator responders, avoiding many assumptions of other approach

* Permutt and Li, Pharmaceut. Statist., 2017, 16, 20-28

Further reflections on trimmed means

- Use with outcomes.
  - As noted, short therapeutic trials occur if an early marker can be measured to guide switching.
  - TMs can be used to estimate the effect on markers in tolerators/responders.
  - The feasibility and interpretation of using TM based on ranking via a marker (after switching based on a marker) to estimate effects on outcomes in non-switchers requires further consideration.
- When non-responders may have impaired endpoints (harm on primary)
  - Thrombolytics post stroke can increase the incidence of full recovery and of bleeds leading to death or severe disability, while decreasing the incidence of mild to moderate residual disability. Unilateral trimmed means may allow undiluted estimates of both efficacy and safety.