Statistical Challenges in Evaluating Safety of Response-guided Dose-titrated Drugs

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1. Introduction

- In some therapeutic settings, drug dose is titrated to optimize the benefit-risk tradeoffs of treatment.
- Response-guided titration is based on individual patient's therapeutic response, as measured by an objective clinical parameter of interest.
- However, safety assessment of response-guided dose-titrated drugs in clinical trials can be complicated, due to:

  1) inter- and intra-individual variability in exposure, and,

  2) potential for confounding if the adverse event of interest is associated with the clinical marker used to guide the dose-titration regimen.

- In this study, we discuss statistical challenges in evaluating safety of response-guided dose-titrated drugs in clinical trials and illustrate the use of a sensitivity analysis to examine the magnitude of potential confounding.

2. Background

- Schuck et al. (2019) examined the labeling of all new molecular entities FDA-approved from 2013 – 2017 to understand how frequently response-guided titration strategies were utilized.
- Among 181 drugs that were FDA approved from 2013 – 2017, 30 drugs had response-guided dose titration information in the drug label (Schuck et al., 2019).

  1) Interestingly, in only 16 among the 30, the dosing strategy was studied in at least one pivotal trial.

  2) Otherwise, the dose titration was not evaluated in the drug development program in the remaining 14 trials.

  3) Among the 16 studied drugs, four drugs had dose titration strategy solely based on level of biomarkers of clinical response.

3. Confounding by Response-guided Dose-titration

- When there is an important safety risk to be evaluated for drugs that are dose-titrated based on a clinical response, it is important to be mindful of a potential confounding by the response-guide dose-titration, when the trial is placebo-controlled.
- **Motivating Case Example**:

  i. Consider a study design that randomized independent patients $i = 1, \dots, n$ over two treatment arms A_i, coded 1 for treatment and 0 for placebo.

  ii. Assume that the trials recorded longitudinal measurements of the biomarker of the treatment response, which we denote $M_{i1}, \dots, M_{ik,}$ at visits $1, \dots, k$, along with a time-to-event endpoint T_i.

  iii. We consider measurements of $M_{i1}, \dots, M_{ik}$ until the end-of-study time k or until the safety event of interest happens.

  iv. The causal diagram in Figure 1 illustrates the data-generating mechanism that can be postulated, underlying potential confounding by response-guided dose-titration.

  v. In this hypothetical case example, we assume that the biomarker of the treatment response (M) levels during the study are affected by the treatment (A), which in turn, might affect the outcome (T).

  vi. The main question of interest in evaluation of the safety risk, is to understand, to what extent is the effect of randomized treatment (A) on a time to event endpoint (T) was explained by the effect of treatment on the mediator of interest (M).

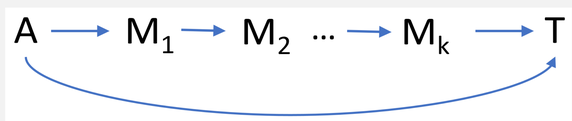

Figure 1. Causal diagram illustrating the data generating mechanism postulated in the case example.

4. A Framework for Sensitivity Analysis

- A sensitivity analysis could be considered, to investigate the potential effects of differential control in the biomarker of the treatment response (M), in the comparative assessment of the safety risk between the active treatment and placebo arms. This method was proposed by Vansteelandt and colleagues (2019), under a causal mediation framework.
- **Mediation Analysis Approach**:
  - Mediation analysis approach dissects the causal pathway into two paths:

    i. a direct path (effect of active treatment on safety risk independent of the levels of M during the treatment), and

    i. an indirect path (effect of active treatment on safety risk through its influence on the M levels during the trial).

  - After such distinction of the causal pathway into direct and indirect paths, **safety event probabilities for the placebo arm at time *k*** can be estimated by conditioning on:

    i. the levels of M observed in the placebo arm during the treatment period (which we denote as $S_{11}(t)$), or

    i. the levels of M observed in the active treatment arm during the treatment period (which we denote as $S_{10}(t)$).

  - The two quantities allow for elucidation of expected differences in the safety risk in the placebo arm (i.e., $S_{11}(t)$ - $S_{10}(t)$) under the differential control of M levels during the trial in the placebo group.
  - The event free probabilities under the two conditions can be identified as the following.

$$S_{a,a^*}(t) = \int f\left(T > t \mid T > \lfloor t \rfloor, \bar{m}_{\lfloor t \rfloor}, A = a\right) \prod_{s=1}^{\lfloor t \rfloor} f(m_s \mid T > s, \bar{m}_{s-1}, A = a^*)\, dm_s,$$

  - where ⌊ ⌋is the visit time prior to (and including) time , and we define $m_{ss} \equiv (\ _1, \dots, m\ _s,)$.
  - Please see Vansteelandt et al. (2019) for further details about the model specification and estimation in the mediation analysis approach.

5. References

- Schuck RN, et al. Use of Titration as a Therapeutic Individualization Strategy: An Analysis of Food and Drug Administration-Approved Drugs. Clin Transl Sci. 2019 May;12(3):236-239.
- Vansteelandt S, et al. Mediation analysis of time-to-event endpoints accounting for repeatedly measured mediators subject to time-varying confounding. Statistics in Medicine. 2019;38:4828–4840.

6. Disclaimer

- This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.