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Sharing some interim data in trial monitoring can mislead or unmask trial investigators: A scenario-based survey of trial experts

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ABSTRACT

Background: Sharing masked interim results by the Data Safety Monitoring Board (DSMB) with non-DSMB members is an important issue that can affect trial integrity. Our survey's objective is to collect evidence to understand how seemingly masked interim results or result extrapolations are interpreted and discuss whether these results should be shared at interim.

Methods: Conducted a 6 scenario-question survey asking trial experts how they interpreted three kinds of seemingly masked interim results or result extrapolation measures (interim combined event rate, adaptive conditional power and "unconditional" conditional power).

Results: Thirty-one current Consolidated Standards of Reporting Trials group affiliates were invited for survey participation (February 2015). Response rate: 71.0% (22/31). About half, 52.6% (95% CI: 28.9%–74.0%), (10/19), correctly indicated that the interim combined event rate can be interpreted in three ways (drug X doing better than placebo, worse than placebo or the same) if shared at interim. The majority, 72.2% (95% CI: 46.5%–89.7%), (13/18), correctly indicated that the adaptive conditional power suggests relative treatment group effects. The majority, 53.3% (95% CI: 26.6%–77.0%), (8/15), incorrectly indicated that the "unconditional" conditional power suggests relative treatment group effects.

Discussion/Conclusion: Knowledge of these three results or result extrapolation measures should not be shared outside of the DSMB at interim as they may mislead or unmask interim results, potentially introducing trial bias. For example, the interim combined event rate can be interpreted in one of three ways potentially leading to mistaken guesswork about interim results. Knowledge of the adaptive conditional power by non-DSMB members is telling of relative treatment effects thus unmasking of interim results.

1. Introduction

The Data Safety Monitoring Board (DSMB) is responsible for trial stewardship [1,2], typically charged with protecting participant safety and potential trial biases [1,2]. An issue that can negatively affect trials is the introduction of bias if the DSMB were to share interim trial results or result extrapolations with non-DSMB members, especially those responsible for the trial's conduct [1,3,4]. Those individuals could potentially act upon that information, consciously or subconsciously, modifying the objectivity of the trial's design to the point that the observed treatment difference is altered away from the truth. Conscious or subconscious alterations that introduce bias, by those non-DSMB members in the know of interim results, could be changes to treatment group adherence, endpoints, endpoint evaluation, accrual rates and enrollment, trial design, and the timing of trial termination [1]. This is an especially serious issue for phase III trials because they are usually used to provide definitive evidence on efficacy and safety endpoints to inform practice or regulatory approvals [5,6].

A case described [7] prompted us to investigate further the issue of sharing seemingly masked interim results or result extrapolations. The interim combined event rate (an interim result), and the adaptive conditional power and "unconditional" conditional power (both result extrapolations) provided at interim can be considered seemingly masked because they do not directly reveal the trial's interim event

Abbreviations: CI, Confidence Interval; CONSORT, Consolidated Standards of Reporting Trials; DSMB, Data Safety Monitoring Board; PI, Principle Investigator

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rates per group. However, the interim event rates per group could be indirectly revealed when given the interim combined event rate, if the control event rate is known from the trial's protocol or previous studies, or which group is doing relatively better to another when given the adaptive conditional power. In this case [7], the funding sponsor of a trial asked the trial's steering committee and DSMB to provide the interim adaptive conditional power before approving a request for additional funding. Adaptive conditional power is the probability of finding a statistically significant result at the end of the trial, given the data collected so far, assuming that the interim estimates of efficacy remain the same to the end of the trial [7]. The DSMB refused to share this information because they thought it would unmask the trial's interim results and thus jeopardize trial integrity. Instead, they provided the funding sponsor the "unconditional" conditional power; the probability of correctly rejecting the null hypothesis of no effect at the end of the trial (i.e. finding a statistically significant effect in favour of the intervention) and accepting the alternative hypothesis if it is indeed true, at some interim point in the trial, using the interim combined event rate [7]. They shared this instead because it is thought to mask the interim efficacy results, but provide reassurance that the trial will have the power to answer the primary hypothesis initially set out. There is evidence to suggest that the issue of the DSMB sharing potentially unmasking interim results with non-DSMB members is prevalent and can happen in other circumstances including when there is a DSMB recommendation for early trial termination, the DSMB has concerns about the interim results given to them, the trial's completion is threatened, there is a concern about patient safety, and there is a need to share with regulators for early drug approval [8]. Other special circumstances can be in adaptive confirmatory trials where interim results are used to make trial adjustments and in trials with a long follow-up period where certain interim results may help a certain patient population and their physicians with an important treatment decision [8]. In many of these cases, unmasked interim results may be shared. However, how useful is it to provide non-DSMB members the "unconditional" conditional power, and how is it interpreted? How useful is it to share other interim results or result extrapolations such as the interim combined event rate or the adaptive conditional power respectively? This is a question posed by trialists, who regularly serve on DSMBs and have encountered requests from principal investigators (PIs) to provide them with the interim combined event rate. The objective of our survey was to collect empirical evidence from a focus group of trial experts to better understand how seemingly masked interim results or result extrapolations are interpreted and discuss whether these results should be shared or not. Such evidence could have implications as to what should or should not be shared at interim during a trial.

2. Methods

2.1. Design of survey

2.1.1. Constructing a hypothetical scenario for survey questions

We had access to a published report of a completed trial that described within their publication the interim event rate for their primary outcome of interest [9]. The trial's outcome of interest was overall all cause 28-day mortality. We also used all-cause 28-day mortality as our outcome of interest for our hypothetical scenario question-based survey. We used the interim event rates from this trial's publication to create six hypothetical scenario questions where the interim combined event rate (an interim result), and the adaptive conditional power and "unconditional" conditional power (both results extrapolations) were shared. Definitions of these interim result and result extrapolations are provided in Table 1 (Table 1: Definitions of interim result and results extrapolations). We gave respondents some information about trial assumptions usually mentioned in the trial protocol, including the assumed control event rate used to help calculate the sample size of the trial. Most people who are involved in the operation of a trial are aware of the assumed control event rate prior to the start of the trial as it is in the protocol. Thus, to make the scenarios as realistic as possible, we included this information.

2.1.2. Constructing and administering scenario-based survey

We designed our survey to have scenario-based questions enabling the respondents to answer a multiple choice question, indicating how they interpreted three different kinds of interim results or result extrapolations regarding the relative treatment effects between treatment groups; in our case Drug X verses placebo. We asked the respondent to provide their interpretation for one kind of interim result or result extrapolation per scenario-based question. The definitions of the three kinds of interim result or result extrapolations were on the relevant survey pages for the respondent. We asked six scenario-based questions within the survey (See Appendix A: Scenario-based survey questions). We also had a general comments section under each question to allow the respondent to provide comments about the scenario or any other comment they may have had. The online survey was constructed and administered using fluidsurvey.com. We sent the first version of the online survey to 10 trial experts at McMaster University, Hamilton, Ontario for pilot testing for content validity, clarity and for any other feedback. Nine out of 10 of trial experts responded to the survey for pilot testing and feedback. We modified the online survey based on this feedback and created the final version of the online survey.

2.2. Sampling

2.2.1. Target group and sampling

The target focus group for this survey was trial experts and we contacted the Consolidated Standards of Reporting Trials (CONSORT) group in November 2014 to ask for permission to contact and solicit recent CONSORT members for their participation in our scenario-based survey. We chose members of CONSORT group because they are trial experts and as a group, they develop guidelines about the proper reporting of trials in journal publications. Writing such guidelines would require a member to have some appreciable understanding of the intricacies and workings of trials including interim analyses and possible information generated at trial interim. The CONSORT group sent out an initial email on our behalf in December 2014 based on their own mailing list, letting potential respondents know about the online survey, its purpose and the coming survey's email invitation. We first sent out the invitation to the online survey in February 2015 via Fluidsurveys.com and following the Dillman's principles [10] a reminder email 2 weeks later to encourage a good response.

2.3. Data collection and analysis

We used FluidSurveys.com to disseminate the survey, and collect responses. A link to the survey through Fluidsurveys.com was sent to potential respondents via email. Responses were collected anonymously. The software used to analyse the results was integrated software within Fluidsurvey.com and Microsoft Excel 2010. We report results anonymously and in aggregate by count and percentages, indicating how many respondents chose a particular multiple-choice option stemming from a particular scenario-based question along with the a proportion's associated Fisher's Exact 95% Confidence Interval (CI). All respondents solicited were current members of the CONSORT group. We did not collect information on demographics to minimize respondent burden, and therefore unable to perform a subgroup analysis.

3. Results

Out of 31 invitations sent, we received 22 responses (16 complete responses and 6 partial or incomplete responses) for a total response rate of 71.0% (22/31). Fig. 1 (Fig. 1: Results from Survey) provides the