

ISSUES WITH THE DSMB SHARING INTERIM TRIAL RESULTS

**ISSUES REGARDING THE SHARING OF INTERIM RESULTS BY THE DATA SAFETY
MONITORING BOARD OF A TRIAL WITH THOSE RESPONSIBLE FOR THE CONDUCT OF
THE TRIAL**

By

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Requirements for the Degree Doctor of Philosophy**

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TITLE: Issues regarding the sharing of interim results by the Data Safety Monitoring Board of a trial with those responsible for the conduct of the trial.

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LAY ABSTRACT

Sharing of interim results by the Data Safety Monitoring Board (DSMB) with non-DSMB members is currently an important issue that can affect phase III trial integrity by way of introducing potential bias affecting final results. The key goal was to generate evidence on the views of those involved or interested in trials via surveys and assess what interim results should be shared with non-DSMB members and if so, with whom and under what condition. Results suggest that the interim combined event rate (ICombinedER), interim control event rate (IControlER), adaptive conditional power (ACP) and unconditional conditional power (UCP) should not be shared with any non-DSMB member. Knowledge generated will inform practices in protecting interim results so as to guard trials against bias and the investigation of factors found to be associated with sharing certain types of interim results.

ABSTRACT

Background and Objectives: Sharing of interim results by the Data Safety Monitoring Board (DSMB) with non-DSMB members is an important issue that can affect trial integrity. The objective of this dissertation was to determine the views of the stakeholders on what kind of interim results can or should be shared by the DSMB, why, and with whom among those responsible for the conduct of a trial.

Methods: We first conducted a systematic search of the literature to assess views and current evidence on sharing interim results. Secondly, we conducted two cross-sectional surveys aimed at those involved in trials to solicit their views on what type of interim results should be shared by the DSMB with non-DSMB members, with whom and under what circumstances. Thirdly, we assessed for any potential association of demographic factors with the sharing of certain interim results and their perceived usefulness, using regression analysis.

Results: Mixed views exist in the literature on interim result sharing practices. Evidence from the surveys conducted resulted in the following findings.

What to share: Based upon the survey results from our cross-sectional survey (Chapter 4), the interim control event rate (IControlER), the adaptive conditional power (ACP) and the unconditional conditional power (UCP) should not be shared. Most respondents from this survey thought the interim combined event rate (ICombinedER) could be shared provided proper conditions and provisions are in place. However, based on our cross-sectional scenario-based survey (Chapter 3), it was demonstrated that the ICombinedER, when shared at interim, is compatible with three possible interim results (Drug X doing better than placebo, worse than placebo or performing the same as placebo).

Why share or not share: Respondents indicate that the ICombinedER can be shared because it does not unmask relative effects between groups, and keeps the steering committee (SC) informed about the trial's progress; however, with the condition that sharing this type of result should be specified *a priori* including for what purpose and be at the DSMB's discretion,

especially if the control group rate is known from the literature. However, it is important to note that the ICombinedER, demonstrated with evidence from our cross-sectional scenario-based survey (Chapter 3), is compatible with three possible interim results and should not be shared because it has low usefulness and is flawed due to multiple interpretations. The IControlER and the ACP should not be shared because they are unmasking of interim results. It was mentioned that ICombinedER is usually known by the SC and sponsor making it easy to determine group rates if the IControlER is known. The UCP should not be shared because it is a technical measure that is potentially misleading of interim results.

With whom to share: Survey results from Chapter 4 indicated that the ICombinedER can be shared with the SC and that the IControlER, the ACP, and the UCP should not be shared with any non-DSMB members by the DSMB. However, evidence from Chapter 3 also indicates that the ICombinedER should not be shared with any non-DSMB member.

Factors associated with sharing: Having experience with greater than 15 trials with private industry sponsorship was found to be associated with not sharing the IControlER and an increase in perceived usefulness in sharing the ACP. Though some other demographic factors were found to be associated with sharing the ICombinedER and the UCP, they were sensitive to missing data upon our sensitivity analysis and will require more validation.

Conclusions: Though mixed views exist within an extensive literature review on interim result sharing practices, survey evidence from this dissertation suggests that the ICombinedER, IControlER, the ACP and the UCP should not be shared with any non-DSMB member. The IControlER and ACP can be unmasking of interim results and the UCP is a technical measure that is potentially misleading. We agree with this reasoning. The majority of respondents from the survey in Chapter 4 indicated that the ICombinedER can be shared with the SC because it does not unmask relative effects between groups, however it was also stipulated that sharing this measure should be specified *a priori* and for what purpose and be at the DSMB's discretion, especially if the control group rate is known from the literature. Even though the majority from

our second survey in Chapter 4 indicate sharing the ICombinedER with the SC, we do not recommend sharing the ICombinedER at interim with any non-DSMB member because, as demonstrated with evidence from our cross-sectional scenario-based survey in Chapter 3, this measure is compatible with three possible interim results potentially leading to the introduction of trial bias at interim by those privy this interim measure and their interpretation. Based on the findings from the survey from Chapter 4, there appears to be a lack of awareness in how sharing the ICombinedER is flawed, of low usefulness, and potentially dangerous. The perceived desire to have this measure shared seems misguided. Experience with greater than 15 trials with private industry sponsorship was found to be associated with not endorsing the sharing the IControlER and an increase in perceived usefulness in sharing the ACP by the DSMB at interim. In regards to implications for future research, this characteristic should be further evaluated to see if this subgroup has insight into interim trial management practices that protect from trial bias.

Results from this research have implications for practice and guidelines concerning trial design and protocols, and DSMB charters. These results can also help assess the need for proper safeguards around sharing an interim result when deemed appropriate by the DSMB and under their discretion, that prevent the introduction of bias that could alter the final trial results generated.

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DECLARATION OF ACADEMIC ACHIEVEMENT

This is a sandwich thesis which combines four papers that were prepared for peer-reviewed journals and publication. At this time, the first two papers (Chapters 2 and 3) have been published in open access journals and are open access articles under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>) and Creative Commons Attribution- Non Commercial- No Derivatives 4.0 International License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>) respectively. The latter two papers (Chapters 4 and 5) at this time have also been prepared and submitted to an open access journal that will apply the Creative Commons Attribution 4.0 International License to a published article. The following outlines the contributions to this research. V. Borg Debono was the lead of this thesis and all papers included in this dissertation and thesis. This included developing the research question, designing the studies, protocols and statistical analyses, data collection, and management, conducting the analyses, interpreting of results, writing all manuscripts, submitting manuscripts for publication and responding to reviewer comments. Co-authors were substantially involved in supervision of study design and critical revisions to the studies, manuscript review and provided continual guidance and support throughout. All co-authors read and approved the final manuscripts for publication. This work was conducted between Spring 2013 and Summer 2017.

CHAPTER 1

I. INTRODUCTION

One of the controversial issues affecting trials today pertains to the sharing of interim trial results, especially the extent to which interim result measures, if any, should be shared by the Data Safety Monitoring Board (DSMB) with individuals who are non-DSMB members, particularly those directly responsible for the trial's conduct. These non-DSMB members can be the sponsor(s), steering committee (SC), principal investigator(s) (PIs), other study investigators(s), funder(s), data analysis center (DAC), primary trial statisticians/trial's statistical center, and the independent statisticians who do the interim analyses. Other groups who are not directly responsible for the trial's conduct but may have an impact on the future conduct of the trial are study participants, the institutional ethics review board (IERB), the regulatory agency, advocacy groups and other DSMBs. The DSMB interacts on occasion with different trial party components, some more than others [1]. Most DSMB interaction takes place between the sponsor or the PI, who may be a part of a steering committee (SC) when one is in place [1], and the statistician/statistical center doing the interim statistical analysis for the DSMB's interim review. This debate on what interim result measures to share, if any, is ongoing within the trial methodology community [1-5]. One of the major fears driving the controversy concerning sharing interim result measures, particularly in phase III randomized controlled trials (RCT), is the potential to introduce trial bias that will affect the final results [2, 6]. Even pooled results which appear to mask interim treatment group or group comparative effects may in some way reveal information on treatment efficacy and safety endpoints.

II. DSMB Stewardship

Much has been written over last 20 years on the function of DSMBs and their role as trial stewards [1, 3-5, 7-15]. Trial sponsor(s) will typically solicit suitable members in the research community for an independent DSMB when there is a need to ensure that a trial retains its

objectivity, credibility, and validity [6, 12, 16, 17]. The DSMB acts in an advisory capacity to the trial's sponsor(s) and investigators [1, 18]. They are tasked with protecting patient safety and trial integrity by reviewing accumulating interim trial data for safety or efficacy when asked to, on a periodic basis, and responding to information or trends that threaten the safety and validity of the trial by making recommendations to the trial's SC or sponsor [7, 12, 19]. The DSMB's priority in the following order is to: 1) Protect the interests and safety of the study participants [20], 2) Preserve the trial's credibility and validity [1, 5, 20] and 3) Wisely facilitate, based on all the interim evidence evaluated, the availability of timely and reliable findings to the clinical community [1]. DSMBs can also be asked by the sponsor to review the initial study protocol, monitor trial conduct by assessing patient accrual and eligibility, protocol compliance, losses to follow-up and other information as needed [21].

Trial objectivity can be jeopardized by bias. The potential loss of objectivity then affects the credibility and validity of a clinical trial. Having an independent DSMB monitor a phase III trial can help protect a trial from the introduction of bias. One of the many ways bias can be introduced into the trial is if those responsible for the trial's conduct, such as the sponsor or investigator, or those participating in the trial, are privy to unmasked interim trial results regarding efficacy or safety outcomes as the trial is still ongoing [22]. Access to interim trial result measures by non-DSMB members is very controversial, especially in phase III, confirmatory RCTs [1, 3, 7] as the bias introduced that can jeopardize a trial to the point where it becomes questionable to make decisions based on its results. This is particularly important for phase III, confirmatory RCTs designed and used to produce definitive evidence on efficacy and safety endpoints [23] for regulatory submission [24] or to help bring about change in clinical practice. For the results to be credible, these kinds of definitive phase III confirmatory RCTs may need to use a formal independent DSMB who can objectively assess unmasked interim results as a removed neutral party. Members of an independent DSMB are selected carefully to

minimize individuals with strong financial, intellectual or emotional conflicts of interest that could potentially influence their judgment and ability to act as monitors [1, 25].

On the contrary, results from phase I and II trials are not usually used to provide the kind of definitive evidence on efficacy and safety endpoints needed for regulatory approval or to bring about change to clinical practice [7]. For this reason, the protocol and investigator team brought together by the sponsor can generally handle safety monitoring during these earlier trial phases if deemed appropriate [7]. Cases when a DSMB may be needed for a phase I or II trial are: 1) when the medical or psychosocial risk to trial participants appears high [26], 2) there is a high administrative risk to the trial, particularly when the trial is being conducted at several locations and there is a risk of fragmented data monitoring at different sites and variegation in trial conduct [26], 3) there is a risk to trial integrity, particular when PIs need to be masked to outcome data during trial conduct [26] or 4) when there would be a conflict of interest with having those conducting the trial also monitoring the trial at interim [15, 26]. Phase III RCTs then apply what was learned from phase I and II trials regarding dosing, treatment schedule, proper treatment use and the appropriate target population, and are designed to provided evidence on the efficacy and safety of the new intervention against competing interventions with the statistical precision required for regulatory submission and subsequent marketing approval [7]. So while certain trials may not need a DSMB, trials that address major and critically patient-important health outcomes [22] and are designed to provide more definitive evidence on intervention/treatment efficacy and safety, should consider integrating an independent DSMB to uphold study validity and credibility [1].

III. Potential Sources of Bias in Trials

It was recognized early in the development of trial methodology that awareness of accumulating interim trial results by the investigators, sponsors, and participants could affect the course of the trial and the validity of the final results [1, 5, 27]. Ultimately, the concern is that there will be prejudgment of early unreliable interim results on efficacy and safety outcomes

based on limited data [1, 27, 28]. This prejudgement, in addition to one's conflicts of interest [29] can consciously or subconsciously motivate actions that lead to introducing trial bias [28], potentially producing false positive or false negative results for the outcomes of interest [30]. Thus, in a more defined way, bias in a trial context is the conscious or subconscious absence of objectivity where the observed treatment difference can be due to effects other than just the treatment or intervention. These effects can be non-objective actions during a trial's operation or with the evaluation of outcomes and can be considered systematic/non-random error in the estimate of a treatment difference [7]. The impact of bias on the result can be complex and hard to measure [31]. Some of the different sources of bias that can be introduced when non-DSMB members are privy to interim trial results are described below.

i. Changes to Adherence

If the investigators were aware of the interim trial results favouring one treatment group over another, there might be a hesitancy for the investigator to encourage continued adherence to certain treatment groups [8]. If trial participants are also aware of interim trial results and have an idea of which group they are in, their choice to continue to adhere to the treatment to which they have been randomized might also diminish, further biasing the end results for the trial [1]. Participants may even ask that they are unmasked and insist on being placed into the alternative treatment group that seems to be faring better [1]. These actions dilute estimates of the true treatment effect that would be seen at the trial's completion [1].

ii. Changes to Endpoints

In the context of financial or intellectual conflicts of interest, if the sponsor or the investigator has knowledge of interim results, potentially showing that the new treatment had little to no effect on the primary endpoint but a strong effect on an important secondary endpoint, where both endpoints were specified *a priori*, they may be tempted to switch the designation of the two endpoints where the secondary endpoint becomes the primary and the primary becomes the secondary [1].

iii. Changes to Accrual Rates

Prejudgement of interim results by all parties including the investigators, sponsors, participants, and the public may adversely impact patient accrual rates [23, 25]. Investigators and sponsors may lose their interest to accrue patients. The power of the trial could be eroded by this decline in rates [1, 8]. There is evidence to suggest that this kind of adverse effect on the trial's integrity is possible with the early release of interim data to non-DSMB members [1]. An example given in the area of oncology trials is within a study done by Green et al. [1, 32] that compared trials done from two major cancer research groups. The results of the Green et al. study presented empirical evidence that refraining from disseminating interim results by the DSMBs positively protected trial integrity and the potential for biasing trial results [32]. One cancer research group only shared trial interim results with their DSMB. The other group did not have a DSMB and shared their trials' interim results with the investigators and to others. The trials in the first group were free from the problems the latter group had. The group that did not have a DSMB for their trials and who widely shared interim results saw a correlation between the absence of the DSMB and 50% of their trials showing a decline in patient accrual over time. Other trials in the no-DSMB group also experienced inappropriate early termination associated with prejudgement of interim results and the inability to complete accrual, possibly biasing and introducing uncertainty in those trial's end results. The final results from other completed trials in the no-DSMB group were also inconsistent with early positive results that were published [1].

iv. Changes to Enrollment

If the investigators were aware of interim results favouring one treatment group over another there might be hesitancy on their part to continue to enroll patients if they no longer believe a different result is possible. They may also modify the type of patient they enroll. Also, potential participant's may prejudge certain interim results which in turn could also slow or stop further enrollment [1].

v. Trial Modifications

Certain members of an SC or sponsor, who are privy to certain interim results of their trial, if such information were shared with them, will be in a difficult situation if the DSMB were to recommend a trial modification. If the DSMB were to recommend a trial modification, those individuals on the SC, or representatives of the sponsor who were privy to those interim results, would know how that modification would affect the possible trajectory of the final results. In this case, there is a conflict of interest for those SC members to participate in a discussion about the recommended modification given by the DSMB. Their participation will make it appear that any decision made about the recommended modification will be based on their knowledge of certain interim results [1], even if those individuals do not do anything to influence the SC's discussion towards an agreement or disagreement with the recommended modification.

vi. Changes to Endpoint Evaluations

If certain interim result measures were shared with investigators, sponsors, or other non-DSMB members responsible for the conduct of the trial, prejudgment of those interim results may modify the behaviour of investigator assessed endpoints thus biasing the results of those endpoints upon final analysis, especially those endpoints that are not concrete like death. For harder to evaluate endpoints that require a more in-depth degree of evaluation, continuing to treat patients enrolled as specified by the protocol may be more challenging [1, 33].

Patients/participants may also behave differently, such as adding their own adjunct therapies or not properly adhering to what has been given in their assigned treatment group because of their prejudgment of the trial investigated treatments based on any interim results potentially shared with them [2]. In turn, this can alter or bias the results from the true effect between treatment groups. Depending on how widely interim results of a trial were released, circulation of these interim results may also impact other similar trials that are concurrently underway and their endpoint evaluations [1]. The direction in which the results could be biased depends greatly on

the change in behaviour by those who know the interim results and have an impact on trial conduct.

vii. Early Termination and Publication

Wide knowledge of interim results outside of the DSMB can cause inappropriate early trial termination due to prejudgements of the effect size and the direction of the effect between groups. Investigators and patients may not feel motivated to continue the trial after knowing interim results and there could be difficulties completing the trial causing early termination. Investigators' concern for trial participants could motivate them to recommend trial termination based on an early trend favouring the control or treatment group, even when these early results might be spurious based on chance and could easily reverse upon study continuation. In another case, the sponsor who may be financially invested in the trial may want to interpret early results as definitive and stop the trial to save costs and gain earlier regulatory approval if there appears to be a strong favourable result [1]. On the other end of that spectrum, a sponsor may not want to stop a trial early, even when the interim results are definitive in fear that the trial results will not be persuasive [1]. Regardless, early termination, prompted by prejudice of the interim results and the effect that prejudice has on the trial when trial results are not yet definitive, can bias the final results. Trials stopped early for benefit may be spurious in turn potentially resulting in the publication of early results that may be inconsistent compared to similar studies that will be completed and published [1]. Ellenberg [1] notes that *“Even in settings in which investigators are aware of the treatment assignments of their own patients, trials are more likely to be completed successfully when these investigators are blinded to the comparative data from patients managed by other investigators and at other centers.”*

IV. Impetus Case

The case that triggered us to further assess this issue of sharing certain interim result measures was described by Anand et al. [3]. They highlight a time when the funding sponsor

asked the SC and DSMB of a confirmatory phase III trial to provide them the interim adaptive conditional power. The SC and PI had initially asked the funding sponsor for additional funding needed for one year to complete the cardiovascular trial and the funding sponsor then asked for the adaptive conditional power explaining that they needed this interim measure to help them make a decision regarding the approval of additional funds. The adaptive conditional power the sponsor was asking for would give them the probability of the trial being successful at showing a statistically significant result for the primary outcome at the end of the trial, given the data collected thus far. The DSMB refused to give this information because they considered that sharing the conditional power could be unmasking of the trial's results and hence jeopardize trial integrity. The DSMB also indicated to the sponsor that a decision to continue or terminate a trial should not be based on one kind of statistic. The funding sponsor decided that it could not approve the additional funding without knowledge of this interim measure. Luckily, for the SC and the PI of that trial, they were able to find the additional funding from other sources. If they were not able to find this funding, it could have meant the trial ending sooner before definitive results could be found.

V. Potential interim result measures that could be shared

There are four main forms of seemingly masked interim result measures that could potentially be shared with non-DSMB members by the DSMB that were published with Chapter 3 [34] and submitted for publication with Chapter 4. Table 1 provides a summary of these measures and was the focus of investigation for this thesis.

Table 1: Summary of four main forms of seemingly masked interim result measures that could be shared by the DSMB with non-DSMB members	
Interim Control Event Rate (IControlER)	<p><i>“The number of events observed among control participants at some planned interim point into the trial divided by the number of control participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial)</i></p> <p><i>Example:</i></p>

	<ul style="list-style-type: none"> • <i>Total # of Deaths in the placebo group, six months from the start of the trial = 15</i> • <i>Total # of Participants in the placebo group, six months from the start of the trial = 250</i> • <i>Calculation: $15/250 = 0.06$ or 6%</i> <p><i>Therefore the Interim Control Event Rate at the trial's interim analysis, six months from the start of the trial, is 6%” [from Chapter 4, paper submitted for publication]</i></p>
<p>Interim Combined Event Rate (ICombinedER)</p>	<p><i>“The total number of events observed at some planned interim point into the trial divided by the total number of participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial or after enrolling a certain number of participants).</i></p> <p><i>Example:</i></p> <ul style="list-style-type: none"> • <i>Total # of Deaths in both the placebo group and new intervention group, six months from the start of the trial = 80</i> • <i>Total # of Participants in both the placebo group and the new intervention group, six months from the start of the trial = 700</i> • <i>Calculation: $80/700 = 0.114$ or 11.4%</i> <p><i>Therefore the Interim Combined Event Rate at the trial's interim analysis, six months from the start of the trial, is 11.4%” [34]</i></p>
<p>Adaptive Conditional Power (ACP)</p>	<p><i>“The probability of rejecting the null hypothesis of no effect by the end of the trial (i.e. finding a statistically significant effect in favour of the intervention), at some predetermined interim point in the trial when the adaptive conditional power is scheduled to be calculated. The assumption made is that the observed interim effect (i.e. relative risk reduction) in the trial will remain the same until the end of the trial.</i></p> <p><i>Example statement:</i></p> <p><i>Given the interim data (data collected 2 years into the trial that is planned to last for 3 years), and assuming the observed interim effect (i.e. relative risk reduction) at the two year point to be the true effect for the remainder of the trial, the probability of rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 60%.</i></p> <p><i>The following pieces of information are used to calculate Adaptive Conditional Power at trial interim:</i></p> <ul style="list-style-type: none"> • <i>Control event rate and experimental event rate</i>

	<ul style="list-style-type: none"> • <i>Information Fraction; a ratio of the planned sample size and the number of patients recruited in the trial at the interim analysis</i> • <i>Z score and B value at interim</i> • <i>Drift parameter” [34]</i>
Unconditional Conditional Power (UCP)	<p><i>“The <u>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 when indeed the alternative hypothesis is true, at some interim point in the trial.</u></i></p> <p><i>The following pieces of information are used to calculate Unconditional Conditional Power at interim:</i></p> <ol style="list-style-type: none"> 1. <i>The <u>hypothesized treatment effect at the design stage (i.e. relative risk reduction) of the trial, assuming the hypothesized treatment effect at the design stage to be true and correct for the remainder of the trial;</u></i> 2. <i>The <u>sample size calculated at the design stage for the trial AND;</u></i> 3. <i>The <u>combined event rate calculated at the trial’s interim, assuming this rate to be true for the remainder of the trial.</u></i> <p>Example statement: <i>Given the interim combined event rate and assuming the treatment effect (i.e. relative risk reduction) hypothesized at the design stage of the trial to be true for the remainder of the trial, the probability of correctly rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 89%.” [34]</i></p>
DSMB (Data Safety Monitoring Board), IControlER (Interim Control Event Rate), ICombinedER (Interim Combined Event Rate), ACP (Adaptive Conditional Power), UCP (Unconditional Conditional Power)	

VI. The Research Setting

This thesis focused on collecting evidence from those involved in trial research and soliciting their views on what interim result measures should be shared during the interim of a phase III trial by the DSMB with non-DSMB members. Our sampling population was members of the CONSORT group [35], the Society of Clinical Trials (SCT) [36] and the International Society for Clinical Biostatistics (ISCB) [37].

VII. Thesis Objectives and Outline

The overall objective of this thesis is to better understand what kind of interim RCT result measures should be shared by the DSMB with non-DSMB members, particularly those responsible for the conduct of the RCT. This was done by engaging in a review of the literature and collecting original data from those who are involved with or are interested in trials in the form of a sandwich thesis of four papers (Chapters 2, 3, 4 and 5) to answer the following questions:

1. What does the literature state about the current views and opinions on the issue of the DSMB sharing interim results during the conduct of a clinical trial, particularly phase III trials, with non-DSMB members, and what interim results should the DSMB share, if anything at all, with whom, and under what circumstances?
2. How useful is it for the DSMB to provide non-DSMB members three of the four main forms (ICombinedER, ACP, and UCP) of seemingly masked interim result measures and how are these measures interpreted?
3. What are the professional opinions of those interested or involved in clinical trials on what interim information should be shared (including the following four main forms of seemingly masked interim result measures: ICombinedER, IControlER, ACP and UCP) with non-DSMB members at interim and if so, with whom and under what circumstance(s)?
4. What trialist characteristics are associated with thinking certain interim result measures should be shared, specifically the ICombinedER, IControlER, ACP and UCP, and what is the perceived usefulness of sharing any of this information?

Chapter 2 is a narrative review of the literature using a systematic search strategy of several databases and major health research stakeholders and primarily addresses question 1 above. We report on literature with an opinion, argument, or evidence regarding any of the following categories with regards to sharing interim results:

- 1) Against sharing interim results, stating that they should remain confidential with the DSMB;
- 2) Against sharing interim results with an exception(s); and
- 3) In favour of sharing interim results by the DSMB with non-DSMB members.

We also report on 11 circumstances that potentially warrant the DSMB sharing interim results with non-DSMB members under 5 themes. Chapter 3 addresses question 2 above, where we report our findings from a scenario question-based survey sent to trial experts from the CONSORT group in 2015, seeing how they interpret 3 kinds of seemingly masked interim result measures (ICombinedER, ACP, and UCP). Within the scenario, they were given some known information about trial assumptions usually mentioned in a trial's protocol. We interpreted the usefulness in sharing these three forms of interim result measures with potential non-DSMB members from the results of this survey. Our hypothetical scenario-based questions in this survey were constructed on real published interim trial results [38]. Chapter 4 addresses question 3 above, where we report our findings from the second survey we conducted. This survey was sent to members of the SCT and ISCB in 2015 asking for their professional views and experience with sharing interim results, and what interim result measures should be shared with non-DSMB members. Finally, Chapter 5 addresses question 4 from above. It contains the second part of the analysis stemming from the data collected from the second survey in Chapter 4. Here we assess participant characteristics potentially associated with sharing certain pieces of interim trial results by the DSMB with non-DSMB members and its usefulness if shared, using logistic and multiple linear regression respectively.

VIII. Methodological Issues Addressed

This thesis used 2 main forms of research methods to address our research questions above. Chapter 2 employs a narrative review using a systematic search strategy for literature within several databases and with major health research stakeholders. This was an appropriate method to use to address question 1 above because it allowed us to explore the literature and inductively and concurrently evaluate qualitative and quantitative information. Such an inductive

approach was needed for thematic analysis and categorization of literature that predominately consisted of opinions, policies or guidelines. Chapters 3, 4 and 5 employ survey methodology using Dillman's principles [39]. Data from Chapter 3 comes from a different survey than Chapter 4 and 5 which used data from a second, larger survey to SCT and ISCB members. Chapter 3 employed scenario-based questions to help understand the usefulness of sharing three seemingly masked interim result measures. The second survey used for Chapter 4 and 5 asked more traditional survey questions without the use of scenarios. Chapter 5, the second part of an analysis on the survey data from Chapter 4, uses logistic and multiple linear regressions to understand demographic factors potentially associated with sharing the four main forms of interim result measures and their usefulness in sharing, respectively.

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REVIEW

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Sharing interim trial results by the Data Safety Monitoring Board with those responsible for the trial's conduct and progress: a narrative review

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Abstract

Background: Sharing interim data, results or result extrapolations is an important issue that can affect trial integrity. The different ways in which Data Safety Monitoring Boards (DSMBs) share interim results with non-DSMB members and the acceptability of such practices are poorly understood. Our objective was to undertake a narrative review specifically on what kind of interim results, if any, should be shared by the DSMB with non-DSMB members and why.

Methods: We conducted a narrative review using a systematic search strategy of several databases and major health research stakeholders. Literature was included if there was some discussion within the full text about sharing interim trial results with non-DSMB members.

Results: About 79.6% (129/162) of included citations were based on author's views, 16.7% (27/162) on research guidelines and 3.7% (6/162) on surveys. The largest group of citations, 73/162 (45%), expresses the opinion or argument against sharing interim results with exceptions. Trailing closely, 71/162 (43.8%) of the included citations support the opinion or argument that interim results should not be shared and should remain confidential with the DSMB. Half of the six surveys support sharing in some capacity, while the other three do not. Eleven circumstances were found that potentially warrant interim result sharing by the DSMB; they relate to (1) usual practices by DSMBs, (2) trial completion threatened, (3) patient safety, (4) regulatory approval and (5) other circumstances. Dominant risks for sharing under these conditions are associated with introducing trial bias.

Discussion/conclusion: There was no majority view in the literature. However, the largest group of citations included express the idea that interim results should remain confidential with the DSMB but also acknowledge circumstances when they could be shared with non-DSMB members. Limitations of this review are that (1) the included literature predominately provides personal perspectives, not evidence, and (2) surveys found globally focus on trial monitoring practices lacking detailed information on what specifically to share, with whom and why. More research is needed with the use of a detailed survey of the clinical trial community focused on DSMB sharing interim results, to better understand and guide DSMB interim result sharing practices.

Keywords: Data Safety Monitoring Board, Data Monitoring Committee, Interim data sharing, Narrative review

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Background

The Data Safety Monitoring Board (DSMB) or the Data Monitoring Committee (DMC) is responsible for the stewardship of a trial. This group can help oversee the safety of patients in the trial by looking at unmasked safety or efficacy data to make recommendations to the Steering Committee (SC). They can also oversee, in sequential designs, if the trial results have reached the predefined amount of information needed to finish the trial. Importantly, they also protect the trial from the bias that could be introduced during the trial conduct [1, 2].

The case that triggered us to assess further this issue of sharing interim trial information was described by Anand *et al.* [3] when the funding sponsor asked the SC and DSMB of a cardiovascular trial to provide them with interim adaptive conditional power before approving the request for additional funding requested by the investigators. Adaptive conditional power “is the probability that the trial will reach statistical significance if continued to completion if the difference specified in the trial protocol is true, given the outcome events that have already been observed, and the time remaining to observe additional events among patients who are currently event free” [3, 4]. It is a result extrapolation based on interim relative efficacy results [2]. The DSMB refused to give this information because they considered that sharing adaptive conditional power would unmask the trial’s interim results.

When we consider a review done by Grant *et al.* back in 2005 [5] that globally looks at many issues related to data monitoring and interim analysis, we see that there seems to be an accord that interim results and DSMB deliberations remain confidential. However, the review also mentions instances where interim results may be shared with the independent unmasked statisticians or other individuals such as the chair of the SC if the DSMB deems it best to do so because of a safety issue. See the Discussion section for a further discussion of this review. Still, the review lacks certain details such as the specifics of what kind of interim results are shared and with whom. Sharing of interim trial data, results or result extrapolations by the DSMB with individuals who are non-DSMB members, who are responsible for the conduct of the trial, can negatively affect trials [6]. One of the major concerns related to sharing interim trial results [1] is the potential for non-DSMB members to consciously or subconsciously introduce bias that will affect the final trial’s results [1, 7]. This is an especially important issue for phase III trials, which are usually designed and used to find definitive evidence on efficacy and safety endpoints to inform practice or for regulatory drug approvals [1, 2]. This case [2] and the review [5] brought to mind the following questions: Is it possible that there are other circumstances where the DSMB is

justified in sharing interim data, results or extrapolations with non-DSMB members? If so, what information would be shared in such circumstances and with whom?

The overall objective of this review and commentary is to (1) provide a summative narrative review of the views and opinions on the issue of the DSMBs sharing interim results during the conduct of a clinical trial, particularly phase III trials, with the Principal Investigators (PIs), the sponsor, the SC, other parties responsible for the conduct of the trial or any other non-DSMB member(s); and (2) discuss what interim data, results or result extrapolations the DSMB should share, if anything at all, with whom and under what circumstances. The information required to inform this narrative review was gathered from a systematic literature search. For simplicity, the remainder of this review will refer to any assortment of interim data, interim results or interim result extrapolations as interim results. Throughout the rest of the review we will also refer to PIs, the sponsor, the SC, investigators, site managers, independent unmasked statisticians, the funder(s), or patients enrolled in the trial or any other party responsible for the conduct or completion of the trial as non-DSMB members; we will be more specific when needed.

Methods

A narrative review was considered the most appropriate method to use because it allowed us to explore the literature and inductively evaluate qualitative and quantitative information. We anticipated that most of the literature we would find would be opinions, policies or guidelines, and a narrative review would require an inductive approach for theme analysis and categorisation. To find literature discussing the issue of DSMBs sharing interim results, a broad and comprehensive systematic search of the literature was done in December 2015 within the databases of PubMed (includes all MEDLINE citations), Web of Science, EMBASE and CINAHL from the inception of all four databases using a detailed search strategy for each of them, as outlined in Additional file 1. Key phrases related to ‘Data Safety Monitoring Boards’ were utilised in each of the four databases as well as a filter for articles in the English language.

The title and abstract for each citation that came up within the search of each of the four databases were reviewed. Citations were eligible and included for full-text review if the title or abstract associated with a particular citation met the following inclusion criteria: [(1) related to DSMB issues OR (2) related to the management, operation, conduct, use, experience, or discussion of DSMBs] AND (3) the article associated with the citation was published in English. Subsequently, citations from the full-text review were eligible and included for full-text information extraction if there was some focused discussion or

statement, within the full-text, about sharing interim trial results with parties outside of the DSMB. Reference lists from included articles were searched for other unique articles discussing the issue of DSMBs sharing interim trial results using the same inclusion criteria. Additionally, two major textbooks that solely focused on the operation and management of DSMBs were also reviewed and consulted [1, 2]. These were found upon discussion with a professor who is a health methodologist with expertise in clinical trials.

We also searched regulatory, governmental and guideline groups from the USA, Canada, UK, European Union and Australia, and two international groups, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [8] and the World Health Organisation (WHO) [9]. For a list and details of the organisations that were searched directly for relevant literature or information from their respective websites, see Additional file 1. Two strategies were used in combination to find relevant literature on the issue of interim result sharing by the DSMB within major governmental/regulatory/funding bodies and guideline groups (Additional file 1). Documents and webpages on an organisation's website that had information about clinical trial research and DSMBs, as indicated from a webpage's or document's title or within the full text, were eligible and included for full-text information extraction. A full-text review was done immediately because most webpages or documents found on these organisation websites are not structured like most journal articles with an abstract. Documents and pages from the full-text review were eligible and included for full-text information extraction if there was some focused discussion or statement within the full text about sharing interim trial results with parties outside of the DSMB. Please note that within the Results and Discussion sections, not all the citations included from our systematic search of the literature for this review are cited in this paper. A full citation list of articles found to support this review in its entirety is given in Additional file 2. All screening and full-text extraction was done independently by one of the authors (VBD) for this narrative review and then checked by co-reviewers (LM and LT). Information extracted from the included full text pertained to the sharing of interim trial results with parties outside of the DSMB. Any disputes or concerns were resolved by consulting co-reviewers (LM and LT). We worked inductively and thus retrospectively with the included literature to perform a categorisation and thematic literature analysis. Analyst triangulation was used among co-reviewers (LM and LT) with VBD to ensure that categorisation and thematic analysis of literature were sound. No changes were made to the review process that was initially planned. Our review is principled in pragmatism review because we

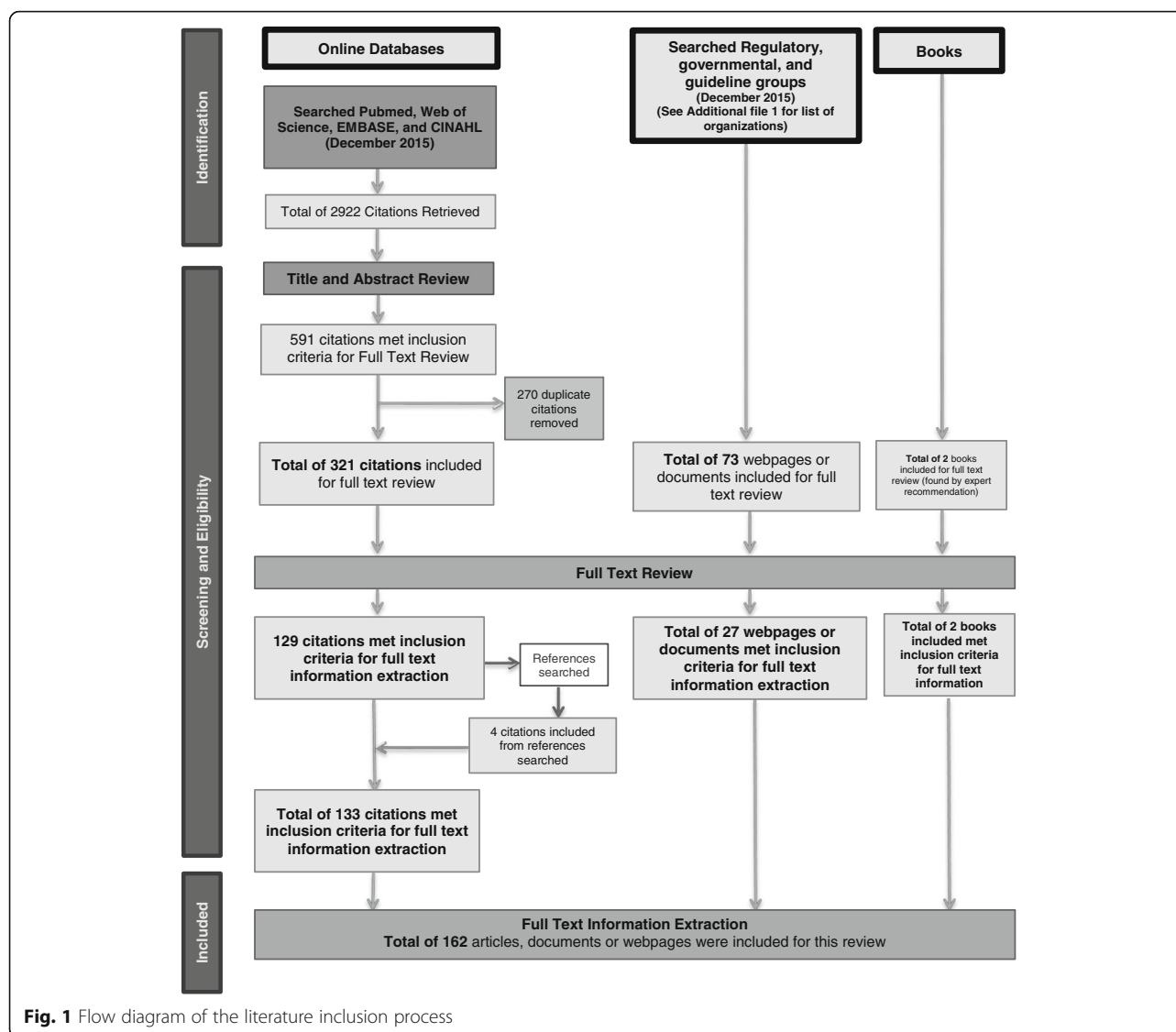
were not initially sure what categories or themes would emerge from the literature. Please see the RAMESES checklist [10] attached as Additional file 3.

Results

A total of 162 articles, documents, policies, guidelines books or webpages were included for this review. See Fig. 1 for a flow diagram showing the inclusion process and the number of articles included.

There are mixed views and opinions on the issue of the DSMBs sharing interim results during the conduct of a clinical trial with non-DSMB members. Out of the 162 included articles, 129 (79.6%) were based on author's views, 27 (16.7%) on DSMB or trial research guidelines and 6 (3.7%) on surveys of trialists. The literature falls into three categories of opinions: Category 1 - literature that expresses the opinion or argument *against* sharing interim results, stating that they should remain confidential with the DSMB (71/162, 43.8%); Category 2 - literature that expresses the opinion or argument *against* sharing interim results with *exceptions* (73/162, 45.0%); and Category 3 - literature that expresses the opinion or argument *in favour* of sharing interim results by the DSMB with a non-DSMB group (18/162, 16.8%). No one group held the outright majority. However, the largest two literature groups that were very close percentage wise were Category 1 (43.8%) and Category 2 (45.0%).

Six surveys were also found out of the 162 included articles that looked globally at trial monitoring practice as described in detail in Table 1. These surveys did not specifically focus on the issue of DSMBs sharing interim results during the conduct of a clinical trial with non-DSMB members. However, all of them asked at least one question that was related to the issue and surveyed those who were somehow involved in trials. Two of the six surveys report results that are quantitatively unclear, as their results are qualitatively described. The remaining four of the six surveys report results quantitatively. The target populations for these surveys varied, ranging from directors of the statistical centres from 12 cancer cooperative groups sponsored by the National Cancer Institute (NCI) in the USA from 1993 [11], trialists of past and ongoing trials [5, 12], PIs and biostatisticians on DSMBs and Institutional Review Board (IRB) community representatives [13], major funders of trials, regulatory agencies and other relevant organisations related to trial research [5]. Methods to obtain the sample also varied. Sampling frames included statistical centres from 12 cancer cooperative groups sponsored by the NCI in the US in 1993 [11], the US National Institutes of Health (NIH) [12], ClinicalTrials.gov, a MEDLINE search of articles pertaining to randomised controlled trials (RCTs) from Biometrics or Statistics in Medicine, the Office of Human Research Protection website [13], a database of



Health Technology Assessment (HTA) programme and Medical Research Council (MRC) trials [5] and a list of 25 handpicked organisations that are major funders of trials, regulatory agencies and other relevant organisations related to trial research [5]. Response rates ranged from 40% to 100% [5, 11–13]. The number of responses to these surveys varied from 12 to 309 [5, 11–13]. Respondents were not chosen at random in two cases [11, 12]. The other four surveys had some method to select respondents at random [5, 13]. Survey collection methods included telephone interviews [5], email surveys [5] and mail/paper surveys [5, 11–13].

Three of the six surveys [5, 11, 13] (one qualitatively and two quantitatively reported) support the view against sharing interim results, stating that they should remain confidential with the DSMB (Category 1 view). For one of the two surveys reported quantitatively [11],

all respondents ($n = 9$) indicated that NCI groups, at the time the survey was administered, did not provide unmasked outcome reports to the participants. For a second question in the same survey asking about which non-DSMB members had access to interim data reports [11], it was reported that 70% of the respondents ($n = 10$) indicated that non-DSMB members do not access interim data reports. For the remaining three respondents who answered this question, who alternatively stated that non-DSMB members do have access to interim data reports, there is no mention as to who specifically gets this information and why. For the second survey [13], as can be seen in Table 1, the majority of respondents, all of whom were biostatisticians, PIs or IRB community members, indicate that the sponsor should be masked to interim data or results (percentages can be viewed in Table 1). Masking of other non-DSMB

Table 1 Surveys looking globally at trial monitoring practices

Year of survey	Reference	Sampling frame	Number of people to whom survey was sent (n) and survey response rate	Number of people (n) who answered the question related to interim data or results sharing	Results	Interpretation of their results
1993	[12]	Trialists from the NIH for the USA	n = 12 Response rate: 100%	n = 12	Quantitative results are unclear Only qualitatively reported as: "DMC reports are confidential, with access to DMC members and selected institute staff."	Respondents from the NIH support that DSMB reports are to be confidential and privy only to DSMB members with access also granted to selected NIH US staff.
1993	[11]	Directors of the statistical centres from 12 cancer cooperative groups sponsored by the NCI in the USA	n = 13 Response rate: 100%	First question about reporting interim results by treatment regimen: n = 9 Second question related to non-DSMB member access to interim data reports: n = 10	First question: 0% of the respondents (0) indicated that NCI groups provided unmasked outcome reports to the participants. Second question: 70% of the respondents (7) indicate interim data reports are not accessed by non-DSMB members	The majority of respondents indicate interim data reports are not accessed by non-DSMB members.
2000	[5]	Trialists from completed trials	n = 45 Response rate: 62%	Unclear	Quantitative results are unclear Only qualitatively reported as: "Views on sharing the interim information with other DMCs were consistent; the investigators were not enthusiastic about the DMC consulting others"	Based on the qualitative reporting it appears that investigators are not supportive of DSMB consulting others outside of the DSMB.
2002	[5]	Trialists from ongoing trials	n = 40 Response rate: 80%	n = 20	50% of respondents (10) agree with the DSMB sharing interim data or results, if it is necessary, with non-DSMB members • Many of these 10 respondents said it should be done if there was a safety concern • 1 respondent from this group felt it was acceptable to share safety but not efficacy data • 2 respondents from this group felt that the SC should make the decision if the DSMB were to share data or results on an individual basis 30% of respondents (6) have no provision for the DSMB sharing data or results with non-DSMB members • 1 respondent from this group indicated that the need to share should be dealt with by the SC on an ad hoc basis 20% of respondents (4) disagree with	Variation and disagreement in the responses about whether the DSMB should share interim data or results with non-DSMB members. The largest group of respondents (50%) agree with DSMBs sharing interim data or results with non-DSMB members when it is necessary, particularly for safety.

Table 1 Surveys looking globally at trial monitoring practices (Continued)

2001/2002	[5]	Review of DSMB policies of major funders of trials, regulatory agencies and other relevant organisations related to trial research	n = 25 Response rate:100%	n = 17	<p>the DSMB interim data or results sharing with non-DSMB members</p> <ul style="list-style-type: none"> • 1 respondent from this group indicated that the DSMB can seek external advice but not share interim data or results <p>All the respondents indicated that some non-DSMB members had access to interim data or results. Who had access to interim data or results was as follows:</p> <ul style="list-style-type: none"> • 41% of respondents (7) indicated that everyone has access to interim data or results except the participants • 35% of respondents (6) indicated that key institute staff has access to interim data or results • 1 respondent from this group said there was also provision for interim data to be seen occasionally and confidentially by the DSMB of another trial • 18% of respondents (3) indicated that only the trial statistician and the DSMB had access to interim data or results • 6% of respondents (1) allow data centre personnel to access interim data or results <p>All respondents from major agencies that are involved in trials indicate that interim data or results are shared with certain non-DSMB members. The largest minority of respondents (41%) indicate interim data/results are shared with everyone except the participants.</p>
2011	[13]	PIs and biostatisticians on DSMBs and IRB community representatives	Total n = 309 Response rate: 31% from PIs 51% for biostatisticians 40% from IRB community members	n = 246 PIs = 152 Biostatisticians = 40 IRB community members = 54	<p>The majority of PIs and biostatisticians on DSMBs and IRB community representatives believe that the sponsor should be masked to interim data or results.</p> <ul style="list-style-type: none"> • 78.3% of PIs (119) indicate that the sponsor should be masked to interim data or results • 63.0% of IRB community members (34) indicate that the sponsor should be masked to interim data or results <p>The majority of PIs and biostatisticians on DSMBs and IRB community representatives believe that the sponsor should be masked to interim data or results. Details about sharing with other non-DSMB members were not discussed</p>

IRB Institutional Review Board, NCI National Cancer Institute, NIH National Institutes of Health for the USA, SC Steering Committee, PI Principal Investigator, UK United Kingdom

members besides the sponsor was not mentioned. For the minority of respondents who said “No” to this question asking if the sponsor should be masked to interim data or results (0% biostatisticians, 21.7% PIs and 37.0% IRB community members), there was no mention as to why this information should be shared with the sponsor. For the one survey that qualitatively reported their results indicating “Views on sharing the interim information with other DMCs were consistent; the investigators were not enthusiastic about the DMC consulting others” [5], there was no mention of whether there were respondents with another view.

One survey [5] (quantitatively reported) supported the Category 2 view: *against* sharing interim results but with *exceptions*. The largest group of respondents from this survey, for the question related to interim data or results sharing (50%, 10/20), agreed with DSMBs sharing interim results with non-DSMB members if it was necessary, particularly for concerns related to participant safety [5]. Specifically with whom this information would be shared was not clear. For the remaining respondents to this question, 30% (6/20) of respondents had no provision for, or idea about, the DSMB sharing interim data or results with non-DSMB members, and 20% (4/20) of respondents disagreed with the DSMB interim data or results sharing with non-DSMB members.

Two surveys [5, 12] (one qualitatively and one quantitatively reported) supported the view *in favour* of sharing interim results by the DSMB with a non-DSMB group (Category 3 view). For the survey that was reported quantitatively [5], all of the respondents to the question related to interim data or results sharing ($n = 17$) indicated that someone outside of the DSMB had access to interim data or results during their trial. With whom interim results were shared was indicated as follows: 41% of respondents indicated everyone except the participants, 35% of respondents indicated key institute staff (one respondent from this group said there was also provision for interim data to be seen occasionally and confidentially by the DSMB of another trial), 18% of respondents indicated only the trial statistician and the DSMB and 6% stated that the data centre personnel had access to interim data or results. Why information was shared with these non-DSMB members was not discussed. For the other survey [12] that reported results qualitatively, it was indicated that respondents ($n = 12$) from the US NIH support that DSMB reports are to be confidential and privy only to DSMB members. However, access is also granted to selected US NIH staff, these being non-DSMB members. Why information was shared with selected US NIH staff was not discussed.

For the other 158 documents, which were not describing surveys, we assessed for a time trend to see where the views and policies lie for the last ten years, back to

2006, in regard to the three categories we identified. For the literature in Category 1, dating back to 1981, 54% (37/68) of the literature comes from the past ten years alone. For Category 2, the literature dates back to 1998. About 24% (4/17) of the literature comes from the last decade. For the literature in Category 3, dating back to 1991, 52% (38/73) of the literature comes from the past ten years. The most recent literature, count and percentage wise, has predominately supported the DSMB not sharing or not sharing but with some exceptions. We also found that regulation, policy or guideline documents predominately support Category 3 (55%, i.e. 15/27 of the 27 regulation, policy or guideline documents included in our review).

In regard to our second objective, there is a subset of the literature within Category 2 or 3 literature that discusses what interim results the DSMB should share, with whom and the circumstance (why). Eleven circumstances that may warrant the DSMB sharing interim results with non-DSMB members are explained in Table 2, generally categorised under four themes: (1) current usual practice by DSMBs, (2) trial completion is threatened, (3) concern about patient safety and (4) regulatory approval). There is also a category for other special circumstances that includes three unique situations for DSMB sharing of interim results that did not fit into a theme. Six of these eleven circumstances are supported in the literature with real-life examples. What is shared by the DSMB with non-DSMB members varies depending on the particular circumstance. For many of the cases where sharing may be warranted, a risk or counter argument to sharing is indicated where applicable. Most of the risks with sharing in these circumstances are predominately associated with introducing bias in the trial that will affect the final trial results. It is indicated in the literature that there is always the potential that sharing interim results with non-DSMB members may do harm to a trial by disturbing equipoise [14, 15], as people may make inaccurate impressions about what is happening between treatment groups [3, 16–18]. It is explained that when equipoise is disturbed with knowledge of interim results by those operating and managing the trial and those participating in the trial, there may be actions people can take, either consciously or subconsciously [19], that can bias the trial's results [1, 16, 19]. The introduction of bias can reduce the credibility and integrity [16, 20, 21] of the trial, rendering the results questionable [16, 20, 22].

Discussion

What are the findings from the review?

We found three main views on the DSMB sharing interim results with non-DSMB members. These views were (1) *against* sharing (Category 1), (2) *against* sharing interim results with *exceptions* (Category 2) and (3) *in*

Table 2 Circumstances where interim result sharing may be warranted by the DSMB

Circumstance	With whom would the DSMB share?	What to share?	Risk or counter argument	Reference
Theme 1) Current usual practice by DSMBs				
Circumstance 1: When the DSMB recommends early termination and the recommendation needs to be evaluated by the SC and sponsor	Specified representative(s) of their trial's SC and sponsor	Unmasked interim results	Risk: If the trial were to continue despite the recommendation to terminate, those few individuals privy to the interim data should not be a part of making future trial decisions. This will protect the trial's integrity from potential biasing of results	[6]
Circumstance 2: When the DSMB has concerns about the interim data or results given to them by the unblinded independent statistician or DAC for their interim review	Trial's independent statistician or DAC	Anything needed	None made	[16, 20, 27–38]
Theme 2) Trial completion is threatened				
Circumstance 3: When the trial may have to stop early because of poor accrual due to special circumstances, and it may be possible to improve accrual by sharing interim data or results, when all other efforts to improve accrual are exhausted	The public	Some type of unmasked interim result that will encourage accrual	Risk: Risk of biasing trial results even when special conditions are met as indicated by Stephens et al. [39]. Sharing interim results should be a judgement call that weighs the benefits of sharing against the potential risk of biasing trial results	[16, 30, 39–43] [39]*
Circumstance 4: When there is a need to restore equipoise when one of two related trials finishes first and threatens the completion of the unfinished trial	The public	Sharing unmasked but limited comparative interim results that will help restore equipoise	Counter argument: The unfinished trial(s) might not need to share interim information if it will contribute important information beyond what was reported by a similar trial that finished earlier. This sentiment should be expressed to all stakeholders to help restore confidence in trial completion	[1, 16, 44] [1]*
Theme 3) Concern about patient safety				
Circumstance 5: When an uncertain severe safety issue appears at interim in a trial and there is another similar trial still underway	The DSMB of the similar trial	Safety: Unmasked interim safety result	Risk: Sharing may erode the independence of each trial in regards to the independent confirmation of results	[1, 5, 6, 17, 23, 44–52] [1]*
Circumstance 6: When the DSMB assesses the risk of there being a serious adverse event at interim for enrolled patients in a particular treatment group, but	Trial patients	Safety: Unmasked interim safety results	Risk: Unmasking of interim safety results with the trial patients may risk biasing the trial results, but in some cases it is ethically imperative to let the patients know of the severe	[1, 14, 18, 53, 54] [1]*

Table 2 Circumstances where interim result sharing may be warranted by the DSMB (*Continued*)

continuing the trial may still be desirable because getting a definitive result on a patient primary endpoint is important to the public and medical community			safety risks to allow them to decide whether they want to continue in the trial and before allowing the trial itself to continue	
Theme 4) Regulatory approval				
Circumstance 7: When the regulator is currently assessing licensing approval for a new drug/treatment submitted with results from a completed trial and there is still a similar trial underway that will provide important new substantial information regarding results	The regulators	Relevant unmasked interim results that will help with assessing the status that should be given for a licensing application	Risk: Interim review of the second ongoing trial could jeopardise its own integrity and introduce bias, as the public could prognosticate the results of that trial based on the regulator's subsequent decision to either approve or delay a manufacturer's licensing application	[1, 20] [1]*
Circumstance 8: When a regulatory wants to assess a drug for conditional or accelerated/expedited approval for a manufacturer to be able to market a drug early	The regulators	Unmasking interim results	Risk: Bias could also be introduced to the trial with knowledge of regulatory decisions made based on interim results and known threshold criteria for approval, even if exact interim endpoints are not shared publically	[1, 5, 16, 28, 55–61] [57, 60]*
Other special circumstances				
Circumstance 9: When adaptive confirmatory trials base interim trial adaptive changes on the trial's interim results	Authorised qualified persons at the sponsor (1 or 2 people) who are not participating in the trial but can assist with trial adaptations	Whatever is agreed upon a priori	Risk: Unmasking of interim data or results can introduce bias and risk trial integrity	[30, 62–68]
Circumstance 10: When patients outside of the trial are facing important treatment decisions and may benefit from some interim results from non-inferiority or superiority trials with a long follow-up	The public and patients and physicians facing important treatment decisions	Relevant unmasked interim results that will help with treatment decision	Risk: Knowledge of an interim endpoint result could influence a clinical decision to have a new treatment before safety of that treatment is determined more definitively in ongoing trial	[11, 69, 70]
Circumstance 11: When sponsors, investigators or regulators are planning for future studies, new products or allocating resources for future use	Sponsors, investigators or regulators	Unmasked yet non-comparative interim information. This could be: <ul style="list-style-type: none"> • Control group event rates OR • Control group adverse event rates OR • Pooled event rate 	Risk: Bias can be introduced to the unfinished trial if new plans are to be published and can be interpreted by a wider audience. Planning errors could result from using uncertain interim results	[1, 6, 20, 71–74]

DAC Data Analysis Centre, DSMB Data Safety Monitoring Board, SC Steering Committee

Circumstances 3–8 have a real-life example and an asterisk (*) next to the associated reference(s) with the example

favour of sharing interim results (Category 3). The literature predominately supported Category 1 and Category 2 in similar proportions. We found that the literature in Category 2 and Category 3 presented 11 cogent reasons for sharing interim results by the DSMB with various non-DSMB members in certain circumstances (Table 2). The three surveys [5, 12] that support the Category 2 and Category 3 views do not specifically indicate what

should or should not be shared in circumstances that may warrant sharing interim results. However, one of the surveys [5] that support Category 2 indicates that the DSMB having a safety concern is a circumstance that justifies the DSMB sharing interim results with non-DSMB members. In these 11 circumstances, what is shared and with whom depends on the circumstance. Six of the 11 circumstances (see Table 2) have real-life

examples (anecdotal evidence) where interim result sharing by the DSMB with a non-DSMB member helped the trial and the patients who were enrolled. However, for most of these 11 circumstances, there are risks acknowledged—mainly in regard to introducing bias that may affect the trial's final results. Based on these 11 circumstances that may occur, there is possible legitimacy in the notion that what may or may not be shared and with whom at interim should be a judgement call made by a trial's DSMB, where the DSMB as a group balances the apparent risks and benefits in those circumstances that arise regarding the need to protect both the safety of the patients enrolled and the trial's integrity. Sometimes the DSMB may find that the benefits of sharing seem to outweigh the risks, as was illustrated by some real-life examples that supported 6 of the 11 circumstances. The DSMB may also find that the risks of sharing are not worth the benefits that could result. The opinion of the DSMB sharing interim results is also supported in part by both Chalmers et al. [23] and Shah et al. [24]. Chalmers et al. [23] comment on the need to share interim results when the occasion is appropriate and to identify and plan for such situations a priori when possible.

How do these findings compare with those of similar works?

While our review is unique in that it solely focuses on the issues of interim result sharing by the DSMB with non-DSMB members, another review, done earlier in 2005 by Grant et al. [5] under the auspices of the National Health Service (NHS) in the UK, looks globally at many issues related to data monitoring and interim analysis. One of 23 questions they ask addresses in part the issue with DSMB confidentiality of interim data. They found within their literature review under *Question 8: Should the DMC deliberations be open or closed (confidential or secret as opposed to publicly available)?* that “There is near unanimity that the interim data and the deliberations of the DMC should be absolutely confidential” [5], which supports what we found in our review with Category 1 literature which held a large percentage of the literature reviewed (43.8%). However, a sub-question to their Question 8 asked: *Who outside the committee should see the interim analysis and how is this changed by whether the analyses were blinded or unblinded?* They indicate that some have suggested that an independent unmasked statistician should see the interim analysis [5], which is what we found for Circumstance 2 described in our Table 2. They also indicate that the DSMBs may allow certain individuals such as the chair of the SC to become unmasked to certain interim results, especially if this is deemed by the DSMB of the trial to serve patient/participant safety best [5]. For Circumstances 5 and 6 in Table 2, we also find that a severe safety issue in the trial is a potential driving factor

to share unmasked interim safety results with non-DSMB members. Thus, their review [5] also supports what we found in Category 2 literature: even though interim results should remain confidential with the DSMB, there are circumstances the DSMB must consider that could warrant interim sharing outside of the DSMB. Our review goes into detail about the circumstances that may warrant sharing (see Table 2), and we do our best to summarise all the views on this issue. Our intent was also to discuss what to share and with whom in those circumstances and, as described above, we found that it greatly depends on the circumstance in which the DSMB finds itself, in regard to the trial.

What are the key limitations?

One limiting factor of this review is that the majority of the included literature was based on personal perspectives (79.6%). Though these perspectives brought up important points, these views represent a small fraction of all the professionals who are involved in trials and are not based on evidence. Many of these views contributed to describing the 11 circumstances found in Table 2, where only 6 out of the 11 circumstances were supported by anecdotal evidence. The other 7 circumstances were based on the author's experience or view that would warrant sharing by the DSMB if the DSMB deemed it necessary and safe to do so.

Another limitation is that the six surveys do not fully help us with our objective to understand, with empirical evidence, what interim results, if any, the DSMB should share, with whom and under what circumstances. They globally focus on trial monitoring practices and not in depth or specifically on the issue of DSMB sharing interim results. At most, one or two questions within each survey ask a question related to the DSMB sharing interim results with other non-DSMB groups, but the questions are not asked in a consistent way for all the surveys. For instance, for three of these surveys, the questions related to interim result sharing asks respondents about their current practices regarding who has access to unmasked outcome reports [5, 11, 12] at their research institutions. For another survey, the question very specifically asks respondents if the sponsor should be masked to interim results [13]. For two of the surveys [5], the question related to interim result sharing asks respondents if they think unmasked interim results should be shared with non-DSMB members. So, although we can understand overall where support lies from each survey in regard to sharing interim results, and in some surveys we have a bit of information about with whom interim results may be shared, it is still extremely unclear what specific kind of interim result should be shared, with whom that result should be

shared and for what reason or circumstance. There is not one survey that consistently asks the same group of respondents who are trialists, what interim results specifically should be shared, with a direct follow-up question about who outside of the DSMB should share that specific interim result and for what reason (why). This is a complex topic. It is challenging for any survey soliciting responses about global trial monitoring practices to use one or two questions to sufficiently address and provide enough information clarifying what interim results the DSMB should share, if anything at all, with whom, and why. Multiple questions or an entire survey dedicated to the topic of DSMB interim result sharing is needed.

Implications of the findings

Our findings inform trialists and those who enact trial policies and guidelines that there are mixed views on the DSMB sharing interim results with non-DSMB members. We could argue that out of the three categories, the literature in Categories 1 and 2 dominates in that the DSMB should not share interim results with non-DSMB members, but the literature in Category 2 suggests that there may be exceptions. The exceptions include 11 possible circumstances as described in Table 2. However, the findings from this review need to be substantiated with more research. The empirical evidence found within three of the six surveys [5, 13] suggests there is support for sharing interim results with certain non-DSMB members, but the details on what specifically should be shared and for what reason are unclear. Based on the limitations described in the previous section, more empirical evidence is needed to clarify specifically what interim results should or should not be shared by the DSMB with non-DSMB members, with whom and for what reason or circumstance, to better inform monitoring practices, policies and guidelines that protect the safety of the participants enrolled and trial validity.

For the situation described earlier by Anand *et al.* [3], we also question: How useful is it to share unmasking yet non-comparative interim results (e.g. control group event rates without knowledge of the pooled events rates)? Also, how useful is it to share results that appear masking of comparative results (e.g. adaptive conditional power or aggregate/pooled results by treatment group)? It is thought that knowledge of aggregate/pooled results can lead to concerns about making assumptions about interim results [25, 26] that are not necessarily true, which could lead to introducing bias in the trial. Knowledge of such potentially unmasking information, such as the adaptive conditional power, could jeopardise the integrity of the trial, as it does indicate the probability of the trial showing a favourable significant result [2]. In the case described by Anand *et al.* [3], the request for the adaptive conditional power by the trial sponsor was

denied by the trial's DSMB, and the decision to not share was additionally supported by the trial's SC, PI and others outside of the trial who were consulted. There was also mention of the DSMB sharing an 'unconditional' conditional power with the sponsor. This 'unconditional' conditional power calculation [3] was shared with the sponsor because it is thought to mask the efficacy results if given out at interim, but also provide reassurance to the sponsor that the trial will have the power to answer the primary hypothesis initially set out at the design stage of the trial, when the trial is completed [3]. Is providing the 'unconditional' conditional power a helpful alternative to sharing aggregate/pooled results? Should a result extrapolation such as aggregate/pooled results or adaptive conditional power be shared? How is such information interpreted? The issue of sharing aggregate/pooled interim results needs further investigation. More clarity is also required on the specifics of sharing aggregate/pooled interim results, particularly interim results that are thought to be masking, such as the combined event rate, and result extrapolations, such as adaptive conditional power, that have been requested in the past [3].

Conclusions

Interim result sharing is an important issue because it affects the validity of the results from confirmatory trials on which we base regulatory and practise decisions, impacting the health and lives of many. From this review, two categories of the literature dominate (Category 1 and Category 2), but not in majority as distinct groups. Category 1 is against sharing interim results, stating that they should remain confidential with the DSMB, and Category 2 shares the same sentiment as Category 1 but additionally acknowledges exceptions, that there are circumstances that may warrant the DSMB to share interim results with certain non-DSMB groups/members. What is shared with these non-DSMB members depends on what the situation calls for and should be assessed by the DSMB using their expertise to balance risk(s) with the potential benefit(s) regarding participant safety and trial validity and integrity. Because of the limitations of the evidence found, collecting more empirical evidence through a survey of the general clinical trials community focused on the issue of DSMB sharing interim results (what, if any, interim result(s) to share, with whom and under what circumstance) is needed to better understand and guide DSMB interim information sharing practices.

Additional files

Additional file 1: Search strategies for literature. (DOCX 33 kb)

Additional file 2: Citations of included articles for review. (DOCX 33 kb)

Additional file 3: RAMESSES checklist. (DOCX 18 kb)

Abbreviations

CRO: Contract Research Organisation; DAC: Data Analysis Centre; DMC: Data Monitoring Committee; DSMB: Data Safety Monitoring Board; FDA: Food and Drug Administration; IRB: Institutional Review Board; ISC: Independent Statistical Centre; NCI: National Cancer Institute; NHS: National Health Service; NIH: National Institutes of Health; PI: Principal Investigator; RCT: Randomised controlled trial; SC: Steering Committee; SDAC: Statistical Data Analysis Centre; SOP: Standard Operating Procedure; UK: United Kingdom

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Authors' contributions

VBD was involved in all aspects of this study from study design and conception, acquisition of information, information synthesis and writing of the manuscript. LM was substantially involved in supervision of study design and critical revisions to this paper. LT was substantially involved in primary supervision, study design and conception and critical revisions to this paper. All authors read and approved the final manuscript.

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Additional file 1: Search Strategies for Literature**Search Strategy for PubMed (December 2015)**

The *PubMed* (includes all *MEDLINE* citations) database was searched for all articles pertaining to the discussion of Data Safety Monitoring Boards from 1946, with some older material, to December 2015.

896 citations were found using the search strategy below.

The following was the search strategy used:

Search Number	Number of Citations Found	Search Query
#2	896	Search ("english"[Language]) AND #1
#1	934	Search "data monitoring committees"[Title/Abstract] OR "data monitoring committee"[Title/Abstract] OR "data monitoring boards"[Title/Abstract] OR "data monitoring board"[Title/Abstract] OR "data safety monitoring boards"[Title/Abstract] OR "data safety monitoring board"[Title/Abstract] OR "data safety monitoring committee"[Title/Abstract] OR "data safety monitoring committees"[Title/Abstract] OR "data safety and monitoring boards"[Title/Abstract] OR "data safety and monitoring board"[Title/Abstract] OR "data and safety monitoring board"[Title/Abstract] OR "independent data monitoring boards"[Title/Abstract] OR "independent data monitoring board"[Title/Abstract] OR "independent data monitoring committees"[Title/Abstract] OR "independent data monitoring committee"[Title/Abstract] OR "independent data safety monitoring committees"[Title/Abstract] OR "independent data safety monitoring committee"[Title/Abstract] OR Clinical Trials Data Monitoring Committees [Mesh Terms] OR data and safety monitoring boards[MeSH Terms]

Search Strategy for Web of Science (December 2015)

The *Web of Science* database was searched for all articles pertaining to discussion of Data Safety Monitoring Boards from inception of the database to December 2015, Timespan: All years. Indexes: using the Web of Science Core Collection: Citation Indexes, specifically the Science Citation Index Expanded (SCI-EXPANDED) --1976-present.

627 citations were found using the search strategy below.

The following was the search strategy used:

Search Number	Number of Citations Found	Search Query
#3	627	#2 OR #1 Indexes=SCI-EXPANDED Timespan=All years

#2	627	(TS=("data monitoring committees" OR "data monitoring committee" OR "data monitoring boards" OR "data monitoring board" OR "data safety monitoring boards" OR "data safety monitoring board" OR "data safety monitoring committee" OR "data safety monitoring committees" OR "data safety and monitoring boards" OR "data safety and monitoring board" OR "data and safety monitoring board" OR "independent data monitoring boards" OR "independent data monitoring board" OR "independent data monitoring committees" OR "independent data monitoring committee" OR "independent data safety monitoring committees" OR "independent data safety monitoring committee")) AND LANGUAGE: (English) <i>Indexes=SCI-EXPANDED Timespan=All years</i>
#1	98	(TI=("data monitoring committees" OR "data monitoring committee" OR "data monitoring boards" OR "data monitoring board" OR "data safety monitoring boards" OR "data safety monitoring board" OR "data safety monitoring committee" OR "data safety monitoring committees" OR "data safety and monitoring boards" OR "data safety and monitoring board" OR "data and safety monitoring board" OR "independent data monitoring boards" OR "independent data monitoring board" OR "independent data monitoring committees" OR "independent data monitoring committee" OR "independent data safety monitoring committees" OR "independent data safety monitoring committee")) AND LANGUAGE: (English) <i>Indexes=SCI-EXPANDED Timespan=All years</i>

Search Strategy for EMBASE (Decmeber 2015)

The EMBASE database for all articles pertaining to discussion of Data Safety Monitoring Boards from inception of the database to December 2015, through OVID technologies.

1271 citations were found using the search strategy below.

The following was the search strategy used:

Search Number	Number of Citations Found	Search Query
#2	1271	Limit 1 to english language
#1	1290	("data monitoring committees" or "data monitoring committee" or "data safety monitoring boards" or "data safety monitoring board" or "data safety monitoring committee" or "data safety monitoring committees" or "data safety and monitoring boards" or "data safety and monitoring board" or "data and safety monitoring board" or "independent data monitoring boards" or "independent data monitoring board" or "independent data monitoring committees" or "independent data monitoring committee" or "independent data safety monitoring committees" or

		"independent data safety monitoring committee" or "data monitoring committees" or "data monitoring committee").ab. or ("data monitoring committees" or "data monitoring committee" or "data safety monitoring boards" or "data safety monitoring board" or "data safety monitoring committee" or "data safety monitoring committees" or "data safety and monitoring boards" or "data safety and monitoring board" or "data and safety monitoring board" or "independent data monitoring boards" or "independent data monitoring board" or "independent data monitoring committees" or "independent data monitoring committee" or "independent data safety monitoring committees" or "independent data safety monitoring committee" or "data monitoring committees" or "data monitoring committee").ti. or ("data monitoring committees" or "data monitoring committee" or "data safety monitoring boards" or "data safety monitoring board" or "data safety monitoring committee" or "data safety monitoring committees" or "data safety and monitoring boards" or "data safety and monitoring board" or "data and safety monitoring board" or "independent data monitoring boards" or "independent data monitoring board" or "independent data monitoring committees" or "independent data monitoring committee" or "independent data safety monitoring committees" or "independent data safety monitoring committee" or "data monitoring committees" or "data monitoring committee").kw.
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Search Strategy for CINAHL (December 2015)

The *CINAHL* database for all articles pertaining to discussion of Data Safety Monitoring Boards from inception of the database to December 2015, through the EBSCOhost Research Databases Interface, Search Screen - Advanced Search, Database – CINAHL

128 citations were found using the search strategy below.

The following was the search strategy used:

Search Number	Number of Citations Found	Search Query	Limiters and Expanders
#1	128	TI (("data monitoring committees" OR "data monitoring committee" OR "data monitoring boards" OR "data monitoring board" OR "data safety monitoring boards" OR "data safety monitoring board" OR "data safety monitoring committee" OR "data safety monitoring committees" OR "data safety and monitoring boards" OR "data safety and monitoring board" OR "data and safety monitoring board" OR "independent data monitoring boards" OR "independent data monitoring board" OR "independent data monitoring committees" OR "independent data monitoring committee" OR "independent data safety monitoring committees" OR "independent data safety monitoring committee" or "data monitoring committees" or "data monitoring committee").kw.	<ul style="list-style-type: none"> • Limiters - English Language • Expanders - Apply related words; Also search within the full text of the articles; Apply equivalent subjects • Search modes - Boolean/Phrase

		<p>monitoring boards" OR "independent data monitoring board" OR "independent data monitoring committees" OR "independent data monitoring committee" OR "independent data safety monitoring committees" OR "independent data safety monitoring committee") OR AB ("data monitoring committees" OR "data monitoring committee" OR "data monitoring boards" OR "data monitoring board" OR "data safety monitoring boards" OR "data safety monitoring board" OR "data safety monitoring committee" OR "data safety monitoring committees" OR "data safety and monitoring boards" OR "data safety and monitoring board" OR "data and safety monitoring board" OR "independent data monitoring boards" OR "independent data monitoring board" OR "independent data monitoring committees" OR "independent data monitoring committee" OR "independent data safety monitoring committees" OR "independent data safety monitoring committee") OR SU ("data monitoring committees" OR "data monitoring committee" OR "data monitoring boards" OR "data monitoring board" OR "data safety monitoring boards" OR "data safety monitoring board" OR "data safety monitoring committee" OR "data safety monitoring committees" OR "data safety and monitoring boards" OR "data safety and monitoring board" OR "data and safety monitoring board" OR "independent data monitoring boards" OR "independent data monitoring board" OR "independent data monitoring committees" OR "independent data monitoring committee" OR "independent data safety monitoring committees" OR "independent data safety monitoring committee"))</p>	
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Search Strategy for the major governmental and regulatory funding bodies and guideline groups search (December 2015)

For each of major, governmental regulatory/health research/funding bodies, and international guideline groups for health research listed further below, if they had a search feature for their

website, the following key terms were used one at a time to find relevant material or documents on DSMBs or clinical trials:

1. data monitoring committees
2. data monitoring committee
3. data monitoring boards
4. data monitoring board
5. data safety monitoring boards
6. data safety monitoring board
7. data safety monitoring committee
8. data safety monitoring committees
9. data safety and monitoring boards
10. data safety and monitoring board
11. data and safety monitoring board
12. independent data monitoring boards
13. independent data monitoring board
14. independent data monitoring committees
15. independent data monitoring committee
16. independent data safety monitoring committees
17. independent data safety monitoring committee
18. Clinical Trials Data Monitoring Committees
19. clinical trials
20. randomized controlled trials
21. randomised controlled trials

One search strategy was to search each website with key terms within a search box, if this feature was available for the website. If one of the organizations listed above had a search box feature for their website, 21 key terms related to DSMBs or clinical trial research were used one at a time to find relevant material or documents or grey literature on DSMBs and clinical trials. The first 5 pages of the search results generated from the search box (if the feature was available) were reviewed for each of the search terms used. The other search strategy used to find relevant literature or grey literature was to explore the organization's websites by clicking on relevant main headings and subheading respectively, related to clinical/medical research or DSMBs on the home page or index page of the organization's website, if an index page was available.

Documents and pages dedicated to clinical trial research or DSMBs as indicated from the webpage's or document's title and abstract (if an abstract was available) were included for full text review from each of the 14 organization's websites mentioned below. Documents and pages from the full text review were included for full text information extraction if there was discussion within the full text of the document or webpage about sharing interim trial data by the DSMB with parties outside of DSMB. This search strategy resulted in 73 webpages or documents included for the full text review in total and 27 webpages or documents included for full text information extraction.

The following major, governmental regulatory/health research/funding bodies, and international guideline groups for health research were searched directly for relevant literature or information from their respective websites:

1) For the US: *National Institutes of Health (NIH)* [1]. The search of the NIH website resulted in finding literature on policies and guidance for Data and Safety Monitoring of Clinical Trials from associated research divisions within the NIH. These associated research divisions included the following 17 divisions [2]:

1. *National Institute of Neurological Disorders and Stroke (NINDS)* [3]
2. *National Heart, Lung, and Blood Institute (NHLBI)* [4]
3. *National Eye Institute (NEI)* [5]
4. *National Cancer Institute (NCI)* [6]
5. *National Institute of Allergy and Infectious Diseases (NHLBI)* [7]
6. *National Institute on Alcohol Abuse and Alcoholism (NIAAA)* [8]
7. *National Institute on Aging (NIA)* [9]
8. *National Institute of Nursing Research (NINR)* [10]
9. *National Institute of Mental Health (NIMH)* [11]
10. *National Institute of General Medical Sciences (NIGMS)* [12]
11. *National Institute of Environmental Health Sciences (NIEHS)* [13]
12. *National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)*[14]
13. *National Institute of Dental and Craniofacial Research (NIDCR)* [15]
14. *National Institute on Deafness and Other Communication Disorders (NIDCD)* [16]
15. *National Institute on Drug Abuse (NIDA)* [17]
16. *National Institute of Child Health and Human Development (NICHD)*[18]
17. *National Centre for Complementary and Integrative Health (NCCIH)* [19, 20]

And the *U.S. Food and Drug Administration (FDA)* [21];

2) For Canada: *Health Canada* [22], *Canadian Institutes for Health Research (CIHR)* [23], and *Panel on Research Ethics* [24];

3) For the UK: *UK Department of Health* [25], *Medical Research Council (MRC)* [26], *National Institute for Health Research (NIHR)* [27], and the *National Health Service; Health Research Authority (NHS HRA)* [28]

4) For the European Union: *European Medicines Agency (EMA)* [29]

5) For Australia: *The National Health and Medical Research Council* [30] and *Therapeutic Goods Administration* [31] via the Department of Health

6) International Groups: *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)* [32], which is a group that brings together regulatory authorities and the pharmaceutical industry to discuss the science and technical parts of drug registration and medical studies, and the *World Health Organization (WHO)* [33]

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[<http://www.nih.gov/>]
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[http://grants.nih.gov/grants/policy/hs/data_safety.htm]
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4. **NHLBI Policy for Data and Safety Monitoring of Extramural Clinical Studies**
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[<https://nei.nih.gov/funding/policy/policy6>]
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[<http://www.niaid.nih.gov/labsandresources/resources/toolkit/guidance/Pages/guidance.aspx>]
8. **Data and Safety Monitoring Guidelines**
[<http://www.niaaa.nih.gov/ResearchInformation/ExtramuralResearch/ResourcesAppGrantees/guidelines.htm>]
9. **Implementation of Policies for Human Intervention Studies**
[<https://www.nia.nih.gov/research/dea/implementation-policies-human-intervention-studies>]
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[<https://www.ninr.nih.gov/sites/www.ninr.nih.gov/files/NINR%20DSM%20Policy%202014%20FINAL.pdf>]
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12. **NIGMS Guidelines for Data and Safety Monitoring in Clinical Trials**
[<http://www.nigms.nih.gov/Research/bioethics/Pages/clinicaltrials.aspx>]
13. **Policy for Data and Safety Monitoring of Human Subject Research Studies**
[<http://www.niehs.nih.gov/research/clinical/patientprotections/dsmb/index.cfm>]
14. **Data & Safety Monitoring Plans** [<http://www.niddk.nih.gov/research-funding/process/human-subjects-research/policies-for-clinical-researchers/data-safety-monitoring-plans/Pages/data-and-safety-monitoring-plans.aspx>]
15. **NIDCR Policy for Data and Safety Monitoring of Clinical Research**
[<http://www.nidcr.nih.gov/Research/ToolsforResearchers/Toolkit/DataandSafetyMonitoring.htm>]
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[<http://www.nidcd.nih.gov/research/clinicalstudies/Information-for-Researchers-and-Health-Professionals/Pages/NIDCD-Guidelines-for-Data-and-Safety-Monitoring-of-Clinical-Trials.aspx>]
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[<http://www.drugabuse.gov/funding/clinical-research/guidelines-developing-data-safety-monitoring-plan>]

18. **Data and Safety Monitoring Guidelines**
[http://www.niams.nih.gov/Funding/Clinical_Research/data_safety_monitoring_guidelines.pdf]
19. **Data and Safety Monitoring of NCCIH-Funded Clinical Research**
[<https://nccih.nih.gov/grants/policies/data-safety-monitoring>]
20. **Guidelines for NCCIH-Appointed Data and Safety Monitoring Boards**
[<https://nccih.nih.gov/research/policies/datasafety>]
21. **U.S. Food and Drug Administration** [<http://www.fda.gov/>]
22. **Health Canada** [<http://www.hc-sc.gc.ca/index-eng.php>]
23. **Canadian Institutes of Health Research** [<http://cihr-irsc.gc.ca/e/193.html>]
24. **Panel on Research Ethics** [<http://www.pre.ethics.gc.ca/eng/index/>]
25. **UK Department of Health** [<https://www.gov.uk/government/organisations/department-of-health>]
26. **Medical Research Council** [<http://www.mrc.ac.uk/>]
27. **National Institutes for Health Research** [<http://www.nihr.ac.uk/>]
28. **National Health Service** [<http://www.nhs.uk/Pages/HomePage.aspx>]
29. **European Medicines Agency** [<http://www.ema.europa.eu/ema/>]
30. **National Health and Medical Research Council** [<http://www.nhmrc.gov.au/>]
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Additional file 2: Citations of included articles for review

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[<http://www.niehs.nih.gov/research/clinical/patientprotections/dsmb/index.cfm>]

Additional file 3: RAMESES checklist**RAMESES 2013 Checklist from Wong et al. [1]**

Section	Checklist Item	Page
TITLE		
1	In the title, identify the document as a meta-narrative review or synthesis	1
ABSTRACT		
2	While acknowledging publication requirements and house style, abstracts should ideally contain brief details of: the study's background, review question or objectives; search strategy; methods of selection, appraisal, analysis and synthesis of sources; main results; and implications for practice.	2
INTRODUCTION		
3 Rationale for review	Explain why the review is needed and what it is likely to contribute to existing understanding of the topic area.	3
4 Objectives and focus of review	State the objective(s) of the review and/or the review question(s). Define and provide a rationale for the focus of the review.	3
METHODS		
5 Changes in the review process	Any changes made to the review process that was initially planned should be briefly described and justified.	5
6 Rationale for using meta-narrative review	Explain why meta-narrative review was considered the most appropriate method to use.	4
7 Evidence of adherence to guiding principles of meta-narrative review	Where appropriate show how each of the six guiding principles (pragmatism, pluralism, historicity, contestation, reflexivity and peer review) have been followed.	5
8 Scoping the literature	Describe and justify the initial process of exploratory scoping of literature.	4
9 Searching processes	While considering specific requirements of the journal or other publication outlet, state and provide a rationale for how the iterative searching was done. Provide details on all the sources accessed for information in the review. Where searching in electronic databases has taken place, the details should include (for example) name of database, search terms, dates of coverage and date last searched. If individuals familiar with the relevant literature and/or topic area were contacted, indicate how they were identified and selected.	4 and Additional file 1
10 Selection and appraisal of documents	Explain how judgements were made about including and excluding data from documents, and justify these.	4, 5 and Additional file 1

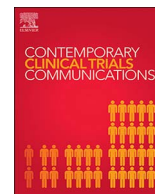
11 Data extraction	Describe and explain which data or information were extracted from the included documents and justify this selection.	5
12 Analysis and synthesis processes	Describe the analysis and synthesis processes in detail. This section should include information on the constructs analysed and describe the analytic process.	5
RESULTS		
13 Document flow diagram	Provide details on the number of documents assessed for eligibility and included in the review with reasons for exclusion at each stage as well as an indication of their source of origin (for example, from searching databases, reference lists and so on). You may consider using the example templates (which are likely to need modification to suit the data) that are provided.	Figure 1
14 Document characteristics	Provide information on the characteristics of the documents included in the review.	5
15 Main findings	Present the key findings with a specific focus on theory building and testing.	5, Table 1 and Table 2
DISCUSSION		
16 Summary of findings	Summarise the main findings, taking into account the review's objective(s), research question(s), focus and intended audience(s).	8 and 9
17 Strengths, limitations and future research	Discuss both the strengths of the review and its limitations. These should include (but need not be restricted to) (a) consideration of all the steps in the review process and (b) comment on the overall strength of evidence supporting the explanatory insights which emerged. The limitations identified may point to areas where further work is needed.	10
18 Comparison with existing literature	Where applicable, compare and contrast the review's findings with the existing literature (for example, other reviews) on the same topic.	9
19 Conclusion and Recommendations	List the main implications of the findings and place these in the context of other relevant literature. If appropriate, offer recommendations for policy and practice.	11, 12
20 Funding	Provide details of funding source (if any) for the review, the role played by the funder (if any) and any conflicts of interests of the reviewers.	13

1. Wong G, Greenhalgh T, Westhorp G, Buckingham J, Pawson R: **RAMESES publication standards: meta-narrative reviews**. *BMC Medicine* 2013, **11**(1):20.



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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 versus 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

Table 1

Definitions of interim result and results extrapolations.

Interim combined event rate	<p>The total number of events observed at some planned interim point into the trial divided by the total number of participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial or after enrolling a certain number of participants).</p> <p>Example:</p> <ul style="list-style-type: none"> • Total # of Deaths in both the placebo group and new intervention group, six months from the start of the trial = 80 • Total # of Participants in both the placebo group and the new intervention group, six months from the start of the trial = 700 • Calculation: $80/700 = 0.114$ or 11.4% <p>Therefore the Interim Combined Event Rate at the trial's interim analysis, six months from the start of the trial, is 11.4%</p>
Adaptive conditional power	<p>The probability of rejecting the null hypothesis of no effect by the end of the trial (i.e. finding a statistically significant effect in favour of the intervention), at some predetermined interim point in the trial when the adaptive conditional power is scheduled to be calculated. The assumption made is that the observed interim effect (i.e. relative risk reduction) in the trial will remain the same till the end of the trial.</p> <p>Example statement:</p> <p>Given the interim data (data collected 2 years into the trial that is planned to last for 3 years), and assuming the observed interim effect (i.e. relative risk reduction) at the two year point to be the true effect for the remainder of the trial, the probability of rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 60%.</p> <p>The following pieces of information are used to calculate Adaptive Conditional Power at trial interim:</p> <ul style="list-style-type: none"> • Control event rate and experimental event rate • Information Fraction; a ratio of the planned sample size and the number of patients recruited in trial at the interim analysis • Z score and B value at interim • Drift parameter
“Unconditional” conditional power	<p>The <u>probability of correctly</u> 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 when indeed the alternative hypothesis is true, at some interim point in the trial.</p> <p>The following pieces of information are used to calculate Unconditional Conditional Power at interim:</p> <ol style="list-style-type: none"> 1. The <u>hypothesized treatment effect at the design stage</u> (i.e. relative risk reduction) of the trial, assuming the hypothesized treatment effect at the design stage to be true and correct for the remainder of the trial; 2. The <u>sample size calculated at the design stage</u> for the trial AND; 3. The <u>combined event rate calculated at the trial's interim</u>, assuming this rate to be true for the remainder of the trial. <p>Example statement:</p> <p>Given the interim combined event rate and assuming the treatment effect (i.e. relative risk reduction) hypothesized at the design stage of the trial to be true for the remainder of the trial, the probability of correctly rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 89%.</p>

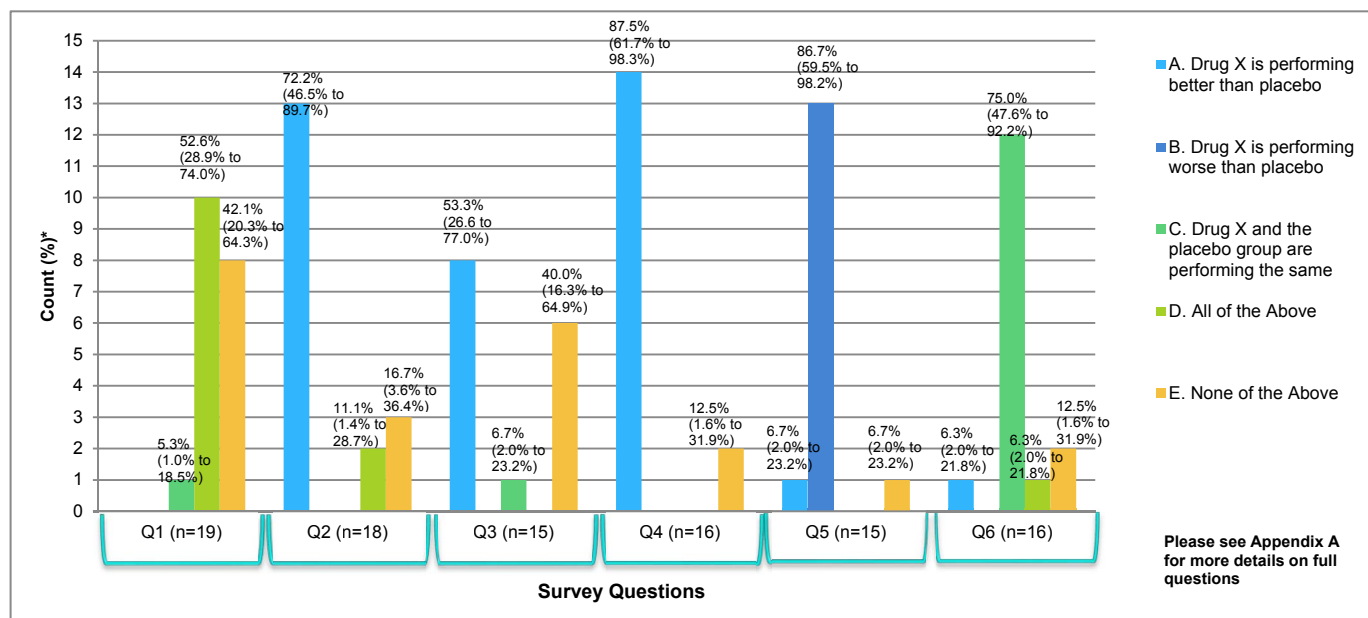


Fig. 1. Results from Survey.

Question 1 (Q1): “This Interim Combined Event Rate is compatible with which of the following conclusions below? Please select the case option that best fits with this scenario”.

Question 2 (Q2): “This Adaptive Conditional Power is compatible with which of the following conclusions? Please select the case option that best fits with this scenario”.

Question 3 (Q3): “This “Unconditional Conditional” Power is compatible with which of the following conclusions? Please select the case option that best fits with this scenario”.

Question 4 (Q4): “What does the information, including the two extra pieces of information, given above suggest?” [about the interim combined event rate].

Question 5 (Q5): “What does the information, including the two extra pieces of information, given above suggest?” [about the interim combined event rate].

Question 6 (Q6): “What does the information, including the two extra pieces of information, given above suggest?” [about the interim combined event rate].

*Each proportion is also reported with its associated 95% Confidence Interval (Fisher's exact) in brackets.

Please see Appendix A for more details on full questions.

results from our survey for each of the six scenario-based questions asking respondents what they interpreted as the most compatible answer, in regards to the relative treatment effects between two treatment groups, based on the interim results or result extrapolations provided in the scenario.

Fig. 1 summarizes the results for Question 1 to Question 6. Question 1 is in regards to how trial experts interpreted the effect of Drug X relative to the placebo after seeing the interim combined event rate of 0.34. Just over half of the respondents, 52.6% (95% CI: 28.9%–74.0%), (10/19), correctly assumed “D. All of the above”, that any one of the three options (A. drug X doing better than placebo, B. worse than placebo or C. the same) could be true. These 3 possible options were also demonstrated to be so empirically from the responses to Questions 4, 5 and 6, as summarized in Fig. 1 (See Appendix A for details about the questions), as additional information in these questions was given about event rates in both the Drug X group and the placebo group. This is information typically not given as it is unmasking of event rates per group. It should be noted for Question 1 that 42.1% (95% CI: 20.3%–64.3%), (8/19), of respondents answered answer “E. None of the Above”. Though the more correct answer is “D. All of the Above”, in that any one of the three options (A. drug X doing better than placebo, B. worse than placebo or C. Drug X and the placebo group are performing the same) could be true of the relative interim results, one could have also interpreted that none of the options, A, B or C are correct as a sole answer by themselves. This hypothesis seems to be supported by the fact that most of the respondents correctly answered questions 4, 5 and 6.

For Question 4 (see Fig. 1 and Appendix A), the majority of respondents, 87.5% (95% CI: 61.7%–98.3%), (14/16), correctly assumed Option A that Drug X is performing better than placebo when given two additional pieces of information where the Drug X event rate given was 0.291 and the placebo event rate given was 0.389. This is a 25% relative risk reduction in 28-day mortality between Drug X and the placebo, hypothesized and specified in the trial protocol, as indicated in the scenario presented. For Question 5, the majority of respondents, 86.7% (95% CI: 59.5%–98.2%), (13/15), correctly assumed Option B that Drug X is performing worse than placebo when given two additional pieces of information where the Drug X event rate given was 0.389 and the placebo event rate given was 0.291. This is a 25% relative risk increase in 28-day mortality, contrary to what was hypothesized and specified in the trial protocol, as indicated in the scenario presented. And for Question 6, the majority of respondents, 75.0% (95% CI: 47.6%–92.2%), (12/16), correctly assumed Option C that Drug X and the placebo group are performing the same when given two additional pieces of information where the Drug X event rate given was 0.337, and the placebo event rate given was 0.343. This is a 2% relative risk reduction in 28-day mortality, different from what was hypothesized and specified in the trial protocol, as indicated in the scenario presented.

In regards to the two questions about the interim result extrapolations, Fig. 1 also summarizes the results about how trial experts interpreted the efficacy of Drug X relative to the placebo after seeing the adaptive conditional power (Question 2) and the “unconditional” conditional power (Question 3). For Question 2, the majority of respondents, 72.2% (95% CI: 46.5%–89.7%), (13/18), correctly assumed that an adaptive conditional power of 99% meant that Drug X is performing better than placebo (Option A) according to the assumptions used to calculate the adaptive conditional power (See Appendix A and Table 1 for definitions of interim measures). However, for the “Unconditional: Conditional Power (see Fig. 1 and Appendix A), the results indicate that there is more confusion about the meaning of this measure. A minority of respondents for Question 3 answered correctly “E. None of the above”, 40.0% (95% CI: 16.3%–64.9%), (6/15). The majority of respondents incorrectly answered, “A. Drug X is performing better than placebo” 53.3% (95% CI: 26.6%–77.0%), (8/15) and one respondent, 6.7% (95% CI: 2.0%–23.2%), (1/15), answered, “C. Drug X

and the placebo group are performing the same”.

4. Discussion

4.1. Key findings

Our results empirically show that sharing the interim combined event rate is a well-understood measure but is one that can be interpreted in one of three ways, when presented by itself, without additional knowledge about interim control event rate and the interim new intervention event rate; information which is not shared during a trial with non-DSMB members because it is unmasking of group effects. There are three assumptions that can be made about relative treatment effects (A. drug X doing better than placebo, B. worse than placebo or C. the same) when just given the interim combined event rate. These three possible assumptions were demonstrated to be empirically plausible from the responses to Questions 4, 5 and 6 when additional knowledge about interim control event rate and the interim new intervention event rate (Drug X) was provided. Knowledge of the interim combined event rate can lead non-DSMB members to guess about how a trial is progressing. Sharing this interim result with a non-DSMB member, such as a trial investigator, who could very well make one of three different assumptions or guesses about the interim relative treatment effect, may in turn influence a change in their behaviour towards the operation of the trial and hence introduce bias. Thus, we believe the interim combined event rate should not be shared with non-DSMB members by the DSMB because of the potential assumptions that could be made by non-DSMB members about relative treatment effects, which may lead to introducing trial bias.

As for the adaptive conditional power, it is clear that trialists understand this measure and that the higher the adaptive conditional power, based on the assumptions given in our scenario, the more likely Drug X was performing better than placebo. With this evidence, the adaptive conditional power is a dangerous measure to share because it is unmasking as it indirectly gives a non-DSMB member an idea how a treatment group is doing relative to another. This knowledge could influence a change in a non-DSMB member's behaviour regarding the operation or conduct of the trial thus introducing trial bias.

The majority of respondents were unclear about how to interpret the “unconditional” conditional power. It is believed that the majority of respondents being unclear on this measure have to do with it not being very familiar to many, as it does not appear to be used often. The reason option “E. None of the above” is correct for question 3 is because the “unconditional” conditional power is not giving you any information about the relative efficacy between treatment groups. Simply put, it tells you the power your trial will have to answer your primary research question if you were to complete the trial given the sample size, the hypothesized effect size determined at the trial's design stage and the combined event rate at interim; much like the power calculation done before the trial commences. It only gives the non-DSMB member some reassurance that your trial will have the desired amount of power needed to sufficiently answer your primary question once it has reached its planned sample size and is complete. We found one case of it being used [7] to reassure the sponsor that the trial underway will be properly powered to answer the primary question given that the predetermined sample size is reached. Most people also associate an interim power calculation with the adaptive conditional power and may think the “unconditional” conditional power is a variation of the adaptive conditional power and that it may convey the same information. We know this is not the case, however comments made for this question seem to suggest that trialists think it is similar to the adaptive conditional power. Knowledge of the “unconditional” conditional power can lead to non-DSMB members misinterpreting how a trial is progressing. This too may in turn influence a change in their behaviour towards the operation of the trial and hence introduce bias. Because of the confusion around how to interpret the “unconditional” conditional power, it may

not be a good measure to share as one could confuse the measure as suggestive of the relative treatment effect between treatment groups.

4.2. Findings compared to similar studies

There were no other studies found that empirically evaluated how commonly generated pieces of interim results or extrapolations are interpreted by trial experts. This study is unique in its ability to evaluate how three interim results or extrapolations used are interpreted by trial experts with a survey asking hypothetical scenario-based questions, using real trial interim information.

4.3. Key limitations

In regards to limitations of our study, the comments we received by respondents mentioned that it would have been helpful to provide confidence intervals for our estimate of the interim combined event rate and the additional information regarding the individual group event rates we provided for our scenarios in Questions 4, 5 and 6 (see [Appendix A](#)). It was noted that there was too much uncertainty to judge the difference of the true effect in the absence of confidence intervals. This is true; however, we do not believe this would have changed the respondents' answers because it is generally known at interim that the confidence intervals will be wide since the precision of the estimates will be low when only half the needed sample size is enrolled.

Though we had a good response rate for our survey, it is likely that we did not have a big enough sample size. However, this survey was designed to focus on a specific group of trial experts familiar with interim trial analyses. Due to the detailed nature of the questions and the feedback we received in the survey's testing stage, we knew that such questions would be best answered by trial experts who have familiarity and knowledge of the workings of interim analyses and the kind of interim results generated. A larger and more general survey given to those interested or are involved in trials, asking their views on the usefulness and the need to share certain types of interim results or results extrapolations, can be done to further understand if there are cases that may warrant sharing of such information or not.

4.4. Implications for practice

Trials are susceptible to bias and it is important to have a protocol with safeguards in place to prevent the introduction of biases that could alter trial results generated, away from the most true effect size, especially in phase III trials used to generate definitive results on efficacy and safety endpoints that provide evidence for practice and regulatory approval. As previously noted, there are some circumstances in the literature where interim results may be shared by the DSMB with non-DSMB members and knowledge gained from this survey may have implications on what is shared in those circumstances [8]. In cases where there may be a request from non-DSMB members to have interim results or extrapolations shared with them by the trial's DSMB, we do not recommend sharing the interim combined event rate, “unconditional” conditional power or the adaptive conditional power. The reasons why are as follows. The interim combined event rate is a well-understood measure and the majority of respondents correctly indicated that having it alone, without knowledge of the interim control event or the interim new intervention event rate, can be interpreted in one of three ways. This measure thus provides no useful information and only invites the mistaken opportunity for guesswork about how one group is doing compared to another. The “unconditional” conditional power is a measure that is mostly misinterpreted. Moreover, the adaptive conditional power seems to be well-understood and is unmasking of interim relative treatment effects, based on the empirical evidence we collected and evaluated. Knowledge of any of these three

kinds of interim results or extrapolations may influence a change in behaviour in those responsible for the operation or conduct of the trial or those who participate in the trial in some way and hence, may introduce trial bias. If information had to be shared with a particular non-DSMB member, safeguards should be in place that prevents other non-DSMB members directly responsible for the operation or conduct of the trial or those participating in the trial in some way, from knowing such interim results or extrapolations.

5. Conclusion

From this survey, we have some empirical evidence to suggest that the interim combined event rate, the adaptive conditional power and the “unconditional” conditional power should not be shared. The interim combined event rate and the adaptive conditional power are well-understood measures. However, the interim combined event rate can suggest any one of three plausible relative group effects at interim if shared at interim making it a useless measure to share that invites guesswork about relative effects. The adaptive conditional power is unmasking of relative treatment effects at interim. The “unconditional” conditional power on the other hand is misinterpreted most likely because the measure is unfamiliar. There is a danger with the DSMB sharing any of these three measures with non-DSMB members as it may lead non-DSMB members to consciously or subconsciously alter their behaviour towards a trial, possibly introducing trial bias.

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Competing interests

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.conctc.2017.05.005>.

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Appendix A: Scenario-based survey questions

Scenario-based question 1 (about Interim Combined Event Rate):

Hypothetical trial based on real trial data: A placebo-controlled RCT is evaluating the efficacy of a new drug (Drug X) in decreasing all-cause 28-day mortality in patients with chronic heart failure (multicenter and superiority trial, where the patients and the investigator are blinded to treatment allocation). Based on a thorough review of the literature, the trial protocol specified the following trial assumptions:

- An assumed control event rate of 35%.
- A hypothesized effect size was a 25% relative risk reduction in 28-day mortality.
- The study was designed to have a power of 90% and an alpha of 0.05 ($p = 0.05$), for a planned final enrollment of 1987 patients.

The trial protocol includes a provision for periodically providing the Principal Investigator with the Interim Combined Event Rate

After enrolling 722 participants, the Interim Combined Event Rate is 0.34

Definition of Interim Combined Event Rate:

The total number of events observed at some planned interim point into the trial divided by the total number of participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial or after enrolling a certain number of participants).

Example:

- Total # of Deaths in both the placebo group and new intervention group, six months from the start of the trial = 80
- Total # of Participants in both the placebo group and the new intervention group, six months from the start of the trial = 700
- Calculation: $80/700 = 0.114$ or 11.4%

Therefore the Interim Combined Event Rate at the trial's interim analysis, six months from the start of the trial, is 11.4%

Question: This Interim Combined Event Rate is compatible with which of the following conclusions below? Please select the case option that best fits with this scenario.

Response Choices

- Drug X is performing better than placebo
- Drug X performing worse than placebo
- Drug X and the placebo group are performing the same
- All of the Above
- None of the Above

Please feel free to provide comments below about this scenario or any other comments you have (optional):

Scenario-based question 2 (about Adaptive Conditional Power):

Hypothetical trial based on real trial data: A placebo-controlled RCT is evaluating the efficacy of a new drug (Drug X) in decreasing all-cause 28-day mortality in patients with chronic heart failure (multicenter and superiority trial, where the patients and the investigator are blinded to treatment allocation). Based on a thorough review of the literature, the trial protocol specified the following trial assumptions:

- An assumed control event rate of 35%.
- A hypothesized effect size was a 25% relative risk reduction in 28-day mortality.
- The study was designed to have a power of 90% and an alpha of 0.05 ($p = 0.05$), for a planned final enrollment of 1987 patients.

The trial protocol includes a provision for periodically providing the Principal Investigator with the Adaptive Conditional Power

After enrolling 722 participants, the Adaptive Conditional Power (assuming the observed effect (i.e. relative risk reduction) during the interim of the trial to be the true effect) is 99%

Definition of Adaptive Conditional Power:

The probability of rejecting the null hypothesis of no effect by the end of the trial (i.e. finding a statistically significant effect in favour of the intervention), at some predetermined interim point in the trial when the adaptive conditional power is scheduled to be calculated. The assumption made is that the observed interim effect (i.e. relative risk reduction) in the trial will remain the same till the end of the trial.

Example statement:

Given the interim data (data collected 2 years into the trial that is planned to last for 3 years), and assuming the observed interim effect (i.e. relative risk reduction) at the two year point to be the true effect for the remainder of the trial, the probability of rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 60%.

The following pieces of information are used to calculate Adaptive Conditional Power at trial interim:

- Control event rate and experimental event rate
- Information Fraction; a ratio of the planned sample size and the number of patients recruited in trial at the interim analysis
- Z score and B value at interim
- Drift parameter

Question: This Adaptive Conditional Power is compatible with which of the following conclusions? Please select the case option that best fits with this scenario.

Response Choices

- Drug X is performing better than placebo
- Drug X performing worse than placebo
- Drug X and the placebo group are performing the same

- D. All of the Above
- E. None of the Above

Please feel free to provide comments below about this scenario or any other comments you have (optional):

Scenario-based question 3 (about “Unconditional” Conditional Power):

Hypothetical trial based on real trial data: A placebo-controlled RCT is evaluating the efficacy of a new drug (Drug X) in decreasing all-cause 28-day mortality in patients with chronic heart failure (multicenter and superiority trial, where the patients and the investigator are blinded to treatment allocation). Based on a thorough review of the literature, the trial protocol specified the following trial assumptions:

- An assumed control event rate of 35%.
- A hypothesized effect size was a 25% relative risk reduction in 28-day mortality.
- The study was designed to have a power of 90% and an alpha of 0.05 ($p = 0.05$), for a planned final enrollment of 1987 patients.

The trial protocol includes a provision for periodically providing the Principal Investigator with the "Unconditional Conditional" power

After enrolling 722 participants, the “unconditional conditional” power is 99%.

Definition of “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 when indeed the alternative hypothesis is true, at some interim point in the trial.

The following pieces of information are used to calculate Unconditional Conditional Power at interim:

1. The hypothesized treatment effect at the design stage (i.e. relative risk reduction) of the trial, assuming the hypothesized treatment effect at the design stage to be true and correct for the remainder of the trial;
2. The sample size calculated at the design stage for the trial AND;
3. The combined event rate calculated at the trial’s interim, assuming this rate to be true for the remainder of the trial.

Example statement:

Given the interim combined event rate and assuming the treatment effect (i.e. relative risk reduction) hypothesized at the design stage of the trial to be true for the remainder of the trial, the probability of correctly rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 89%.

Question: This "Unconditional Conditional" Power is compatible with which of the following conclusions? Please select the case option that best fits with this scenario.

Response Choices

- A. Drug X is performing better than placebo
- B. Drug X performing worse than placebo
- C. Drug X and the placebo group are performing the same
- D. All of the Above
- E. None of the Above

Please feel free to provide comments below about this scenario or any other comments you have (optional):

Scenario-based question 4 (about Interim Combined Event Rate with Additional Information):

Hypothetical trial based on real trial data: A placebo-controlled RCT is evaluating the efficacy of a new drug (Drug X) in decreasing all-cause 28-day mortality in patients with chronic heart failure (multicenter and superiority trial, where the patients and the investigator are blinded to treatment allocation). Based on a thorough review of the literature, the trial protocol specified the following trial assumptions:

- An assumed control event rate of 35%.
- A hypothesized effect size was a 25% relative risk reduction in 28-day mortality.
- The study was designed to have a power of 90% and an alpha of 0.05 ($p = 0.05$), for a planned final enrollment of 1987 patients.

The trial protocol includes a provision for periodically providing the Principal Investigator with the Interim Combined Event Rate

After enrolling 722 participants, the Interim Combined Event Rate is 0.34

IMPORTANT: We are now giving you **TWO EXTRA PIECES OF INFORMATION** that would typically not be shared with the investigator.

The mortality rate in the placebo group at interim was 0.389 AND
The mortality rate in the Drug X group at interim was 0.291.

Definition of Interim Combined Event Rate:

The total number of events observed at some planned interim point into the trial divided by the total number of participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial or after enrolling a certain number of participants).

Example:

- Total # of Deaths in both the placebo group and new intervention group, six months from the start of the trial = 80
- Total # of Participants in both the placebo group and the new intervention group, six months from the start of the trial = 700
- Calculation: $80/700 = 0.114$ or 11.4%

Therefore the Interim Combined Event Rate at the trial's interim analysis, six months from the start of the trial, is 11.4%

Question: What does the information, including the two extra pieces of information, given above suggest?

Response Choices

- Drug X is performing better than placebo
- Drug X performing worse than placebo
- Drug X and the placebo group are performing the same
- All of the Above

E. None of the Above

Please feel free to provide comments below about this scenario or any other comments you have (optional):

Scenario-based question 5 (about Interim Combined Event Rate with Additional Information)

Hypothetical trial based on real trial data: A placebo-controlled RCT is evaluating the efficacy of a new drug (Drug X) in decreasing all-cause 28-day mortality in patients with chronic heart failure (multicenter and superiority trial, where the patients and the investigator are blinded to treatment allocation). Based on a thorough review of the literature, the trial protocol specified the following trial assumptions:

- An assumed control event rate of 35%.
- A hypothesized effect size was a 25% relative risk reduction in 28-day mortality.
- The study was designed to have a power of 90% and an alpha of 0.05 ($p = 0.05$), for a planned final enrollment of 1987 patients.

The trial protocol includes a provision for periodically providing the Principal Investigator with the Interim Combined Event Rate

After enrolling 722 participants, the Interim Combined Event Rate is 0.34

IMPORTANT: We are now giving you **TWO EXTRA PIECES OF INFORMATION** that would typically not be shared with the investigator.

The mortality rate in the placebo group at interim was 0.291 AND
The mortality rate in the Drug X group at interim was 0.389.

Definition of Interim Combined Event Rate:

The total number of events observed at some planned interim point into the trial divided by the total number of participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial or after enrolling a certain number of participants).

Example:

- Total # of Deaths in both the placebo group and new intervention group, six months from the start of the trial = 80
- Total # of Participants in both the placebo group and the new intervention group, six months from the start of the trial = 700
- Calculation: $80/700 = 0.114$ or 11.4%

Therefore the Interim Combined Event Rate at the trial's interim analysis, six months from the start of the trial, is 11.4%

Question: What does the information, including the two extra pieces of information, given above suggest?

Response Choices

- A. Drug X is performing better than placebo
- B. Drug X performing worse than placebo

- C. Drug X and the placebo group are performing the same
- D. All of the Above
- E. None of the Above

Please feel free to provide comments below about this scenario or any other comments you have (optional):

Scenario-based question 6 (about Interim Combined Event Rate with Additional Information)

Hypothetical trial based on real trial data: A placebo-controlled RCT is evaluating the efficacy of a new drug (Drug X) in decreasing all-cause 28-day mortality in patients with chronic heart failure (multicenter and superiority trial, where the patients and the investigator are blinded to treatment allocation). Based on a thorough review of the literature, the trial protocol specified the following trial assumptions:

- An assumed control event rate of 35%.
- A hypothesized effect size was a 25% relative risk reduction in 28-day mortality.
- The study was designed to have a power of 90% and an alpha of 0.05 ($p = 0.05$), for a planned final enrollment of 1987 patients.

The trial protocol includes a provision for periodically providing the Principal Investigator with the Interim Combined Event Rate

After enrolling 722 participants, the Interim Combined Event Rate is 0.34

IMPORTANT: We are now giving you **TWO EXTRA PIECES OF INFORMATION** that would typically not be shared with the investigator.

The mortality rate in the placebo group at interim was 0.343 AND
The mortality rate in the Drug X group at interim was 0.337.

Definition of Interim Combined Event Rate:

The total number of events observed at some planned interim point into the trial divided by the total number of participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial or after enrolling a certain number of participants).

Example:

- Total # of Deaths in both the placebo group and new intervention group, six months from the start of the trial = 80
- Total # of Participants in both the placebo group and the new intervention group, six months from the start of the trial = 700
- Calculation: $80/700 = 0.114$ or 11.4%

Therefore the Interim Combined Event Rate at the trial's interim analysis, six months from the start of the trial, is 11.4%

Question: What does the information, including the two extra pieces of information, given above suggest?

Response Choices

- A. Drug X is performing better than placebo
- B. Drug X performing worse than placebo

- C. Drug X and the placebo group are performing the same
- D. All of the Above
- E. None of the Above

Please feel free to provide comments below about this scenario or any other comments you have (optional):

CHAPTER 4

Survey of professional views on sharing interim results by the Data Safety Monitoring Board

(DSMB): what to share, with whom and why.

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Abstract

Background: Sharing interim results by the Data Safety Monitoring Board (DSMB) with non-DSMB members is an issue that can affect trial integrity. It is unclear what should be shared. This study assesses the views of professionals to understand what interim information should be shared at interim, with whom and why.

Methods: Conducted an online survey of members of the Society of Clinical Trials (SCT) and International Society of Clinical Biostatistics (ISCB) in 2015 asking their professional views on sharing interim results. Email was used to advertise the survey and a link in the email was provided to the online survey.

Results: Approximately 3136 (936 SCT members + 2200 ISCB members) members were invited. Response rate: 12% (371/3136). The majority reported the Interim Control Event Rate (IControlER) (149/237; 62.9% [95% CI: 56.7%-69.0%]), Adaptive Conditional Power (ACP) (144/224; 64.3% [95% CI: 58.0%-70.6%]) and the Unconditional Conditional Power (UCP) (126/208; 60.6% [95% CI: 53.9%-67.2%]) should not be shared with non-DSMB members. The majority reported that the Interim Combined Event Rate (ICombinedER) (168/262; 64.1% [95% CI: 58.0% to 69.9%]) should be shared with non-DSMB members particularly the steering committee (SC) because it does not unmask interim results and helps with monitoring trial progress, safety, and design assumptions.

Conclusion: The IControlER and ACP are unmasking of interim results and should not be shared. The UCP is a technical measure that is potentially misleading and also should not be shared. The ICombinedER is usually known by the SC and sponsor making it easy to determine group rates if the IControlER is known. Though most respondents thought the ICombinedER should be shared with the SC as it does not unmask relative effects between groups, we do not recommend sharing the ICombinedER as it is a flawed measure that it can have multiple interpretations possibly suggesting that one group is performing better, worse or the same as a comparator group, leading to guesses about how groups are doing relative to one another.

Keywords

Data Safety Monitoring Board (DSMB), Data Monitoring Committee (DMC), Interim Result Sharing, Survey

Introduction

Data Safety Monitoring Boards (DSMBs) are responsible for the stewardship of a trial [1, 2]. A trial can be negatively affected by the introduction of bias if the DSMB were to share interim trial results with non-DSMB members [1, 3, 4]. This is a serious concern for phase III trials that are usually used to provide definitive evidence on efficacy and safety outcomes [5, 6].

There is evidence in the literature to suggest that the issue with the DSMB sharing potentially unmasking interim results with non-DSMB members is prevalent [7]. Circumstances, where the DSMB may share potentially unmasking interim results, are when the DSMB makes a recommendation for early termination of a trial, the DSMB has concerns with the interim results given them for their scheduled interim review, the completion of the trial is endangered, the DSMB has a concern about the safety of trial participants, and there is a need to share interim results with a government regulator for early drug approval [7]. Other situations for sharing could be for adaptive confirmatory trials where interim results are needed to make planned study modifications, and when a trial has a long follow-up and some interim results may help a select patient group and their physician with a pivotal treatment choice. In these instances, unmasked interim results may be shared with non-DSMB members [7]. Four forms of interim results that could be shared that may be potentially unmasking are the Interim Combined Event Rate (ICombinedER), the Interim Control Event Rate (IControlER), the Adaptive Conditional Power (ACP), the Unconditional Conditional Power (UCP). Definitions [8] of these interim result measures have been provided in Table 1. The ICombinedER, ACP, and UCP provided at interim can be considered seemingly masked because they do not directly reveal the interim event rates for the trial's treatment groups. However, the ICombinedER could indirectly reveal interim event rates per group if the control group event rate is known from the trial's protocol or previous studies. Likewise, the ACP can reveal which group is doing relatively better. The IControlER, though revealing of the control group's rate at interim, does not deliver information on how groups are doing relative to one another unless the ICombinedER is also given.

It is unclear whether these kinds of interim results measures should be shared, with whom and why. The objective of our survey was to collect empirical evidence and determine the professional opinions of those interested or involved in clinical trials on the issue of what interim information should be shared with

non-DSMB members at interim and if so, with whom and under what circumstance. We will refer to principal investigators (PIs), the steering committee (SC), sponsors, investigators, the independent unmasked statistician, the funder(s), or patients enrolled in the trial or any other party responsible for the conduct or completion of the trial as non-DSMB members and will be more specific when necessary.

Methods

Design of survey

We designed our survey to have 14 questions, many of which have parts to them (See Additional File 1 for all survey questions). Questions 1 to 6 solicits responses enabling a better understanding of what type of interim results or other types of interim information should be shared at interim, with whom and why. These first 6 questions had advanced branching such that latter parts of a particular question would appear depending on how the respondent answered an earlier part of the question (See Additional File 1). The definitions of the interim results were provided on the survey pages. We prioritized these questions first because they were vital to understanding what should be shared or not.

Questions 7 to 14 were demographic questions asking respondents about the roles they had in relations to trials, the number of trials they were involved with, their main profession by training, professional roles they have taken on, the kind of environment(s) they usually work in, the number of trials they were involved with that had some form of private industry sponsorship and the number of trials they have been involved with that had a DSMB.

Constructing and Testing Online Survey: The online survey was constructed using fluidsurvey.com. We sent the first version of the online survey to 10 trial and health research experts at McMaster University, Hamilton, Ontario for pilot testing for content validity and clarity. They were asked for their feedback on the survey via email. We asked them specifically if they found the survey to be clear and the survey questions to be relevant to addressing our overall objective; to determine the professional opinions of those interested or involved in clinical trials on the issue of what interim information should be shared with non-DSMB members at interim. If something was not clear, we solicited their feedback to indicate where more clarity was needed and what they thought should be done to improve the survey. 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.

Sampling

Target group and sampling: The target group for this survey was trialists or those involved in trials. We contacted two societies, the Society of Clinical Trial (SCT) and the International Society of Clinical Biostatistics (ISCB), and asked them for help in distributing our survey to their members. SCT members come from many sectors including industry, government, non-profit and advocacy groups, comprising of professionals who are clinical investigators, biostatisticians, information technology specialists, project manager, clinical research associates and other professionals involved with the design, conduct and analysis of clinical trials [9]. ISCB members consist of clinicians, statisticians and members of other specialities including epidemiologists, clinical chemists and pharmacologists, who work or are interested in clinical biostatistics. Both of these societies agreed to distribute our survey [10]. To get the best response rate possible, multiple emails were sent out to remind potential respondents of the survey. SCT sent out an initial email in February 2015 based on their own member mailing list (approximately 936 members around February 2015), letting potential respondents know about the online survey, its purpose, and the coming survey's email invitation. The first survey email invitation was sent out February 2015 with a link to the online survey via Fluidsurveys.com and following the Dillman's principles [11] a reminder email was sent out 3 more times (March 2015, April 2015 and May 2015) to encourage a good response. ISCB sent out the first survey email invitation in August 2015 based on their member mailing list (approximately 2200 current and past members around July 2015) with a link to the online survey via FluidSurveys.com [12]. A second reminder email was sent out in September 2015. In total, invitations for our survey were sent out to approximately 3136 (936 SCT members + 2200 ISCB members) members from both societies in total.

Data Collection and Analysis

We used FluidSurveys.com to disseminate, and collect responses. The software used to analyse the results was integrated software within Fluidsurvey.com [12], WINPEPI Version 11.65 [13] and Microsoft Excel® 2010 [14]. Responses were collected anonymously. We report results in aggregate by count and percentages, indicating how many respondents chose a particular option and by mean where applicable with 95% Confidence Intervals (95% CIs). We summarized all written responses to questions qualitatively and quantitatively where applicable. For the questions related to whether the ICombinedER, IControlER,

ACP or UCP should be shared, reasons for why an interim result measure should or should not be shared were assessed for emergent themes in relation to trial research. The description and the text given by respondents were first collated and then each response was read carefully. With iterative reading of the responses, similar reasons were grouped together. When no more groups of similar reasons existed, the groups that were there were then assessed for emerging overarching themes that were drawn from the reasons/responses within each group. This study was approved by the Hamilton Integrated Research Ethics Board (HiREB) approval [15].

Results

We received 371 responses (202 complete responses, 169 partial or totally incomplete responses). Totally incomplete responses are participants who submitted a survey but did not answer any questions. Figure 1 summarizes the response rate (Figure 1: Flow diagram of the number of responses from SCT and ISCB after each reminder). Best efforts were made to solicit as many responses as possible through multiple emails. Four reminder emails were sent in total (3 to SCT and 1 to ISCB), as was allowed.

Respondent Demographics

Table 2 summarizes the main respondent demographics (Table 2: Demographics of Respondents). The largest proportion of responses (42.0%) was from statisticians (156 out of 203 people responded to this question) and at least 53.6% of respondents were involved in at least one trial (203 responded to this question). About fifty percent (50.4%) of respondents were involved in at least one trial with DSMB monitoring (197 responded to this question) and the largest proportion of respondents (33.2%) usually work at a University or Academic Institution (202 responded to this question). Percentages are based on the total number of respondents to the survey (n = 371).

Main Results for Questions 1 to 4

Table 3 summarizes the main results regarding sharing the ICombinedER, IControlER, ACP and UCP respectively.

Interim Combined Event Rate (ICombinedER)

The majority of respondents (168/262; 64.1% [95% CI: 58.0% to 69.9%]) reported that the ICombinedER should be shared. The majority of those who said that it should be shared reported it should be shared with the SC (142/262; 54.2% [95% CI: 48.2% to 60.2%]). For those that said that the

ICombinedER should be shared, we then asked how useful it was to share the ICombinedER and those that responded gave it a mean score of 6.97 [95% CI: 6.62 to 7.31] and a median score of 7 [IQR: 6-8], on a scale from 0 to 10 where 0 is Not Useful at All and 10 is Very Useful. Also, for those who said that the ICombinedER should be shared (Yes), we asked those respondents to briefly explain why they thought the ICombinedERs should be shared by the DSMB at interim (n=131/168). One theme emerged from their responses as to why the ICombinedERs should be shared; it is unlikely to threaten the integrity of the trial. A summary of details said by respondents related to this theme are as follows. Firstly, sharing the ICombinedER is unlikely to threaten the integrity of the trial as it does not tell you anything about the effect size between groups and allows investigators, sponsors, and the SC to be informed about trial progress, check design assumptions and make appropriate corrective adaptations to protect the trial's integrity and participant/patient safety. And secondly, most sponsors and SCs would be able to calculate the ICombinedER because they would already have access to the pooled database.

An additional point made as a word of caution was that either the ICombinedER or the IControlER should be shared, not both as it would be unmasking of how the intervention group is doing. If the control event rate is predictable from the literature, then the ICombinedER should not be shared. The default is to not share unless pre-specified with whom and when. Being given the ICombinedER also does not stop guesses about effect sizes to be made by non-DSMB members.

Interim Control Event Rate (IControlER)

The majority of respondents (149/237; 62.9% [95% CI: 56.7% to 69.0%]) reported that the IControlER should not be shared with anyone. These respondents were then asked briefly to explain why the IControlER should not be shared with anyone at interim (n = 120/149). One theme emerged from their responses as to why the IControlER should not be shared; the IControlER is unnecessary to share, misleading and potentially unmasking of interim effects between groups. A summary of details said by respondents related to this theme is as follows. Firstly, the IControlER may be unmasking of interim results as the SC or the sponsor usually has access to pooled data and being given this would allow them to back calculate the interim rate in the intervention group, thus jeopardizing the integrity of the trial. Secondly, the IControlER is an unreliable estimate at interim and there is no reason or need to share the IControlER since the DSMB can make necessary recommendations to the SC if needed to protect the

integrity of the trial and non-DSMB members need to trust the DSMB on that task. And lastly, the SC or the sponsor needing to know the IControlER would have to outweigh the potential threat to trial integrity and validity because of the potential to introduce trial bias.

Adaptive Conditional Power (ACP)

The majority of respondents (144/224; 64.3% [95% CI: 58.0% to 70.6%]) reported that the ACP should not be shared with anyone. These respondents were then asked to briefly explain why the ACP should not be shared with anyone or any party at a trial's interim (n = 117/144). Two themes emerged from their responses as to why the ACP should not be shared; 1) The ACP is potentially unmasking of interim results and 2) The ACP is a highly technical measure to interpret. A summary of details said by respondents related to these themes are as follows. Firstly, the ACP is very informative of the presence or absence of relative treatment effects and hence it is partially unmasking to those responsible for the trial's conduct and it is unlikely that the ACP will remain confidential if shared. Secondly, the ACP gives non-DSMB members an opportunity to do a back calculation for the treatment effect potentially biasing the trial should the behavior of the trial stakeholders and those responsible for trial conduct be modified from knowing such information. And lastly, funders are typically not qualified to assess the relevance of such information.

Unconditional Conditional Power (UCP)

The majority of respondents (126/208; 60.6% [95% CI: 53.9% to 67.2%]) reported that the UCP should not be shared with anyone. These respondents were then asked to briefly explain why the UCP should not be shared with anyone at a trial's interim (n= 96/126). One theme emerged from their responses as to why the UCP should not be shared; the UCP is a technical measure that is potentially misleading. A summary of details said by respondents related to this theme is as follows. There is confusion around what this measure exactly indicates so much so that it could be interpreted incorrectly as an adaptive conditional power and hence releasing this information will result in speculation, most often incorrect, about the components that are used to generate the UCP which could influence behavior at all levels of study conduct. Secondly, the UCP is not useful information and has questionable utility.

Sharing other kinds of information

About half of the respondents to the question about sharing other kinds of information at interim by the DSMB with non-DSMB members reported that no other information should be shared (109/210; 51.9% [95% CI: 45.0% to 58.8%]) while 101 out of 210 (48.1% [95% CI: 41.2% to 55.0%]) respondents said yes, that other information should be shared. Table 4 summarizes all the responses. The top 3 responses for those that said yes to share other information at interim by the DSMB with non-DSMB were information about trial conduct (67; 31.9% [95% CI: 25.7% to 38.6%]), a safety issue or concern (50; 23.8% [95% CI: 18.3% to 30.1%]), and DSMB interim trial recommendations (21; 10.0% [95% CI: 6.3% to 14.9%]). The mean usefulness to share these 3 types of interim information were 9.16 (95% CI: 8.89 to 9.42), 9.35 (95% CI: 9.02 to 9.69) and 9.52 (95% CI: 9.08 to 9.96) respectively. Additionally, the medians for the usefulness to share these 3 types of interim information were 10 [IQR: 8-10], 10 [IQR: 9-10], and 10 [10-10] respectively. With whom to share varied. For information about trial conduct, it was indicated that this should be shared with the sponsor, SC, investigators or any relevant party. For information about safety issue or concern, it was reported that this should be shared with the sponsor, SC, investigators or the ethics committee. For DSMB interim trial recommendation, it was indicated that this should be shared with the sponsor or the SC.

Sharing of interim information as indicated in encountered DSMB charters by respondents

About half (104/207; 50.2% [95% CI: 43.3% to 57.2%]) of the respondents to this question about sharing interim information as indicated by the DSMB charters they encountered reported yes, that they were involved in a trial where sharing such information was explicitly stated in the DSMB charter. Table 5 summarizes all the responses. For those that said yes to the first part of this question, they were then asked which of the following pieces of interim information (ICombinedER, IControlER, ACP and UCP) should be shared during the interim of a trial, with whom and under what circumstance the sharing would happen according to the DSMB charter's they encountered as well as any other additional information. The greatest proportion of respondents (55/207, 26.6% [95% CI: 20.7% to 33.1%]) reported that the ICombinedER would be shared with various parties if the overall rate was much lower than hypothesized, if there was a need to adjust the sample size or re-assess the trial's power, if benchmarks were not met, if there was a safety or ethical issue, or if there was a recommendation from the DSMB to stop the trial

because of futility or efficacy. Various respondents reported that the ICombinedER would be shared with the sponsor, investigator, funder, SC, regulator or another relevant party when deemed appropriate.

Discussion

Key findings

Our results empirically show that the ICombinedER is the only interim result measure where the majority of respondents think the DSMB for an RCT should share with non-DSMB members. The majority of respondents indicate that it could be shared specifically with the SC. However, they did not give the ICombinedER a very high score on usefulness, only a moderate score of 6.97. Their reasoning generally for sharing this measure is that it does not tell you anything about relative effects between compared groups in a trial so it does not do any harm in terms of unmasking interim results and keeps investigators informed about the trial's progress. They do indicate though that guesses can be made and that the ICombinedER should not be shared if the IControlER is known as having both can be unmasking of relative effects. The reason we think this measure was rated in the moderate range (6.97) in terms of usefulness is that a lot of needed changes or decisions about the trial based on the ICombinedER can be suggested by the DSMB from their own interim review without the need to necessarily share the ICombinedER. The minority of respondents who said you do not need to share the ICombinedER indicated that the DSMB can recommend the needed changes or adaptations to the trial to the SC or sponsor without having to release the ICombinedER to them. The usefulness in sharing this measure is questionable if the DSMB is entrusted to guide the SC to make needed changes and decisions based on the DSMB's review of the interim data. Even though the majority of respondents indicated that the ICombinedER should be shared, we do not recommend sharing it. Part of the reason for not sharing was indicated by respondents in that guesses can be made about comparative effects between treatment groups at interim. There is evidence to suggest in the literature [8] that the ICombinedER is a flawed measure to share and rely on as it can be compatible with any of three types of interim results: 1) one group (e.g Drug X) is performing better than another (e.g. placebo), 2) one group is doing worse than another, or 3) both groups are performing the same. For instance, in this scenario question based survey [8], respondents correctly pointed out that having been given the ICombinedER of 0.34 or 34% for mortality in a hypothetical interim trial scenario could mean a 25% relative risk reduction, 25% relative risk

increase or about a 2% relative risk reduction (where both groups are performing about the same). This flaw in sharing this measure is also dangerous as non-DSMB members could make speculations about comparative effects between treatment groups at interim that could consciously or subconsciously alter their behaviour towards the trial, introducing bias.

Our results also empirically show that IControlER, the ACP, and UCP are measures where the majority of respondents think the DSMB for an RCT should not share with any non-DSMB member. Their reasoning generally for not sharing the IControlER and the ACP is that it can be unmasking of interim results, hence jeopardizing the integrity of the trial and potentially introducing bias. The IControlER can be directly unmasking because in many cases, the SC or the sponsor has access to pooled data, and being given the IControlER would allow them to back calculate the event rate for the intervention group. The ACP is very informative of the presence or absence of a relative treatment effect and hence it is partially unmasking to those responsible for the trial's conduct. It was indicated that everyone involved in the trial should remain unaware of such interim results so that they can carry on enrolling, treating and following up with patients without being influenced by speculations and knowledge that could cause the introduction of trial bias. As for the UCP, comments against sharing correctly pointed out there is the potential for misunderstanding this result measure as it is simply computed under the original alternative hypothesis, not the current interim group event rates. Releasing this information could result in speculation of relative effects between groups, most often incorrect, possibly influencing behavior at all levels of study conduct. We think that the majority of respondents are correct when they say that these latter three measures should not be shared with any non-DSMB members because of the potential to introduce bias in the trial from having such information. We believe the ACP to be informative of relative group effects and the UPC to be a confusing measure that is misunderstood and possibly misinterpreted as an ACP as suggested by evidence [8]. If these types of interim results are to be shared by the DSMB, they should be shared with the SC at times when trial futility is in question or there is a major safety concern and such situations should be prespecified in the protocol or DSMB charter. Otherwise, it seems best to let the DSMB be stewards of the trial. Respondents to our survey realize there is a lot of risk to the integrity of the trial when sharing the latter three measures with non-DSMB members.

Beyond these four interim results, respondents indicated sharing other types of information that is typical of what is usually shared in practice. This included information on trial conduct, a safety issue or concern, DSMB interim recommendations, overall patient baseline characteristics and important information from outside the trial; all of which is very useful information that helps those responsible for the study to protect trial integrity and safety. This type of information also scored high by respondents on its usefulness for sharing at interim by the DSMB because such information provides the SC and the sponsor information needed to ensure good trial conduct without needing to unmask any group comparative results on the outcomes of interest. Sharing this type of information, when and for what reason should be determined and agreed upon by the SC and the DSMB *a priori* and stated within the trial protocol and DSMB charter.

We also found out that about half of the respondents were involved in a trial where sharing interim results was explicitly stated in the DSMB charter and with whom that information should be shared during the trial's interim. It is reassuring that there has been consideration given by trialists, before the commencement of a trial, about the possible need to share certain types of interim results with non-DSMB members and that such a need to share is explicitly stated *a priori*. However, this is not enough. We recommend that all trials should consider situations when there may be a need for the DSMB to share certain types of interim information and with whom. It needs to be explicit in DSMB charters how those situations that may entail sharing interim results will be handled to minimize trial bias.

Findings compared to similar studies

This study is unique in that it empirically evaluates and focuses on whether four main forms of interim results should be shared, with whom, the usefulness of sharing that result measure, and why it should be shared, by soliciting the views of those involved in trials. A scenario-based survey published in 2017 asked trial experts how they interpreted the ICombinedER, ACP and UCP when shared in a hypothetical trial scenario. They concluded from their results that knowledge of these three interim measures should not be shared by DSMB with non-DSMB members at interim as they may mislead or unmask interim results, potentially introducing trial bias [8]. This previous survey corroborates our findings in that the majority of trial experts who responded to our survey also think the ACP and UPC should not be shared with non-DSMB members. However, the majority of respondents from our survey thought that the

ICombinedER should be shared because it is not directly unmasking of the event rate per group and keeps investigators informed about the trial's progress. They also indicated in this survey that guesses can be made about the effects between treatment group with this information thus caution and protocol pre-specification should be exercised when sharing this kind of information.

Six other surveys found dating from 1999 to 2011 did not specifically focus on the issue of the DSMB sharing interim results, and were very limited in regards to the amount of detail they collected regarding what should be shared by the DSMB, with whom and why. These surveys globally looked at data monitoring practices and so each one does not provide a complete picture of the issue of the DSMB sharing interim results with non-DSMB members even when assessed as a group of articles. In general, we did find that 3 of the 6 surveys found [16-18] (1 qualitatively and 2 quantitatively reported) support the view that interim results should not be shared by the DSMB with at least one type of non-DSMB member. Two (2) surveys [17, 19] (1 qualitatively and 1 quantitatively reported) showed support for the view that interim results should be shared by the DSMB with at least one type of non-DSMB member. One survey [17] (quantitatively reported) supports that interim results should be not be shared except in particular circumstances.

Key Limitations

In regards to limitations of our study, we had a very low response rate despite best efforts to solicit responses. We do not have any way of knowing how our non-respondents were different from our respondents. We do know from our demographic information that the largest proportion of our respondents were statisticians and about half were involved in at least one trial which reassured us that many of our respondents were most likely familiar with calculated interim results measures in a trial. Another limitation of our survey is that there was a lot of missing data. Though we received 371 responses, 202 were complete responses, meaning they filled all the questions to our survey and 169 were partial or incomplete responses meaning that questions were skipped and left blank. In many cases, especially with our demographic information, we had 40% or more missing information from respondents. Information regarding how respondents viewed sharing the four interim results measures has less missing data, most likely because these were questions situated at the beginning of the survey. A potential reason for the amount of missing data may partially be that some people who are involved in

trials may not be a part of generating or reviewing interim results, or regularly interacting with DSMBs or SCs and were thus less likely to be familiar with interim result measures. Nevertheless, it was important to include those interested or involved in trials as part of the sampling frame to capture the community's understanding of what interim result measures should or should not be shared. On the contrary, it is possible that those that have experience being on or interacting with DSMBs are be more acquainted with interim result measures and were thus more likely to answer the survey questions asked at the beginning that were related to these measures.

Another limitation is the possibility that an individual who is a member of both SCT and ISCB may have filled out the survey twice. We made a respondent's anonymity and privacy a top priority and did not collect identifiable information that would allow us to crosscheck who filled out the survey from both societies. We also had to have a generic link to the survey because the survey was sent on our behalf by both SCT and ISCB. Thus, we could not provide a special and identifiable link to each unique respondent. However, if an individual was a member of both societies, it is possible that they remembered filling out the survey and would not elect to fill it out again as the same survey was used. The survey title page would have been recognizable before clicking the next button to officially start the survey. Additionally, it is important to note that most of our respondents as indicated in Table 2 were statisticians and methodologists. In the future, it may be important to ensure a more balanced group of respondents to any survey related to this topic and make an additional effort to target non-statisticians/methodologists about these interim result measures. Their representation and interpretation on sharing these measures are equally important to understanding what interim result measures should be shared by the DSMB.

Implications for Practice

Trials are susceptible to bias and it is important to have a protocol with safeguards in place to prevent the introduction of biases that could alter trial results away from the true effect size, especially in phase III trials used to generate definitive results on efficacy and safety endpoints and provide evidence for practice and regulatory approval. In cases where there may be a request from non-DSMB members to have interim results shared with them by the trial's DSMB, we do not recommend sharing the ICombinedER, IControlER, ACP or the UCP. Though there may be solid *a priori* plans in place in the trial protocol or DSMB charter to share the ICombinedER, as this measure is not directly unmasking of interim

results on its own as the majority of respondents indicate, we think it lends non-DSMB members to make speculations about group rates, especially if there is a good inkling of the control rate in the literature. As mentioned before, the ICombinedER can also be interpreted to mean any one of three relative effects between groups making it a flawed measure to share and also lends non-DSMB members to mistakenly speculate on group rates. The results of this survey suggest that respondents from the trial community are not aware of this flaw with sharing the ICombinedER and may need to be educated on this issue. We should keep in mind that the DSMB needs to be trusted stewards of the trial and should be using discretion if there comes a time where sharing any of these four measures is needed. If such information had to be shared with a particular non-DSMB member, safeguards should be in place that prevents other non-DSMB members directly responsible for the operation or conduct of the trial, or those participating in the trial in some way, from knowing such interim result measures.

Conclusion

From this survey, we have some empirical evidence that indicates that the IControlER, the ACP, and the UCP should not be shared. Even though the majority of respondents indicated that ICombinedER could be shared, we do not recommend doing so. The ICombinedER can be unmasking of group rates if the IControlER is well known, either through literature or some other source and also allows for mistaken speculation of groups rates as this measure can be interpreted in any of three ways; one group is performing better, worse or the same as the comparator group. The IControlER can be unmasking of group rates and the ACP is unmasking of relative treatment effects at interim. The UCP, on the other hand, is a confusing measure most likely because the measure is unfamiliar. With sharing any of these measures, there is a danger of introducing trial bias by non-DSMB members as it could alter their behaviour towards the trial, consciously or subconsciously.

List of abbreviations

(ACP) Adaptive Conditional Power, (DSMB) Data Safety Monitoring Board, (HiREB) Hamilton Integrated Research Ethics Board, (ICombinedER) Interim Combined Event Rate, (IControlER) Interim Control Event Rate, (ISCB) International Society of Clinical Biostatistics, (PI) Principle Investigator, (RCT) Randomized Controlled Trial, (SC) Steering Committee, (SCT) Society of Clinical Trials, (UCP) Unconditional Conditional Power

Declarations

Ethical Approval and Consent to Participate

Ethics approval for this study was granted by the Hamilton Integrated Research Ethics Board (HiREB), Study #: 14-054. Survey participants were informed before filling out the survey that this survey is anonymous and that their responses will never be linked to their identity. Moreover, they were also informed before filling out the survey that responses will not be shared with anyone outside of our study group, and only aggregated data will be published. By starting the survey they were informed that they are consenting to participate in this survey.

Consent to publish

Not applicable

Availability of supporting data

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

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Author's contributions

VBD was involved in all aspect of this study from study design and conception, acquisition of information, survey design and construction, information synthesis and analysis and wrote the manuscript. LM, JP and NB were substantially involved in supervision of study design and critical revisions to this paper. LT was substantially involved in primary supervision, study design and conception and critical revisions to this paper. All authors read and approved the final manuscript.

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Not applicable

Authors' information

Not applicable

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Additional files

Additional File 1: Survey Questions

File Format: pdf

Table 1: Definitions of 4 main forms of interim results measures

File Format: pdf

Table 2: Demographics of Respondents (n = 317)

File format: pdf

Table 3: Summary of Results for Sharing Certain Interim Results

File format: pdf

Table 4: Other information that should be shared

File format: pdf

Table 5: Sharing of interim information indicated in encountered DSMB charters

File format: pdf

Figure 1: Flow diagram of the number of responses from SCT and ISCB after each reminder

File format: pdf

Table and Figure Title and Legend

Table 1 Title:

Table 1: Definitions of 4 main forms of interim results measures

Table 1 Legend:

DSMB (Data Safety Monitoring Board), IControlER (Interim Control Event Rate), ICombinedER (Interim Combined Event Rate), ACP (Adaptive Conditional Power), UCP (Unconditional Conditional Power)

Table 2 Title:

Table 2: Demographics of Respondents (n = 317)

Table 2 Legend:

^a Based on Survey Question 8. Total of 203 responses to this question, ^A Unknown because 168 respondents did not answer this question, ^b Based on Survey Question 14. Total of 197 responses to this question, ^B Unknown because 174 respondents did not answer this question, ^c Based on Survey Question 13. Total of 201 responses to this question, ^C Unknown because 170 respondents did not answer this question, ^d Based on Survey Question 9. Total of 203 responses to this question, ^D Unknown because 168 respondents did not answer this question, ^e Based on Survey Question 11. Total of 202 responses to this question, ^E Unknown because 169 respondents did not answer this question, ^f Based on Survey Question 14. Total of 197 responses to this question. Respondents to this question were asked to select all roles (or categories) that applied to them, thus a respondent can be in more than one category. ^F Unknown because 268 respondents did not answer this question, ^g Based on Survey Question 7. Total of 200 responses to this question. Respondents to this question were asked to select all roles (or categories)

that applied to them, thus a respondent can be in more than one category. ^G Unknown because 171 respondents did not answer this question, ^h Based on Survey Question 10. Total of 160 responses to this question. Respondents to this question were asked to select all roles (or categories) that applied to them, thus a respondent can be in more than one category. ^H Unknown because 211 respondents did not answer this question, ^q Percentages based on the 371 total respondents to this survey.

* Respondents could have selected more than one option thus it is possible that the percentages add up to more than 100%.

Table 3 Title:

Table 3: Summary of Results for Sharing Certain Interim Results

Table 3 Legend:

IQR (Interquartile Range)

* Respondents could have selected more than one option thus it is possible that the percentages add up to more than 100%.

Table 4 Title:

Table 3: Other information that should be shared

Table 4 Legend:

^A Respondents could have indicated more than one of other type of item thus it is possible that the percentages add up to more than 100%.

*On a scale between 0 to 10 (Where 0 is “Not Useful at All” and 10 is “Very Useful”)

IQR (Interquartile Range)

Table 5 Title:

Table 4: Sharing of interim information indicated in encountered DSMB charters

Table 5 Legend:

Acronyms: Data Safety Monitoring Board (DSMB)

^B Respondents could have indicated more than one item thus it is possible that the percentages add up to more than 100%.

Figure 1 Title:

Flow diagram of the number of responses from SCT and ISCB after each reminder

Figure 1: Flow diagram of the number of responses from SCT and ISCB after each reminder

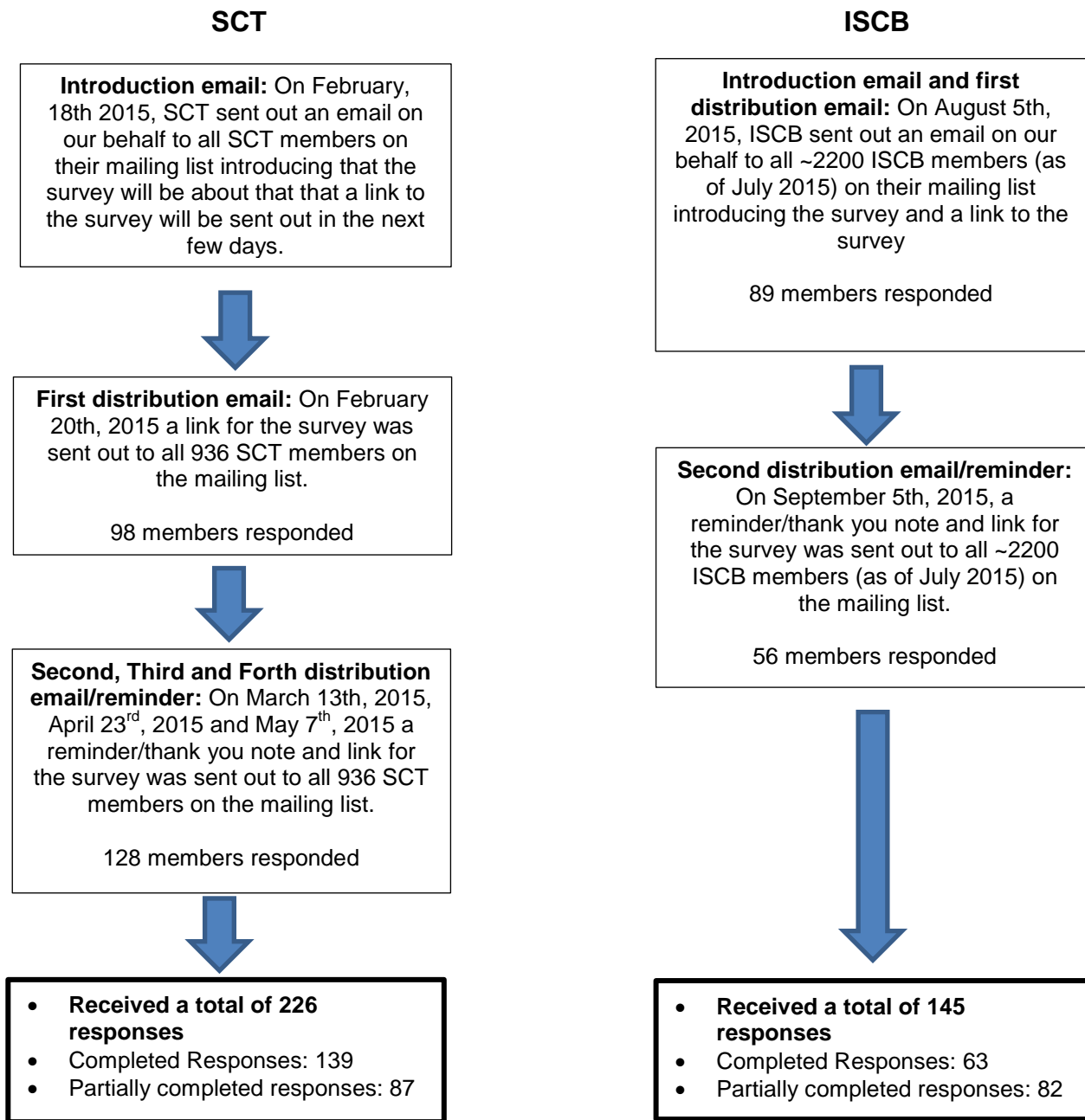


Table 1: Definitions of 4 main forms of interim result measures	
Interim Control Event Rate (IControlER)	<p>The number of events observed among control participants at some planned interim point into the trial divided by number of control participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial)</p> <p>Example:</p> <ul style="list-style-type: none"> • Total # of Deaths in the placebo group, six months from the start of the trial = 15 • Total # of Participants in the placebo group, six months from the start of the trial = 250 • Calculation: $15/250 = 0.06$ or 6% <p>Therefore the Interim Control Event Rate at the trial's interim analysis, six months from the start of the trial, is 6%</p>
Interim Combined Event Rate (ICombinedER)	<p><i>"The total number of events observed at some planned interim point into the trial divided by the total number of participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial or after enrolling a certain number of participants).</i></p> <p>Example:</p> <ul style="list-style-type: none"> • Total # of Deaths in both the placebo group and new intervention group, six months from the start of the trial = 80 • Total # of Participants in both the placebo group and the new intervention group, six months from the start of the trial = 700 • Calculation: $80/700 = 0.114$ or 11.4% <p>Therefore the Interim Combined Event Rate at the trial's interim analysis, six months from the start of the trial, is 11.4%" [33]</p>
Adaptive Conditional Power (ACP)	<p><i>"The probability of rejecting the null hypothesis of no effect by the end of the trial (i.e. finding a statistically significant effect in favour of the intervention), at some predetermined interim point in the trial when the adaptive conditional power is scheduled to be calculated. The assumption made is that the observed interim effect (i.e. relative risk reduction) in the trial will remain the same until the end of the trial.</i></p> <p>Example statement:</p> <p><i>Given the interim data (data collected 2 years into the trial that is planned to last for 3 years), and assuming the observed interim effect (i.e. relative risk reduction) at the two year point to be the true effect for the remainder of the trial, the probability of rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 60%.</i></p> <p><i>The following pieces of information are used to calculate Adaptive Conditional Power at trial interim:</i></p> <ul style="list-style-type: none"> • Control event rate and experimental event rate • Information Fraction; a ratio of the planned sample size and the number of patients recruited in the trial at the interim analysis • Z score and B value at interim • Drift parameter" [33]
Unconditional Conditional Power (UCP)	<p><i>"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 when indeed the alternative hypothesis is true, at some interim point in the trial.</i></p> <p><i>The following pieces of information are used to calculate Unconditional Conditional Power at interim:</i></p> <ol style="list-style-type: none"> 1. The <u>hypothesized treatment effect at the design stage</u> (i.e. relative risk reduction) of the trial, assuming the hypothesized treatment effect at the design stage to be true and correct for the remainder of the trial; 2. The <u>sample size calculated at the design stage</u> for the trial AND; 3. The <u>combined event rate calculated at the trial's interim</u>, assuming this rate to be true for the remainder of the trial.

	<p>Example statement: <i>Given the interim combined event rate and assuming the treatment effect (i.e. relative risk reduction) hypothesized at the design stage of the trial to be true for the remainder of the trial, the probability of correctly rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 89%.” [33]</i></p>
<p>DSMB (Data Safety Monitoring Board), IControlER (Interim Control Event Rate), ICombinedER (Interim Combined Event Rate), ACP (Adaptive Conditional Power), UCP (Unconditional Conditional Power)</p>	

Table 2: Demographics of Respondents (n = 371)			
Number of Trials Respondent Has Been Involved ^a		Number of trials the respondent has been involved with that had a DSMB monitoring the trial ^b	
Number of Trials	n (%)^q	Number of Trials	n (%)^q
None	4 (1.1)	None	10 (2.7)
1 to 5 trials	20 (5.4)	1 to 5 trials	34 (9.2)
6 to 10 trials	25 (6.7)	6 to 10 trials	37 (10.0)
11 to 15 trials	23 (6.2)	11 to 15 trials	28 (7.5)
More than 15 trials	131 (35.3)	More than 15 trials	88 (23.7)
Unknown ^A	168 (45.3)	Unknown ^B	174 (46.9)
Number of trials the respondent has been involved with that had some form of private industry sponsorship ^c		Primary Profession by Training ^d	
Number of Trials	n (%)^q	Main Profession	n (%)^q
None	29 (7.8)	Mathematician/Statistician/Biostatistician	156 (42.0)
1 to 5 trials	69 (18.6)	Methodological Scientist/Research Methodologist	21 (5.7)
6 to 10 trials	25 (6.7)	Physician	10 (2.7)
11 to 15 trials	14 (3.8)	Epidemiologist	5 (1.3)
More than 15 trials	64 (17.3)	Research or Clinical Trial Coordinator	3 (0.8)
Unknown ^C	170 (45.8)	Ethics Specialist	2 (0.5)
		Trialist	2 (0.5)
		Analyst	1 (0.3)
		Computer Programmer	1 (0.3)
		Trial Manager	1 (0.3)
		Trial Monitor	1 (0.3)
		Unknown ^D	168 (45.3)
Usual Work Setting of Respondents ^e		Other Work Settings of Respondents ^{f, *}	
Place of Work	n (%)^q	Other Places of Work	n (%)^q
University or Academic Institution	123 (33.2)	Hospital	36 (9.7)
Private or Contracted Research Company	28 (7.5)	University or Academic Institution	35 (9.4)
Pharmaceutical Company	17 (4.6)	Pharmaceutical Company	18 (4.9)
Government Research Group	13 (3.5)	Private or Contracted Research Company	15 (4.0)
Hospital	10 (2.7)	Government Research Group	15 (4.0)
Government Regulatory Body	5 (1.3)	Medical or Health Clinic	12 (3.2)
Academic University Hospital	3 (0.8)	Government Regulatory Body	11 (3.0)
Medical Device Company	1 (0.3)	Medical Device Company	7 (1.9)
Private Practice	1 (0.3)	Private Practice	4 (1.1)
Retired	1 (0.3)	Consulting Entity	1 (0.3)
Unknown ^E	169 (46.0)	Data Safety Monitoring Board	1 (0.3)
		Health Maintenance Organization (Research Department)	1 (0.3)
		Unknown ^F	268 (72.2)
Roles respondents have taken on in relation to trial operation ^{g, *}		Professional roles a respondents have taken on ^{h, *}	
Roles in relation to the trial	n (%)^q	Professional Roles	n (%)^q
Trial statistician	161 (43.4)	Methodological Scientist/Research Methodologist	89 (24.0)
Data Safety Monitoring Board Member	136 (36.7)	Epidemiologist	63 (17.0)
Trialist or Investigator (i.e. Co-Investigator in a trial)	88 (23.7)	Mathematician/Statistician	48 (12.9)
Data Analyst	68 (18.3)	Data Manager	36 (9.7)
Principal Investigator (PI) of a clinical trial	30 (8.1)	Computer Programmer	35 (9.4)
Sponsor Representative	26 (7.0)	Research or Clinical Trial Coordinator	12 (3.2)
Funder Representative	18 (4.9)	Computer Scientist	10 (2.7)
Data Manager	11 (3.0)	Ethics specialist	10 (2.7)
Steering Committee	11 (3.0)	Physician	9 (2.4)
Independent Unblinded Reporting Statistician to the DSMB	9 (2.4)	Information Technologist	6 (1.6)
Trial Coordinator	7 (1.9)	Lawyer	2 (0.5)
Data Coordinator/Manager	4 (1.1)	Medical Laboratory Technician	1 (0.3)
Government Regulator	3 (0.8)	Medical Laboratory Scientist	1 (0.3)
Consultant	3 (0.8)	Nurse or Nurse Practitioner	1 (0.3)
Unknown ^G	171 (46.1)	Biochemist	1 (0.3)
		Engineer	1 (0.3)
		Regulator	1 (0.3)
		Teacher	1 (0.3)
		Therapist	1 (0.3)
		Trial Management	1 (0.3)
		Unknown ^H	211 (56.9)

^a Based on Survey Question 8. Total of 203 responses to this question, ^A Unknown because 168 respondents did not answer this question, ^b Based on Survey Question 14. Total of 197 responses to this question, ^B Unknown because 174 respondents did not answer this question, ^c Based on Survey Question 13. Total of 201 responses to this question, ^C Unknown because 170 respondents did not answer this question, ^d Based on Survey Question 9. Total of 203 responses to this question, ^D Unknown because 168 respondents did not answer this question, ^e Based on Survey Question 11. Total of 202 responses to this question, ^E Unknown because 169 respondents did not answer this question, ^f Based on Survey Question 14. Total of 197 responses to this question. Respondents to this question were asked to select all roles (or categories) that applied to them, thus a respondent can be in more than one category. ^F Unknown because 268 respondents did not answer this question, ^g Based on Survey Question 7. Total of 200 responses to this question. Respondents to this question were asked to select all roles (or categories) that applied to them, thus a respondent can be in more than one category. ^H Unknown because 171 respondents did not answer this question, ^h Based on Survey Question 10. Total of 160 responses to this question. Respondents to this question were asked to select all roles (or categories) that applied to them, thus a respondent can be in more than one category. ^H Unknown because 211 respondents did not answer this question, ^q Percentages based on the 371 total respondents to this survey.

* Respondents could have selected more than one option thus it is possible that the percentages add up to more than 100%.

Table 3: Summary of Results for Sharing Certain Interim Results	
Interim Combined Event Rate	
1 a) During an ongoing Randomized Controlled Trial (RCT), do you think that the Data Safety Monitoring Board (DSMB) for an RCT should share the Interim Combined Event Rate with ANY of the following parties?	
Response	Results (n; % [95% CI]), n=262
Yes	168; 64.1% [58.0% to 69.9%];
With whom?*	
B. The Steering Committee	142; 54.2% [48.2% to 60.2%];
A. The Sponsor	101; 38.5% [32.7% to 44.4%];
C. The Investigator(s)	80; 30.5% [25.0% to 36.1%];
D. The Funder(s)	64; 24.4% [19.2% to 29.6%];
E. Other, Please Specify:	15; 5.7% [2.9% to 8.5%];
• Institutional Review Board or Research Ethics Boards,	
• Regulatory Bodies,	
• Blinded Statistician on Steering Committee,	
• Study Statistician	
• Participants	
• Professional public	
No (F. None of the Above)	94; 35.9% [30.1% to 41.7%]
1 b) How useful is it to share the Interim Combined Event Rates at interim? (On a scale from 0 to 10 where 0 is Not Useful at All and 10 is Very Useful) Question 1 b. answered only by those who answered A, B, C, D or E to Question 1 a.	
Results (Mean [95% CI]; Median [IQR]), N =146	
6.97 [6.62 to 7.31]; 7 [6-8]	
Interim Control Event Rate	
2 a) During an ongoing Randomized Controlled Trial (RCT), do you think that the Data Safety Monitoring Board (DSMB) for an RCT should share the Interim Control Event Rate with ANY of the following parties?	
Response	Results (n; % [95% CI]), n=237
Yes	88; 37.1% [31.0% to 43.3%]
With whom?*	
B. The Steering Committee	60; 25.3% [19.8% to 30.9%]
C. The Investigator(s)	35; 14.8% [10.3% to 19.3%]
A. The Sponsor	33; 13.9% [9.5% to 18.3%]
D. The Funder(s)	30; 12.7% [8.4% to 16.9%]
E. Other, Please Specify:	22; 9.3% [5.6% to 13.0%]
• Institutional Review Board or Research Ethics Boards,	
• Regulatory Bodies	
• Professional Public	
• Study Statistician	
No (F. None of the Above)	149; 62.9% [56.7% to 69.0%]
2 b) How useful is it to share the Interim Control Event Rates at interim? (On a scale from 0 to 10 where 0 is Not Useful at All and 10 is Very Useful) Question 2 b. answered only by those who answered A, B, C, D or E to Question 2 a.	
Results (Mean [95% CI]; Median [IQR]), N=72	
7.03 [6.55 to 7.50]; 7 [5-8]	
Adaptive Conditional Power	
3 a) During an ongoing Randomized Controlled Trial (RCT), do you think that the Data Safety Monitoring Board (DSMB) for an RCT should share the Adaptive Conditional Power with ANY of the following parties	
Response	Results (n; % [95% CI]), n=224
Yes	80; 35.7% [29.4% to 42.0%]
With whom?*	
B. The Steering Committee	45; 20.1% [14.8% to 25.3%]
A. The Sponsor	34; 15.2% [10.5% to 19.9%]
C. The Investigator(s)	27; 12.1% [7.8% to 16.3%]
D. The Funder(s)	22; 9.8% [5.9% to 13.7%]
E. Other, Please Specify	21; 9.4% [5.6% to 13.2%]
• Trial statistician,	
• Pre-specified members of the sponsor and steering committee,	
• Professional public,	
• Institutional Review Board or Research Ethics Boards	
No (F. None of the Above)	144; 64.3% [58.0% to 70.6%]
3 b) How useful is it to share the Adaptive Conditional Power at interim? (On a scale from 0 to 10 where 0 is Not Useful at All and 10 is Very Useful) Question 3 b. answered only by those who answered A, B, C, D or E to Question 3 a.	
Results (Mean [95% CI]; Median [IQR]), N=66	
6.64 [6.08 to 7.20]; 7 [5-8]	
Unconditional Conditional Power	
4 a) During an ongoing Randomized Controlled Trial (RCT), do you think that the Data Safety Monitoring Board (DSMB) for an RCT should share the Unconditional Conditional Power with ANY of the following parties?	
Response	Results (n; % [95% CI]), n=208
Yes	82; 39.4% [32.8% to 46.1%]
With whom?*	
B. The Steering Committee	57; 27.4% [21.3% to 33.5%]
A. The Sponsor	42; 20.2% [14.7% to 25.6%]
C. The Investigator(s)	30; 14.4% [9.6% to 19.2%]
D. The Funder(s)*	29; 13.9% [9.2% to 18.6%]
E. Other, Please Specify	17; 8.2% [4.4% to 11.9%]

<ul style="list-style-type: none"> • Pre-specified with whom such as selected members of the sponsor or funder who do not see patients • Study statistician • Steering committee • Professional public • Institutional Review Board or Research Ethics Boards 	
No (F. None of the Above)	126; 60.6% [53.9% to 67.2%]
4 b) How useful is it to share the Unconditional Conditional Power at interim? (On a scale from 0 to 10 where 0 is Not Useful at All and 10 is Very Useful) Question 4 b. answered only by those who answered A, B, C, D or E to Question 4 a.	
Results (Mean [95% CI]; Median [IQR]), n=67	
6.64 [6.08 to 7.20]; 7 [5-8]	
IQR (Interquartile Range) * Respondents could have selected more than one option thus it is possible that the percentages add up to more than 100%.	

Table 4: Other information that should be shared				
Do you think any other information should be shared during the interim of a Randomized Controlled Trial by the Data Safety Monitoring Board (DSMB)?				
Total responses to question: 210				
Response	Count; % [95% CI]			
No	109; 51.9% [45.0% to 58.8%]			
Yes	101; 48.1% [41.2% to 55.0%]			
For those that answered Yes, what other information the DSMB should share at a trial's interim, with whom it should be shared, why, and how useful it is to share that information?				
What should be shared?	Count; % [95% CI]^A	With whom should that information be shared?	Why should this information be shared?	Usefulness to share* Mean [95% CI]; Median [IQR]
Information about trial conduct (e.g. Protocol adherence, operational issues, enrollment, recruitment, treatment adherence, trial management, data quality and completeness)	67; 31.9% [25.7% to 38.6%]	<ul style="list-style-type: none"> • Sponsor, • Steering committee, • Investigators, or any relevant party 	To ensure the trial is conducted well with integrity and ethically. Information about trial conduct issues will help instigate corrective measures.	9.16 [8.89 to 9.42]; 10 [8-10]
Safety Issue or Concern	50; 23.8% [18.3% to 30.1%]	<ul style="list-style-type: none"> • Sponsor • Steering Committee • Investigator(s) • Ethics Committee 	Based on the type of safety concern, investigators may need to increase monitoring to protect patient safety, change the trial's protocol or request new consent from enrolled patients based on new safety risk.	9.35 [9.02 to 9.69]; 10 [9-10]
DSMB trial recommendations such as stopping or continuing the trial and possible sample size adjustment. Information shared does not include unmasking group information.	21; 10.0% [6.3% to 14.9%]	<ul style="list-style-type: none"> • Sponsor • Steering Committee 	To protect the trial's integrity, patient safety, and trial resources. Due diligence to patients and the public good.	9.52 [9.08 to 9.96]; 10 [10-10]
Overall Patient Baseline Characteristics	9; 4.3% [2.0% to 8.0]	<ul style="list-style-type: none"> • Any relevant party 	Help study team understand if their enrollment is targeting the intended population. Protect the generalizability of the study. Help evaluate recruitment procedures and analysis plan.	8.0 [7.27 to 8.73]; 8 [8-8]
Any relevant data or raw data	4; 1.9% [0.5% to 4.8%]	<ul style="list-style-type: none"> • Any relevant party 	Sharing allows for broader stakeholder discussion of the benefits of treatment versus the risks of adverse events than	9.33 [8.68 to 9.99]; 9 [9-9.5]

			just a committee with minimum involvement. There is no harm in this if efficacy stopping rules are pre-specified.	
Important information from outside of the trial that is relevant to the current trial, the enrolled patients, the sponsor and the investigators	2; 1.0% [0.1% to 3.4%]	<ul style="list-style-type: none"> Steering Committee Study team members 	During a long term trial, results from other trials may affect the ethics, scientific rationale, care of patients and conduct of the current trial.	9.5 [8.52 to 10]; 9.5 [9.25 – 9.75]
<p>^A Respondents could have indicated more than one of other type of item thus it is possible that the percentages add up to more than 100%.</p> <p>*On a scale between 0 to 10 (Where 0 is “Not Useful at All” and 10 is “Very Useful”)</p> <p>IQR (Interquartile Range)</p>				

Table 5: Sharing of interim information indicated in encountered DSMB charters			
Have you ever been involved in a trial where it was explicitly stated in the Data Safety Monitoring Board (DSMB) charter <i>what interim information/data/results should be shared AND with whom that information should be shared</i> during the trial's interim?			
Total responses to question: 207			
Response	Count; % [95% CI]		
No	103; 49.8% [42.8% to 56.7%]		
Yes	104; 50.2% [43.3% to 57.2%]		
For those that answered yes and according to any DSMB charter(s) they encountered, which of the following pieces of interim information <i>should be shared</i> during the interim of a trial, <i>with whom</i> and <i>under what circumstance</i> the sharing would happen.			
Interim Information	Count; % [95% CI]^a	With whom should that information be shared?	Under what circumstance this information should be shared according to the charter? Summary of responses
Interim Combined Event Rate	55; 26.6% [20.7% to 33.1%]	Various parties indicated: <ul style="list-style-type: none"> • Sponsor • Investigator • Funder • Steering Committee • Regulator • Other relevant parties 	<p>Various responses were given.</p> <p>Singular parties:</p> <ul style="list-style-type: none"> • With the investigator: If the overall rate was much lower than hypothesize and if there was a need to adjust the sample size. • With the steering committee: Always shared at each meeting without restrictions. To help with potential sample size re-estimation and re-assess power without unmasking group event rates. When the overall rate is much lower than anticipated. • With the sponsor: Shared during open session report. To help with potential sample size re-estimation. Help sponsor anticipate the length of the trial. Sharing was up to the DSMB's discretion. • With the regulatory agency: If there was a safety issue. <p>A combination of parties:</p> <ul style="list-style-type: none"> • With select members of the sponsor, steering committee or investigator(s): Pre-specified in the charter. When benchmarks are not met or when there is determined need for a sample size re-estimation. Need to share if there was a recommendation from the DSMB to stop the trial because of futility or efficacy. Such information is only used for internal decision making and is not for publication or further dissemination. • With the sponsor, funder or investigator(s): Once accrual was complete and the primary outcome was known for at least a certain set percentage of those enrolled. It was also indicated that this information was shared at every planned interim look. • With Relevant Parties: For safety and ethical issues
Interim Control Event Rate	16; 7.7% [4.5% to 12.2%]	Various parties indicated: <ul style="list-style-type: none"> • Sponsor • Investigator • Funder • Steering Committee • Regulator • Other relevant parties 	<p>Various responses were given.</p> <p>Singular parties:</p> <ul style="list-style-type: none"> • With the steering committee: Pre-specified in the charter. If the event rate was different from what was pre-specified in the protocol. • With the sponsor: When there is a futility analysis and if the interim control event rate differed majorly from the design assumptions. • With the regulatory agency: If there was a safety issue. <p>A combination of parties:</p> <ul style="list-style-type: none"> • Select members of sponsor/funder, steering committee or investigator(s): <ul style="list-style-type: none"> ○ Pre-specified in the charter. Sharing this information was not data driven. ○ It would be shared once accrual was complete and the primary outcome was known for at least a certain set percentage of those enrolled. It was also indicated in another instance that interim control event rate was shared at every planned interim look. • With Relevant Parties: For safety and ethical issues
Adaptive Conditional Power	19; 9.2% [5.6% to 13.9%]	Various parties indicated: <ul style="list-style-type: none"> • Sponsor • Investigator • Funder • Steering Committee • Other relevant parties 	<p>Various responses were given.</p> <p>Singular parties:</p> <ul style="list-style-type: none"> • With the sponsor: Would be shared at interim at the time of formal futility analysis • With the steering committee: Would be shared at interim at the time of formal futility analysis and when a boundary was crossed. Also shared when there was a need for a management decision to be made. <p>A combination of parties:</p> <ul style="list-style-type: none"> • Select members of sponsor/funder, steering committee or investigator(s): If the adaptive conditional power falls below a prefixed level or when there was data supporting stopping the trial. Pre-specified in the charter. Such information is only used for internal decision making and is not for publication or further dissemination. In one instance it was also shared at the annual meeting report. • With Relevant Parties: For safety and ethical issues
Unconditional Conditional Power	18; 8.7% [5.3% to 13.4%]	Various parties indicated: <ul style="list-style-type: none"> • Sponsor • Investigator • Funder • Steering Committee • Regulator • Other relevant parties 	<p>Various responses were given.</p> <p>Singular parties:</p> <ul style="list-style-type: none"> • With the sponsor: Would be shared at interim at the time of formal futility analysis and for a needed sample size recalculation. • With the steering committee: Would be shared at interim when there was a clear benefit or harm to whatever was being investigated and to reassess power without unmasking interim results. <p>A combination of parties:</p> <ul style="list-style-type: none"> • With select members of sponsor/funder, steering committee or investigator(s): Pre-specified in the charter. When there was data supporting stopping the trial. • With Relevant Parties: For safety and ethical issues <p>There was an argument that such information is implicitly available, even if it is not directly provided.</p>
Other information			
Information about trial conduct	21; 10.1% [6.4% to 15.1%]	Various parties indicated: <ul style="list-style-type: none"> • Sponsor • Investigator • Funder • Steering Committee • Regulator 	<p>A combination of parties:</p> <ul style="list-style-type: none"> • With the sponsor/funder, steering committee, investigator(s) or regulator if needed: This is not confidential information and should be shared during DSMB open sessions according to the charter with any relevant party at the open session and those responsible for the conduct of the trial to ensure the integrity of the trial's conduct and correct problems as soon as possible.
Safety Issue or Concern	16; 7.7% [4.5% to 12.2%]	Various parties indicated: <ul style="list-style-type: none"> • Sponsor • Investigator • Funder • Steering Committee • Regulator 	<p>A combination of parties:</p> <ul style="list-style-type: none"> • With the sponsor/funder, steering committee, investigator(s) or regulator if needed: This is not confidential information and should be shared during DSMB open sessions according to the charter with any relevant party at the open session and those responsible for the conduct of the trial. It is important to share this information to help those responsible for the trial's conduct to ensure participant safety.
DSMB trial recommendations such as stopping or continuing the trial and possible sample size adjustment.	15; 7.2% [4.1% to 11.7%]	Various parties indicated: <ul style="list-style-type: none"> • Sponsor • Steering Committee 	<p>A combination of parties:</p> <ul style="list-style-type: none"> • With the steering committee or sponsor: Pre-specified in the charter. Typical information shared in this circumstance would not include unmasked group information. However it was indicated that if there cases where unmasked information would be shared if the decision to stop the trial has been made (e.g. for futility, efficacy or if some other pre-specified boundary has been reached).
Overall Patient Baseline Characteristics	3; 1.4% [0.3% to 4.2%]	Various parties indicated: <ul style="list-style-type: none"> • Sponsor • Investigator • Funder • Steering Committee • Regulator 	<p>A combination of parties:</p> <ul style="list-style-type: none"> • Sponsor/funder, steering committee, investigator(s) or regulator if needed: This is not confidential information would be shared during DSMB open sessions according to the charter with any relevant party at the open session and those responsible for the conduct of the trial.

Unmasked treatment arm information	1; 0.5% [0.01% to 2.7%]	Various parties indicated: <ul style="list-style-type: none"> • Sponsor • Investigator • Public 	<u>A combination of parties:</u> <ul style="list-style-type: none"> • With the sponsor, investigator(s) or public: It was also mentioned that primary outcome data by treatment group was once shared with the sponsor, investigator or public if the primary outcome is known for at least set percentage of trial patients and the target sample size was enrolled.
Acronyms: Data Safety Monitoring Board (DSMB) ^B Respondents could have indicated more than one item thus it is possible that the percentages add up to more than 100%.			

Appendix A: Survey questions

Question 1

Interim Combined Event Rate

“Interim Combined Event Rate is defined as:

The total number of events observed at some planned interim point into the trial divided by the total number of participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial or after enrolling a certain number of participants).

Example:

- *Total # of Deaths in both the placebo group and new intervention group, six months from the start of the trial = 80*
- *Total # of Participants in both the placebo group and the new intervention group, six months from the start of the trial = 700*
- *Calculation: $80/700 = 0.114$ or 11.4%*
- *Therefore the Interim Combined Event Rate at the trial's interim analysis, six months from the start of the trial, is 11.4%” [1]*

1. Part A

During an ongoing Randomized Controlled Trial (RCT), do you think that the Data Safety Monitoring Board (DSMB) for an RCT should share the Interim Combined Event Rate with ANY of the following parties?

**(Please note that in most cases the sponsor is also the funder of the trial. By funder we are only referring to the entity which provides financial resources for the trial)*

Please select ALL that apply.

- A. Sponsor**
- B. The Steering Committee**
- C. The Investigator(s)**
- D. The Funder(s)***
- E. Other, Please Specify _____**
- F. None of the Above**

Advanced Branching: If answered A, B, C, D or E, show 1. Part B and 1. Part C. If answered F, show 1. Part D

1. Part B

How useful is it to share the Interim Combined Event rate at interim?

0 Not Useful at All	1	2	3	4	5	6	7	8	9	10 Very Useful
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1. Part C

Please briefly explain why the Interim Combined Event Rates should be shared by the DSMB at interim.

1. Part D

Please briefly explain why the Interim Combined Event Rates should not be shared with anyone or any party at a trial's interim.

Question 2

Interim Control Event Rate

“Interim Control Event Rate is defined as:

The number of events observed among control participants at some planned interim point into the trial divided by number of control participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial)

Example:

- *Total # of Deaths in the placebo group, six months from the start of the trial = 15*
- *Total # of Participants in the placebo group, six months from the start of the trial = 250*
- *Calculation: $15/250 = 0.06$ or 6%*
- *Therefore the Interim Control Event Rate at the trial's interim analysis, six months from the start of the trial, is 6%” [1]*

2. Part A

During an ongoing Randomized Controlled Trial (RCT), do you think that the Data Safety Monitoring Board (DSMB) for an RCT should share the Interim Control Event Rate with ANY of the following parties?

*(Please note that in most cases the sponsor is also the funder of the trial. By funder we are only referring to the entity which provides financial resources for the trial)

Please select ALL that apply.

- A. Sponsor**
- B. The Steering Committee**
- C. The Investigator(s)**
- D. The Funder(s)***
- E. Other, Please Specify _____**
- F. None of the Above**

Advanced Branching: If answered A, B, C, D or E, show 2. Part B and 2. Part C. If answered F, show 2. Part D

2. Part B

How useful is it to share the Interim Control Event rate at interim?

0 Not Useful at All	1	2	3	4	5	6	7	8	9	10 Very Useful
------------------------	---	---	---	---	---	---	---	---	---	-------------------

2. Part C

Please briefly explain why the Interim Control Event Rates should be shared by the DSMB at interim.

2. Part D

Please briefly explain why the Interim Control Event Rates should not be shared with anyone or any party at a trial's interim.

Question 3

Adaptive Conditional Power

“Adaptive Conditional Power is defined as:

The probability of rejecting the null hypothesis of no effect by the end of the trial (i.e. finding a statistically significant effect in favour of the intervention), at some predetermined interim point in the trial when the adaptive conditional power is scheduled to be calculated. The assumption made is that the observed interim effect (i.e. relative risk reduction) in the trial will remain the same until the end of the trial.

Example statement:

Given the interim data (data collected 2 years into the trial that is planned to last for 3 years), and assuming the observed interim effect (i.e. relative risk reduction) at the two year mark to be the true effect for the remainder of the trial, the probability of rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 60%.

The following pieces of information are used to calculate Adaptive Conditional Power at trial interim:

- Control event rate and experimental event rate
- Information Fraction; a ratio of the planned sample size and the number of patients recruited in trial at the interim analysis
- Z score and B value at interim
- Drift parameter” [1]

3. Part A

During an ongoing Randomized Controlled Trial (RCT), do you think that the Data Safety Monitoring Board (DSMB) for an RCT should share the Adaptive Conditional Power with ANY of the following parties?

*(Please note that in most cases the sponsor is also the funder of the trial. By funder we are only referring to the entity which provides financial resources for the trial)

Please select ALL that apply.

- A. Sponsor**
- B. The Steering Committee**
- C. The Investigator(s)**
- D. The Funder(s)***
- E. Other, Please Specify _____**
- F. None of the Above**

Advanced Branching: If answered A, B, C, D or E, show 3. Part B and 3. Part C. If answered F, show 3. Part D

3. Part B

How useful is it to share the Adaptive Conditional Power at interim?

0 Not Useful at All	1	2	3	4	5	6	7	8	9	10 Very Useful
------------------------	---	---	---	---	---	---	---	---	---	-------------------

3. Part C

Please briefly explain why the Adaptive Conditional Power should be shared by the DSMB at interim.

3. Part D

Please briefly explain why the Adaptive Conditional Power should not be shared with anyone or any party at a trial's interim.

Question 4

Unconditional Conditional Power

“Unconditional Conditional Power is defined as:
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 when indeed the alternative hypothesis is true, at some interim point in the trial.

The following pieces of information are used to calculate Unconditional Conditional Power at interim:

- The hypothesized treatment effect at the design stage (i.e. relative risk reduction) of the trial, assuming the hypothesized treatment effect at the design stage to be true and correct for the remainder of the trial;
- The sample size calculated at the design stage for the trial AND;
- The combined event rate calculated at the trial's interim, assuming this rate to be true for the remainder of the trial.

Example statement:

Given the interim combined event rate and assuming the treatment effect (i.e. relative risk reduction) hypothesized at the design stage of the trial to be true for the remainder of the trial, the probability of correctly rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 89%.” [1]

4. Part A

During an ongoing Randomized Controlled Trial (RCT), do you think that the Data Safety Monitoring Board (DSMB) for an RCT should share the Unconditional Conditional Power with ANY of the following parties?

*(Please note that in most cases the sponsor is also the funder of the trial. By funder we are only referring to the entity which provides financial resources for the trial)

Please select ALL that apply.

- A. Sponsor**
- B. The Steering Committee**
- C. The Investigator(s)**
- D. The Funder(s)***
- E. Other, Please Specify _____**
- F. None of the Above**

Advanced Branching: If answered A, B, C, D or E, show 4. Part B and 4. Part C. If answered F, show 4. Part D

4. Part B

How useful is it to share the Unconditional Conditional Power at interim?

0	1	2	3	4	5	6	7	8	9	10
Not Useful at All										Very Useful

4. Part C

Please briefly explain why the Unconditional Conditional Power should be shared by the DSMB at interim.

4. Part D

Please briefly explain why the Unconditional Conditional Power should not be shared with anyone or any party at a trial's interim.

Question 5

5. Part A

Do you think any other information should be shared during the interim of a Randomized Controlled Trial by the Data Safety Monitoring Board (DSMB)?

- Yes
- No

Advanced Branching: If answered yes, show 5. Part B

5. Part B

If yes, please briefly indicate what other information the DSMB should share at a trial's interim, with whom it should be shared, why, and how useful it is to share that information. (You have the option of adding up to 5 different items)

What should be shared?	With whom should that information be shared?	Why should this information be shared?	From a scale between 0 to 10 (Where 0 is "Not Useful at All" and 10 is "Very Useful"), how useful is it to provide this information?
1.			0 1 2 3 4 5 6 7 8 9 10
2.			0 1 2 3 4 5 6 7 8 9 10
3.			0 1 2 3 4 5 6 7 8 9 10
4.			0 1 2 3 4 5 6 7 8 9 10
5.			0 1 2 3 4 5 6 7 8 9 10

Question 6

6. Part A

Have you ever been involved in a trial where it was explicitly stated in the Data Safety Monitoring Board (DSMB) charter *what interim information/data/results should be shared AND with whom that information should be shared during the trial's interim?*

- Yes
 No

Advanced Branching: If answered yes, show 6. Part B, 6. Part C and 6. Part D

6. Part B

According to any DSMB charter(s) you encountered, please indicate below whether any of the following pieces of interim information *should be shared* during the interim of a trial, *with whom* and *under what circumstance* the sharing would happen, where applicable.

(*If you would like to see the definitions of the interim pieces of information in this chart below, please select "yes" to the checkbox at the bottom of this page and the definitions will appear below. Deselect "Yes" if you want the definitions to disappear)

Interim Information	Please select if any of the following pieces of interim information should be shared according to any DSMB charter(s) you encountered.	With whom should this interim information be shared? (e.g. Investigator(s), Sponsor, Steering Committee, Funder of the Trial, etc.)	Under what circumstance(s) should this interim information be shared?
Interim Combined Event Rate	<input type="checkbox"/>		
Interim Control Event Rate	<input type="checkbox"/>		
Adaptive Conditional Power	<input type="checkbox"/>		
Unconditional Conditional Power	<input type="checkbox"/>		

6. Part C

According to any DSMB charter(s) you encountered, *should any other information* be shared during the interim of a trial, *with whom* and *under what circumstance*, where applicable.

(You have the option of adding up to 5 different items if you would like)

Interim Information that should be shared	With whom should this interim information be shared? (e.g. Investigator(s), Sponsor, Steering Committee, Funder of the	Under what circumstance(s) should this interim information be shared?
1.		
2.		
3.		
4.		

5.		
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6. Part D

*If you would like to see the definitions for the first chart above, please select "Yes" below. (To make the definitions disappear, deselect "Yes" below)

Yes

Advanced Branching: If answered yes, show 6. Part E

6. Part E

Definitions for Reference

“Interim Combined Event Rate is defined as:

The total number of events observed at some planned interim point into the trial divided by the total number of participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial or after enrolling a certain number of participants).

Example:

- Total # of Deaths in both the placebo group and new intervention group, six months from the start of the trial = 80
- Total # of Participants in both the placebo group and the new intervention group, six months from the start of the trial = 700
- Calculation: $80/700 = 0.114$ or 11.4%
- Therefore the Interim Combined Event Rate at the trial's interim analysis, six months from the start of the trial, is 11.4% [1]

“Interim Control Event Rate is defined as:

The number of events observed among control participants at some planned interim point into the trial divided by number of control participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial)

Example:

- Total # of Deaths in the placebo group, six months from the start of the trial = 15
- Total # of Participants in the placebo group, six months from the start of the trial = 250
- Calculation: $15/250 = 0.06$ or 6%
- Therefore the Interim Control Event Rate at the trial's interim analysis, six months from the start of the trial, is 6% [1]

“Adaptive Conditional Power is defined as:

The probability of rejecting the null hypothesis of no effect by the end of the trial (i.e. finding a statistically significant effect in favour of the intervention), at some predetermined interim point in the trial when the adaptive conditional power is scheduled to be calculated. The assumption made is that the observed interim effect (i.e. relative risk reduction) in the trial will remain the same until the end of the trial.

Example statement:

- Given the interim data (data collected 2 years into the trial that is planned to last for 3 years), and assuming the observed interim effect (i.e. relative risk reduction) at the two year mark to be the true effect for the remainder of the trial, the probability of rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 60%.

The following pieces of information are used to calculate Adaptive Conditional Power at trial interim:

- Control event rate and experimental event rate
- Information Fraction; a ratio of the planned sample size and the number of patients recruited in trial at the interim analysis
- Z score and B value at interim
- Drift parameter” [1]

“Unconditional Conditional Power is defined as:

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 when indeed the alternative hypothesis is true, at some interim point in the trial.

The following pieces of information are used to calculate Unconditional Conditional Power at interim:

1. The **hypothesized treatment effect at the design stage** (i.e. relative risk reduction) of the trial, assuming the hypothesized treatment effect at the design stage to be true and correct for the remainder of the trial;
2. The **sample size calculated at the design stage** for the trial AND;
3. The **combined event rate calculated at the trial’s interim**, assuming this rate to be true for the remainder of the trial.

Example statement:

- *Given the interim combined event rate and assuming the treatment effect (i.e. relative risk reduction) hypothesized at the design stage of the trial to be true for the remainder of the trial, the probability of correctly rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 89%”. [1]*

Question 7

Please identify if you are currently or have been in one of these roles in relation to the operation of a trial.

Please select ALL that apply:

<input type="checkbox"/>	A. Trialist or Investigator (i.e. Co-Investigator in a trial)
<input type="checkbox"/>	B. Principal Investigator (PI) of a clinical trial or RCT
<input type="checkbox"/>	C. Data Safety Monitoring Board (DSMB) Member
<input type="checkbox"/>	D. Research Nurse
<input type="checkbox"/>	E. Trial Coordinator
<input type="checkbox"/>	F. Representative of the sponsor of the trial (The sponsor of the trial is responsible for trial initiation, administration and management. In many case they also help to fund/finance the trial)
<input type="checkbox"/>	G. Representative of the funder** of the trial (**Please note that in most cases the sponsor is also the funder of the trial. By funder we are only referring to the entity which provides financial resources for the project)
<input type="checkbox"/>	H. Trial statistician
<input type="checkbox"/>	I. Data Analyst
<input type="checkbox"/>	J. Data Manager
<input type="checkbox"/>	K. Other role within a trial, Please describe: _____

Question 8

How many trials have you been involved with?

Please select ONLY ONE:

- A. None
- B. 1 to 5 trials
- C. 6 to 10 trials
- D. 11 to 15 trials
- E. More than 15 trials

Question 9

What do you regard as your primary or main profession by training?

Please select ONLY ONE:

- A. Physician
- B. Nurse or Nurse Practitioner
- C. Pharmacist
- D. Dentist
- E. Methodological Scientist/Research Methodologist
- F. Epidemiologist
- G. Medical Laboratory Scientist
- H. Physiotherapist
- I. Occupational Therapist
- J. Optometrist
- K. Psychologist
- L. Midwife
- M. Ethics specialist
- N. Lawyer
- O. Research or Clinical Trial Coordinator
- P. Medical Laboratory Technician
- Q. Mathematician/Statistician
- R. Computer Scientist
- S. Information Technologist

- T. Computer Programmer
- U. Data Manager
- V. Other Profession, Please Describe: _____

Question 10

What other professional roles have you taken on? (Please exclude the option selected in Question 9)

Please select ALL that apply:

<input type="checkbox"/>	A. Physician
<input type="checkbox"/>	B. Nurse or Nurse Practitioner
<input type="checkbox"/>	C. Pharmacist
<input type="checkbox"/>	D. Dentist
<input type="checkbox"/>	E. Methodological Scientist/Research Methodologist
<input type="checkbox"/>	F. Epidemiologist
<input type="checkbox"/>	G. Medical Laboratory Scientist
<input type="checkbox"/>	H. Physiotherapist
<input type="checkbox"/>	I. Occupational Therapist
<input type="checkbox"/>	J. Optometrist
<input type="checkbox"/>	K. Psychologist
<input type="checkbox"/>	L. Midwife
<input type="checkbox"/>	M. Ethics specialist
<input type="checkbox"/>	N. Lawyer
<input type="checkbox"/>	O. Research or Clinical Trial Coordinator
<input type="checkbox"/>	P. Medical Laboratory Technician
<input type="checkbox"/>	Q. Mathematician/Statistician
<input type="checkbox"/>	R. Computer Scientist
<input type="checkbox"/>	S. Information Technologist
<input type="checkbox"/>	T. Computer Programmer
<input type="checkbox"/>	U. Data Manager
<input type="checkbox"/>	V. Other Profession, Please Describe: _____

Question 11

In what setting or environment do you usually work?

Please select ONLY ONE:

- A. Hospital
- B. Medical or Health Clinic
- C. Private Practice
- D. University or Academic Institution
- E. Government Research Group
- F. Government Regulatory Body
- G. Private or Contracted Research Company
- H. Pharmaceutical Company
- I. Medical Device Company
- J. Other. If so, please indicate, in general, the setting you usually work? _____

Question 12

In what other settings or environments do you usually work? (Please exclude the option selected in Question 11)

Please select **ALL** that apply:

<input type="checkbox"/>	A. Hospital
<input type="checkbox"/>	B. Medical or Health Clinic
<input type="checkbox"/>	C. Private Practice
<input type="checkbox"/>	D. University or Academic Institution
<input type="checkbox"/>	E. Government Research Group
<input type="checkbox"/>	F. Government Regulatory Body
<input type="checkbox"/>	G. Private or Contracted Research Company
<input type="checkbox"/>	H. Pharmaceutical Company
<input type="checkbox"/>	I. Medical Device Company
<input type="checkbox"/>	J. Other. If so, please indicate, in general, the setting you usually work? _____

Question 13

How many of the trials that you have been involved with had some form of private industry sponsorship?

Please select **ONLY ONE**:

- A. None
- B. 1 to 5 trials
- C. 6 to 10 trials
- D. 11 to 15 trials
- E. More than 15 trials

Question 14

How many of the trials that you have been involved with had a Data Safety Monitoring Board (DSMB) monitoring the trial?

Please select **ONLY ONE**:

- A. None
- B. 1 to 5 trials
- C. 6 to 10 trials
- D. 11 to 15 trials
- E. More than 15 trials

Reference

[1] V. Borg Debono, L. Mbuagbaw, J. Paul, N. Buckley, L. Thabane, Sharing some interim data in trial monitoring can mislead or unmask trial investigators: A scenario-based survey of trial experts, Contemporary Clinical Trials Communications 7 (2017) 81-85.

CHAPTER 5

Exploring factors associated with views on sharing of certain interim trial result measures by the data safety monitoring board (DSMB) with non-DSMB members

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Abstract

Background: Sharing interim result measures by the Data Safety Monitoring Board (DSMB) with non-DSMB members is an important issue that can affect trial integrity. Currently, it is unclear if there are demographic factors associated with sharing such information. This study's objective is to primarily assess the demographic factors associated with the DSMB sharing certain interim result measures and secondarily, assess demographic factors associated with the perceived usefulness in sharing certain interim result measures, with non-DSMB members.

Methods: We conducted an online survey of members of the Society of Clinical Trials (SCT) and International Society of Clinical Biostatistics (ISCB) in 2015 asking their professional views on the DSMB sharing interim trial results, specifically the interim control event rate (IControlER), interim combined even rate (ICombinedER), adaptive conditional power (ACP), unconditional conditional power (UCP) with non-DSMB members. Binary logistic and multiple linear regressions were used to assess if demographic factors were associated with sharing a certain interim result measure and the perceived usefulness of sharing that interim result measure, respectively. Multiple Imputation (MI) was used to assess the impact of missing data as a sensitivity analysis.

Results: Approximately 3136 (936 from SCT + ~ 2200 from ISCB) members were invited (response rate of 12%; [371/3136]). Two main findings: 1) Involvement in more than 15 private industry-sponsored trials was associated with not endorsing the sharing of the IControlER (Odds Ratio[OR] = 2.92; 95% confidence interval [CI]: 1.31, 6.52]; $p = 0.012$), and 2) Involvement in more than 15 private industry-sponsored trials was associated positively with an increase in the perceived usefulness in sharing the ACP by 2.35 points ($b = 2.35$ [95% CI: 0.45, 4.05], $p = 0.017$). The findings were similar after sensitivity analyses.

Conclusion: An individual involved with more than 15 trials that had some form of private industry sponsorship is a demographic factor associated with NOT sharing the IControlER by the DSMB and an increased perceived usefulness in sharing the ACP at interim. Further studies

are needed to assess for these demographic factors given the limitations of this study related to missing data.

Keywords

Data Safety Monitoring Board (DSMB), Data Monitoring Committee (DMC), Interim Result Sharing, Survey

Introduction

Data Safety Monitoring Boards (DSMBs) are in charge of the stewardship of a trial by protecting patient safety and trial integrity by reviewing accumulating interim trial results, such as safety or efficacy results when asked to, on a periodic basis, and by responding to information or trends that threaten the safety and validity of the trial by making recommendations to the trial's steering committee (SC) or sponsor on how to proceed in light of the information [1, 2]. A trial can be negatively affected if the DSMB were to share interim trial results with non-DSMB members who are involved in the trial [1, 3, 4] as this could introduce bias. This is a grave concern for phase III trials that are typically done to provide definitive evidence on efficacy and safety outcomes [5, 6]. For this study, principal investigator(s) (PIs), study investigators, the SC, sponsors, the independent unmasked statistician, site managers, the funder(s), or patients enrolled in the trial or any other party responsible for the conduct or completion of the trial will be referred to as non-DSMB members.

Evidence in the literature suggests that DSMBs sharing potentially unmasking interim results with non-DSMB members is prevalent and may be an issue [7]. Some circumstances where the DSMB may share potentially unmasking interim results are when the DSMB makes a recommendation for early trial termination, the DSMB has concerns with the interim results given to them for a scheduled interim review, the trial's completion as planned is endangered, the DSMB has a concerns about the safety of the trial participants, and when there is a need to share interim results with a government regulator for early drug approval [7]. Other situations for sharing could be for an adaptive confirmatory trial where interim results are needed to make decisions about planned *a priori* study modifications and trials with a long follow-up where certain types of interim results may help a particular patient group or a treating physician with future treatment [7]. As part of a larger study to investigate what should be shared by the DSMB with non-DSMB members, we conducted a survey asking professionals interested or involved in trials, their views on what interim information should be shared, with whom at interim and why.

We found out that the interim control event rate (IControlER), adaptive conditional power (ACP), and the unconditional conditional power (UCP) should not be shared primarily because it is unmasking of interim results. The interim combined event rate (ICombinedER) is usually known by the SC or the sponsor during a trial making it easy to determine group rate of the new intervention group if the IControlER is known. Most respondents from the survey thought the ICombinedER should be shared with the SC. Reasons indicated for sharing the ICombinedER are that the measure is not unmasking of relative effects between groups and it helps the SC monitor the trial's progress, trial safety and the design assumptions made in the trial's protocol. However, it was indicated that sharing the ICombinedER and for what purpose should be specified *a priori* and be at the DSMB's discretion to share with non-DSMB members, especially if the IControlER is known from the literature or other sources. This paper is an additional analysis of that data. The primary objective will be to look at the demographic factors collected to assess whether any are associated with thinking certain pieces of interim result measures, specifically the ICombinedER, IControlER, ACP and UCP, should be shared by the DSMB with non-DSMB members. The secondary objective will be to look at those same demographic factors collected to assess whether any are associated with the individual's perceived usefulness of sharing any of those previous four interim results measures. Evidence from this study could help us see if certain demographic groups appear to have an interest in particular interim result measures being shared and how useful they find that information, as well as promote future research to see why those groups have that interest.

Methods

The survey was designed with 14 questions. The first 6 questions asked respondents the following: 1) the type of interim result measures they thought should be shared at interim by the DSMB with non-DSMB members, and if so, with whom it should be shared and why it should be shared and 2) the usefulness of sharing that information (on a scale from 0 to 10 where 0 is "not useful at all" and 10 is "very useful"). Additional File 1 provides the definitions of these four

interim results measure that were also given in the survey to respondents. The remaining questions were demographic questions asking about the respondent's experience with trials, their self-identified primary profession by training, and work setting.

The survey was administered online and was conducted using FluidSurveys.com. The initial version was pilot tested with 10 health research methods experts at McMaster University, Hamilton, Ontario for content validity and clarity. Nine trial experts responded to the pilot test and provided feedback on the online survey which was used to modify and create the final version. The target group for this survey were trialists or those interested or involved in trials. The Society of Clinical Trial (SCT), with approximately 936 members around February 2015, and the International Society of Clinical Biostatistics (ISCB), with approximately 2200 current and past members around July 2015, were asked for help in distributing our survey on our behalf to their members. Both societies agreed and helped distribute the survey. Multiple emails were sent out on our behalf to remind potential respondents of the survey to get the best response rate following Dillman's principles [8]. Emails with a link to the survey were sent to potential respondents during the year of 2015. This study received Hamilton Integrated Research Ethics Board approval [9].

Data Collection and Analysis

Responses were collected anonymously. WINPEPI 11.65 [10], Excel 2010® and IBM SPSS Statistics 24® were used to analyse the results. We report results in aggregate by count and percentages, and by means and standard deviation where appropriate, with 95% Confidence Intervals (95% CIs). Five demographic factors were used as exploratory variables for both our binary logistic and multiple linear regressions: 1) Number of Trials Respondent Has Been Involved (≤ 15 trials [coded as 0, reference category] **or** > 15 trials [coded as 1]), 2) Number of trials the respondent has been involved with that had a DSMB monitoring the trial (≤ 15 trials [coded as 0, reference category] **or** > 15 trials [coded as 1]), 3) Number of trials the respondent has been involved with that had some form of private industry sponsorship (≤ 15 trials [coded as

0, reference category] or > 15 trials [coded as 1]), 4) Primary Profession by Training (Mathematician/Statistician/Biostatistician or Methodological Scientist/Research Methodologist or Other (reference category)) and 5) Usual Work Setting of Respondents (University or Academic Institution or Private or Contracted Research Company or Other (reference category)). For the primary objective and analysis, four binary logistic regressions were done for sharing each of the interim result measures by the DSMB with non-DSMB members (Outcome: Yes or No for sharing, the ICombinedER, IControlER, ACP and UCP). A Hosmer-Lemeshow test was done to assess the goodness-of-fit of the binary logistic regressions. A second set of four binary logistic regressions was done using an imputed dataset as a sensitivity analysis to assess for the impact of missing data in the original dataset.

For the secondary objective and analysis, four multiple linear regressions were done for the individual's perceived usefulness of sharing each of the four interim result measures by the DSMB with non-DSMB members (Outcome: On a scale from 0 - Not Useful At All to 10 – Very Useful, treated as a continuous outcome, for the IControlER, ICombinedER, ACP and UCP). Respondents regarding their thoughts on the usefulness of sharing each of the interim results would have first answered in the survey that a particular interim result measure (e.g. IControlER) should be shared with a non-DSMB member(s) before answering the question on their perceived usefulness of having that information shared at interim. Assumptions associated with linear regression were assessed by testing for linearity, normality, homoscedasticity, multicollinearity and independence. Bootstrapping with bias corrected and accelerated CIs was used for the analysis to ensure robustness of 95% CIs and significance values, which protects against any violations of the assumptions for normality or homoscedasticity. A second set of four multiple linear regressions was done using an imputed dataset as a sensitivity analysis to assess for the impact of missing data in the original dataset. Multiple imputation (MI) method [11-13] was used for data imputation using IBM SPSS Statistics 24®. The linear and binary logistic regressions and the sensitivity analyses were also done using IBM SPSS Statistics 24®.

Results

Three-hundred and seventy-one responses (202 complete responses, 169 partial or incomplete responses) were received; response rate of 12% (371/3136). Four reminder emails were sent, 3 to SCT members and 1 to ISCB members, as was allowed.

Demographics

Table 1 summarizes the five demographic factors of the respondents. About 35.3% of the respondents have been involved in more than 15 trials and 42.0% of the respondents identified being a mathematician/statistician/biostatistician as their primary profession by training.

Responses about sharing the IControlER, ICombinedER, ACP and UCP and perceived usefulness in sharing

Table 2 shows the results based on the responses regarding what interim result measure should be shared by the DSMB of a trial with non-DSMB members and their perceived usefulness of sharing a certain interim result measure if they indicated that interim result measure should be shared. The only interim results measure the majority of respondents thought should be shared with non-DSMB members by the DSMB was the ICombinedER (168/262; 64.1% [95% CI: 58.0% to 69.9%]). For those 168 respondents that thought the ICombinedER should be shared, 146 answered the question regarding the usefulness of sharing that information with non-DSMB members with a mean of 6.97 [95% CI: 6.62 to 7.31]. For all other interim measures, the majority of respondents thought it should not be shared (See Table 2 for more details).

Demographic factors associated with sharing the IControlER, ICombinedER, ACP and UCP

Table 3 summarizes the results of the binary logistic regression of potential demographic factors associated with sharing ICombinedER, IControlER, ACP and UCP for our primary analysis before and after the sensitivity analysis. One demographic factor before the sensitivity analysis, the primary profession by training, was significantly associated with not sharing the ICombinedER [Coded as No, do not share the ICombinedER (0), Yes, share the ICombinedER

(1)], with an odds ratio of 0.25 [95% CI: 0.07, 0.89]; $p = 0.019$, for being a Mathematician/Statistician/Biostatistician and an odds ratio 0.50 [95% CI: 0.10, 2.43]; $p = 0.357$, for being a Methodological Scientist/Research Methodologist when compared to Other (reference category). However, this finding was not corroborated with the sensitivity analysis suggestive that this analysis was sensitive to missing data.

The respondent having been involved with more than 15 trials that had some form of private industry sponsorship was significantly associated with not sharing the IControlER [Coded as Yes, share the IControlER (0), No, do not share the IControlER (1)], with an odds ratio of 2.92 [95% CI: 1.31, 6.52]; $p = 0.012$, when compared to baseline. This finding was corroborated with the sensitivity analysis suggestive that this analysis was not sensitive to missing data.

None of the demographic factors were significantly associated with sharing the ACP both before and after the sensitivity analysis suggestive that this analysis was not sensitive to missing data.

One variable with the sensitivity analysis, the primary profession by training, was significantly associated with sharing the UCP [Coded as Yes, share the UCP (0), No, do not share UCP (1)], with an odds ratio of 0.66 [95% CI: 0.29, 1.51]; $p = 0.326$ for being a Mathematician/Statistician/Biostatistician and odds ratio of 0.26 [95% CI: 0.074, 0.94]; $p = 0.039$ for being a Methodological Scientist/Research Methodologist when compared to Other (reference category). This association was not shown before doing the MI sensitivity analysis, suggestive that this analysis was sensitive to and impacted by missing data.

Demographic factors associated with the perceived usefulness in sharing the IControlER, ICombinedER, ACP and UCP

Table 4 summarizes the results of the linear regression of potential factors associated with the perceived usefulness with sharing ICombinedER, IControlER, ACP and UCP for our secondary analysis. A respondent having been involved with more than 15 trials that had some form of private industry sponsorship was the only significant demographic factor [$b = 2.35$ (95%

CI: 0.45, 4.05), $p=0.017$] associated with the perceived usefulness with sharing the ACP with non-DSMB member by the DSMB. Therefore, for this particular factor which was dichotomized, a person having been involved with more than 15 trials that had some form of private sponsorship would suggest an increase of 2.35 points in regards to their perceived usefulness in sharing the ACP on a scale from 0 to 10 where 0 is “not useful at all” and 10 is “very useful”. This finding and the direction of the effect was corroborated with the sensitivity analysis suggesting that this analysis was not sensitive to missing data.

None of the other variables were associated with the perceived usefulness in sharing the ICombinedER, IControlER, ACP or UCP with non-DSMB members by the DSMB which was also corroborated with the sensitivity analysis.

Discussion

Key findings

Our results empirically showed that there may be some key demographic factors of trialists or those interested in trials that are associated with sharing certain pieces of interim results with non-DSMB members by the DSMB. A respondent having been involved with more than 15 trials that had some form of private industry sponsorship was significantly associated with not sharing the IControlER. The relationship with the outcome of interest was a positive one for this demographic factor since we coded the outcome for this analysis as 0 for sharing the IControlER and 1 for not sharing the IControlER. So, if an individual had been involved with more than 15 trials that has some form of private industry sponsorship, their odds for endorsing **NOT** to share the IControlER would be 2.92 times higher when compared to baseline (which was being involved with ≤ 15 trials that had some form of private industry sponsorship). This finding was not sensitive to missing data as it was corroborated by the sensitivity analysis done suggesting that more confidence can be had with this association. It is possible those with more experience with trials with private industry sponsorship (i.e. >15 trials), understand a concept that was found when analysing responses to this survey and that is the IControlER can be

directly unmasking of interim effects between treatment groups because in many cases, the SC or the sponsor have access to interim pooled data. Thus, being given the IControlER in this case would allow them to back calculate the event rate for the intervention group. Those with more trial experience with private industry sponsorship may have had more time to come across and be introduced to this idea than those with less experience with trials that had private industry sponsorship.

The primary profession by training of an individual (Mathematician/Statistician/Biostatistician or Methodological Scientist/Research Methodologist or Other, which could have been a combination of other professionals involved in trials, e.g. Physician, Epidemiologist, Analyst etc.) was significantly associated with not sharing the ICombinedER. The relationship with the outcome of interest was a negative one for this demographic factor since we coded the outcome for this analysis as 0 for not sharing the ICombinedER and 1 for sharing the ICombinedER. So, if an individual was of a statistics or mathematical oriented profession, their odds of endorsing the sharing of the ICombinedER with non-DSMB members would be 0.25 times lower than the reference (Other category). Additionally, if an individual was a Research Methodologist, their odds of endorsing the sharing of the sharing of the ICombinedER with non-DSMB member by the DSMB would be 0.50 times lower than the reference (Other category). However, this finding was sensitive to the missing data we had for this analysis as the sensitivity analysis did not corroborate this result and did not find any demographic factors significant. Caution should thus be exercised when interpreting the validity of this demographic factor's association with endorsing the sharing of the ICombinedER and will require more validation.

None of the demographic factors we assessed demonstrated association with endorsing the sharing the ACP and was corroborated by the sensitivity analysis done suggesting that more confidence can be had in this result. This does not mean that there are not any factors associated with sharing this interim result measure; it is just that we may not have captured the demographic factor with the survey.

The primary profession by training, with the sensitivity analysis, was significantly associated with endorsing the sharing the UCP. The relationship with the outcome of interest was a negative one for this demographic factor since we coded the outcome for this analysis as 0 for sharing the UCP and 1 for not sharing the UCP. So if an individual was of a statistics or mathematical oriented profession, their odds of **NOT** endorsing the sharing of the UCP with non-DSMB members would be 0.66 times lower than baseline (Other). Additionally, if an individual was a Methodological Scientist/Research Methodologist, their odds of **NOT** endorsing the sharing of the UPC would be 0.26 times lower than baseline (Other). This finding was found in only in the sensitivity analysis and none of the demographic variables showed to be significant when the regression was done with the original data. This demonstrates that this analysis was sensitive to missing data. Caution should thus be exercised when interpreting the validity of this demographic factor's association with endorsing the sharing of the UCP and will require more validation.

Our secondary analysis demonstrated once again that a respondent having been involved with more than 15 trials that had some form of private industry sponsorship had a significant association; in this case it was significantly associated with the perceived usefulness with sharing the ACP by the DSMB with non-DSMB members. The relationship was a positive one for this demographic factor where a person having been involved with more than 15 trials that had some form of private sponsorship would suggest an increase of 2.35 points in the perceived usefulness in sharing the ACP. This finding was not sensitive to missing data as it was corroborated by the sensitivity analysis done suggesting that more confidence can be had with this association. It is possible those with more experience with trials with private industry sponsorship (i.e. >15 trials), understand a concept that was found when analysing responses to our survey, that the ACP is extremely informative of the presence or absence of a relative treatment effect between groups within a trial and hence it is partially unmasking to those responsible for the conduct of the trial.

Findings compared to similar studies

This study is unique in that it empirically evaluates key demographic factors of those involved with trials and whether these factors have any association with sharing four main forms of interim results (ICombinedER, IControlER, ACP and UCP) and the perceived usefulness in sharing these interim results with non-DSMB member by the DSMB. This study is an extension to a survey analysis we did that evaluated whether these same four main forms of interim result measures should be shared at interim, with whom, the perceived usefulness of sharing that result measure, and why it should be shared, by soliciting the views of those involved or interested in trials. In that survey analysis, as part of a larger study to investigate what should be shared by the DSMB with non-DSMB members, we found evidence suggesting that the IControlER, the ACP, and the UCP should not be shared with non-DSMB members by the DSMB and that the ICombinedER could be shared when planned to do so in *a priori* manner as indicated in the protocol or the DSMB charter. However, the DSMBs should use discretion when sharing the ICombinedER if the IControlER is well known in the literature or from another source as then it is unmasking of the event rate in the other group. A scenario-based survey we also did asked trial experts how they interpreted the ICombinedER, ACP and UCP when shared in a hypothetical trial scenario [14]. We concluded from that survey that knowledge of these three interim results should not be shared by DSMB with non-DSMB members at interim as they may mislead or unmask interim results, potentially introducing trial bias [14].

Six other surveys dating from 1999 to 2011 [15-18] did not specifically focus on the issue of the DSMB sharing interim results, and were very limited in regards to the amount of evidence collected regarding what information should be shared by the DSMB, with whom and for what reason. None of these surveys did regression analyses to see if demographic factors were associated with sharing the four main forms of interim result measures we have looked at in this study or the perceived usefulness in sharing those interim result measures.

Key Limitations

One limitation with our study is that we had a low response rate for our survey despite strong efforts to solicit and gather responses. Thus, we do not have a definitive way of knowing how our non-respondents were different from those who responded to our survey. However, we do know that the largest proportion of our respondents regarding their primary profession by training self-identified as a Mathematician/Statistician/Biostatistician and about 54% of our respondents had experience with at least one trial. This information gathered was reassuring as many of our respondents were likely aware of what interim trial result measures were. Additionally, our survey had a lot of missing data. We received 371 responses where 202 were complete responses, meaning those 202 respondents filled all the questions to our survey. However, 169 were partially complete or incomplete responses meaning that questions were either skipped or left blank. Particularly with our demographic information, we had 40% or more missing information from respondents. Answers from questions regarding how respondents viewed sharing four main forms of interim result measures had less missing data, most likely because these were questions asked first in the survey. However, to compensate for this missing data in this study, we did a sensitivity analysis using MI which is the most robust form of imputation for missing data including survey data [11-13]. We compared the regression results with the dataset we originally had verses the dataset with MI to see if the analysis was sensitivity to data that was missing. If the results of the same analysis were different with the dataset we originally had verses the dataset with imputation, we exercised caution with interpreting the results. We also used bootstrapping with bias corrected and accelerated CIs for our regressions with the dataset we originally had to ensure robustness of 95% CIs and significance values found.

Implications for Practice

Two robust analyses and findings were generated from this study as they were corroborated in the sensitive analysis; 1) An individual that has been involved with more than 15 trials that

had some form of private industry sponsorship demonstrated a significant positive association for NOT sharing the IControlER and 2) An individual that has been involved with more than 15 trials that had some form of private industry sponsorship demonstrated a significant positive association with the perceived usefulness with sharing the ACP by the DSMB with non-DSMB members. The commonality between the two findings is that an individual who has been involved with more than 15 trials that had some form of private industry sponsorship is the significant demographic factor. This finding warrants more investigation into this subgroup of trialists who have experience with trials with private industry sponsorship. Hypothetically speaking, we could ask the following question based on this finding: Does having more experience with private industry sponsored trials provide trialists with a better understanding about the amount of information the IControlER and ACP provides about treatment group effects and relative group effects respectively, at interim? More knowledge of their experience can provide insight into good interim trial management practices, especially if this subgroup is already doing something preventatively to protect from trial bias.

Conclusion

From this survey, we have done several regression analyses that have provided empirical evidence to indicate that the more trials an individual has been involved with (>15 trials) that had some form of private industry sponsorship is a potential factor associated with NOT sharing the IControlER and the perceived usefulness with sharing the ACP. This demographic factor should be further evaluated to see if this subgroup of trialists has insight into interim trial management practices that protect from trial bias. No demographic factor seemed to be associated with sharing the ACP at interim, which was corroborated with the sensitivity analysis. Though some other demographic factors were found to be associated sharing the ICombinedER and the UCP, they were sensitive to missing data upon our MI sensitive analysis, thus caution should be exercised when interpreting the validity of those results and will require more validation.

List of abbreviation

(ACP) Adaptive Conditional Power, (DSMB) Data Safety Monitoring Board, (HiREB) Hamilton Integrated Research Ethics Board, (ICombinedER) Interim Combined Event Rate, (IControlER) Interim Control Event Rate, (ISCB) International Society of Clinical Biostatistics, (MI) Multiple Imputation, (PI) Principle Investigator, (SC) Steering Committee, (SCT) Society of Clinical Trials, (UCP) Unconditional Conditional Power

Declarations

Ethical Approval and Consent to Participate

Ethics approval for this study was granted by the Hamilton Integrated Research Ethics Board (HiREB). Survey participants were informed before filling out the survey that this survey is anonymous and that their responses will never be linked to their identity. Moreover, they were also informed before filling out the survey that responses will not be shared with anyone outside of our study group, and only aggregated data will be published. By starting the survey they were informed that they are consenting to participate in this survey.

Consent to publish

Not applicable

Availability of supporting data

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

VBD was involved in all aspect of this study from study design and conception, acquisition of information, survey design and construction, information synthesis and analysis and wrote the manuscript. LM, JP and NB were substantially involved in supervision of study design and

critical revisions to this paper. LT was substantially involved in primary supervision, study design and conception and critical revisions to this paper. All authors read and approved the final manuscript.

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Authors' information

Not applicable

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Additional files

Additional File 1: Definitions of interim result measures

File format: pdf

Table 1: Summary of Demographic Factors

File format: pdf

Table 2: Summary of respondents' thoughts on sharing the IControlER, ICombinedER, ACP and UCP and its usefulness

File format: pdf

Table 3: Binary logistic regressions of variables associated with sharing ICombinedER, IControlER, ACP or UCP with non-DSMB members by the DSMB

File format: pdf

Table 4: Multiple linear regressions of variables associated with the usefulness with sharing the ICombinedER, IControlER, ACP or UCP

File format: pdf

Table and Figure Title and Legend

Additional File 1 Title:

Additional File 1: Definitions of interim result measures

Additional File 1 Legend:

[1] V. Borg Debono, L. Mbuagbaw, J. Paul, N. Buckley, L. Thabane, Sharing some interim data in trial monitoring can mislead or unmask trial investigators: A scenario-based survey of trial experts, *Contemporary Clinical Trials Communications* 7 (2017) 81-85.

Table 1 Title:

Table 1: Summary of Demographic Factors

Table 1 Legend:

^a Total of 203 responses to this question, percentages are based on a total of 371 respondents to the survey. ^A Unknown because 168 respondents did not answer this question. ^b Total of 197 responses to this question, percentages are based on a total of 371 respondents to the survey. ^B Unknown because 174 respondents did not answer this question. ^c Total of 201 responses to this question, percentages are based on a total of 371 respondents to the survey. ^C Unknown because 170 respondents did not answer this question. ^d Total of 203 responses to this question, percentages are based on a total of 371 respondents to the survey. ^D Unknown because 168 respondents did not answer this question. ^e Total of 202 responses to this question. ^E Unknown because 169 respondents did not answer this question.

Table 2 Title:

Table 2: Summary of respondents' thoughts on sharing the IControlER, ICombinedER, ACP and UCP and its usefulness

Table 2 Legend:

^A Respondent had to select any of the following parties for a Yes categorization: A. The Sponsor, B. The Steering Committee, C. The Investigator(s), D. The Funder(s), or E. Other, Please Specify), ^B Respondent had to select F. None of the Above for a No categorization

Table 3 Title:

Table 3: Binary logistic regressions of variables associated with sharing ICombinedER, IControlER, ACP or UCP with non-DSMB members by the DSMB

Table 3 Legend:

^A CIs and standard errors based on 1000 bootstrap samples with 95% bias corrected and accelerated CIs reported

^B Results based on pooled results from sensitivity analysis with multiple imputation. The Hosmer Lemeshow Test is not provided for pooled results analysis.

ACP (Adaptive Conditional Power), D.F. (Degrees of Freedom), CI (Confidence Interval), DSMB (Data Safety Monitoring Board), ICombinedER (Interim Combined Event Rate), IControlER (Interim Control Event Rate), UCP (Unconditional Conditional Power), MI (Multiple Imputation)

Table 4 Title:

Table 4: Multiple linear regressions of variables associated with the perceived usefulness with sharing the ICombinedER, IControlER, ACP or UCP

Table 4 Legend:

^A CIs and standard errors based on 1000 bootstrap samples with 95% bias corrected and accelerated CIs reported in brackets.

^B CIs and standard errors based on 997 bootstrap samples with 95% bias corrected and accelerated CIs reported in brackets.

^C CIs and standard errors based on 995 bootstrap samples with 95% bias corrected and accelerated CIs reported in brackets;

Acronyms: ACP (Adaptive Conditional Power), DSMB (Data Safety Monitoring Board) CI (Confidence Interval), ICombinedER (Interim Combined Event Rate), IControlER (Interim Control Event Rate), UCP (Unconditional Conditional Power)

Table 1: Summary of Demographic Factors	
Number of Trials Respondent Has Been Involved ^a	
Number of Trials	n (%)
≤ 15 trials	72 (19.4)
> 15 trials	131 (35.3)
Unknown ^A	168 (45.3)
Number of trials the respondent has been involved with that had a DSMB monitoring the trial ^b	
Number of Trials	n (%)
≤ 15 trials	109 (29.4)
>15 trials	88 (23.7)
Unknown ^B	174 (46.9)
Number of trials the respondent has been involved with that had some form of private industry sponsorship ^c	
Number of Trials	n (%)
≤ 15 trials	137 (36.9)
> 15 trials	64 (17.3)
Unknown ^C	170 (45.8)
Primary Profession by Training ^d	
Main Profession	n (%)
Mathematician/Statistician/Biostatistician	156 (42.0)
Methodological Scientist/Research Methodologist	21 (5.7)
Other	26 (7.0)
Unknown ^D	168 (45.3)
Usual Work Setting of Respondents ^e	
Place of Work	n (%)
University or Academic Institution	123 (33.2)
Private or Contracted Research Company	28 (7.5)
Other	51 (13.7)
Unknown ^E	169 (46.0)
^a Total of 203 responses to this question, percentages are based on a total of 371 respondents to the survey. ^A Unknown because 168 respondents did not answer this question. ^b Total of 197 responses to this question, percentages are based on a total of 371 respondents to the survey. ^B Unknown because 174 respondents did not answer this question. ^c Total of 201 responses to this question, percentages are based on a total of 371 respondents to the survey. ^C Unknown because 170 respondents did not answer this question. ^d Total of 203 responses to this question, percentages are based on a total of 371 respondents to the survey. ^D Unknown because 168 respondents did not answer this question. ^e Total of 202 responses to this question. ^E Unknown because 169 respondents did not answer this question.	

Table 2: Summary of respondents' thoughts on sharing the IControlER, ICombinedER, ACP and UCP and its usefulness	
Interim Combined Event Rate	
1. During an ongoing Randomized Controlled Trial (RCT), do you think that the Data Safety Monitoring Board (DSMB) for an RCT should share the Interim Combined Event Rate with ANY of the following parties?	
Response	Results [n/N; % (95% CI)]
Yes ^A	168/262; 64.1% (58.0% to 69.9%)
No ^B	94/262; 35.9% (30.1% to 41.7%)
2. How useful is it to share the Interim Combined Event Rates at interim? (On a scale from 0 to 10 where 0 is Not Useful at All and 10 is Very Useful) <i>(This question was answered only by those who were categorized as "Yes" to 1. (above))</i>	
Number of responses to question	Results [Mean (95% CI)]
146	6.97 (6.62 to 7.31)
Interim Control Event Rate	
3. During an ongoing Randomized Controlled Trial (RCT), do you think that the Data Safety Monitoring Board (DSMB) for an RCT should share the Interim Control Event Rate with ANY of the following parties?	
Response	Results [n/N; % (95% CI)]
Yes ^A	88/237; 37.1% (31.0% to 43.3%)
No ^B	149/237; 62.9% (56.7% to 69.0%)
4. How useful is it to share the Interim Control Event Rates at interim? (On a scale from 0 to 10 where 0 is Not Useful at All and 10 is Very Useful) <i>(This question was answered only by those who were categorized as "Yes" to 3. (above))</i>	
Number of responses to question	Results [Mean (95% CI)]
72	7.03 (6.55 to 7.50)
Adaptive Conditional Power	
5. During an ongoing Randomized Controlled Trial (RCT), do you think that the Data Safety Monitoring Board (DSMB) for an RCT should share the Adaptive Conditional Power with ANY of the following parties?	
Response	Results [n/N ; % (95% CI)]
Yes ^A	80/224; 35.7% (29.4% to 42.0%)
No ^B	144/224; 64.3% (58.0% to 70.6%)
6. How useful is it to share the Adaptive Conditional Power at interim? (On a scale from 0 to 10 where 0 is Not Useful at All and 10 is Very Useful) <i>(This question was answered only by those who were categorized as "Yes" to 5. (above))</i>	
Number of responses to question	Results [Mean (95% CI)]
64	6.91 (95% CI: 6.42 to 7.39)
Unconditional Conditional Power	
7. During an ongoing Randomized Controlled Trial (RCT), do you think that the Data Safety Monitoring Board (DSMB) for an RCT should share the Unconditional Conditional Power with ANY of the following parties?	
Response	Results [n/N ; % (95% CI)]
Yes ^A	82/208; 39.4% (32.8% to 46.1%)
No ^B	126/208; 60.6% (53.9% to 67.2%)
8. How useful is it to share the Unconditional Conditional Power at interim? (On a scale from 0 to 10 where 0 is Not Useful at All and 10 is Very Useful) <i>This question was answered only by those who were categorized as "Yes" to 7. (above))</i>	
Number of responses to question	Results [Mean (95% CI)]
66	6.64 (6.08 to 7.20)
^A Respondent had to select any of the following parties for a Yes categorization: A. The Sponsor, B. The Steering Committee, C. The Investigator(s), D. The Funder(s), or E. Other, Please Specify), ^B Respondent had to select F. None of the Above for a No categorization	

Table 3: Binary logistic regressions of variables associated with sharing ICombinedER, IControlER, ACP or UCP with non-DSMB members by the DSMB		
ICombinedER^A Hosmer and Lemeshow Test ($\chi^2 = 1.94$, D.F = 6, p = 0.93); [Coded as No, do not share the ICombinedER (0), Yes, share the ICombinedER (1)] n=195		MI Sensitivity Analysis for ICombinedER^B n=264
	Odds Ratio (95% CI); p-value	Odds Ratio (95% CI); p-value
The respondent has been involved with more than 15 trials	0.77 (0.31, 1.89); 0.558	0.74 (0.31, 1.75); 0.484
The respondent has been involved with more than 15 trials that had a DSMB monitoring the trial	0.82 (0.36, 1.84); 0.632	0.73 (0.35, 1.55); 0.414
The respondent has been involved with more than 15 trials that had some form of private industry sponsorship	1.29 (0.61, 2.76); 0.534	1.32 (0.56, 3.10); 0.514
Primary Profession by Training		
• Other (Reference Category)	1	1
• Mathematician/Statistician/Biostatistician	0.25 (0.07, 0.89); 0.019	0.40 (0.13, 1.29); 0.123
• Methodological Scientist/Research Methodologist	0.50 (0.10, 2.43); 0.357	0.84 (0.20, 3.57); 0.813
Usual Work Setting of Respondents		
• Other (Reference Category)	1	1
• University or Academic Institution	0.94 (0.44, 2.02); 0.869	0.96 (0.49, 1.85); 0.892
• Private/Contracted Research Company	1.11 (0.39, 3.17); 0.836	1.13 (0.38, 3.37); 0.820
IControlER^A Hosmer and Lemeshow Test ($\chi^2 = 4.526$, D.F = 8, p = .807); [Coded as Yes, share the IControlER (0), No, do not share the IControlER (1)] n=195		MI Sensitivity Analysis for IControlER^B n=264
	Odds Ratio (95% CI); p-value	Odds Ratio (95% CI); p-value
The respondent has been involved with more than 15 trials	0.87 (0.36, 2.12); 0.774	0.78 (0.34, 1.80); 0.551
The respondent has been involved with more than 15 trials that had a DSMB monitoring the trial	0.82 (0.35, 1.90); 0.674	0.94 (0.40, 2.19); 0.875
The respondent has been involved with more than 15 trials that had some form of private industry sponsorship	2.92 (1.31, 6.52); 0.012	2.79 (1.11, 7.00); 0.031
Primary Profession by Training		
• Other (Reference Category)	1	1
• Mathematician/Statistician/Biostatistician	0.70 (0.26, 1.88); 0.505	0.68 (0.26, 1.80); 0.437
• Methodological Scientist/Research Methodologist	0.38 (0.11, 1.34); 0.154	0.42 (0.13, 1.36); 0.146
Usual Work Setting of Respondents		
• Other (Reference Category)	1	1
• University or Academic Institution	0.10 (0.47, 2.12); 0.993	0.99 (0.49, 1.99); 0.977
• Private/Contracted Research Company	1.06 (0.36, 3.10); 0.900	1.28 (0.39, 4.19); 0.672
ACP^A Hosmer and Lemeshow Test ($\chi^2 = 2.39$, D.F = 7, p = 0.94); [Coded as Yes, share the ACP (0), No, do not share the ACP (1)] n=196		MI Sensitivity Analysis for ACP^B n=264
	Odds Ratio (95% CI); p-value	Odds Ratio (95% CI); p-value
The respondent has been involved with more than 15 trials	1.08 (0.45, 2.59); 0.868	1.06 (0.46, 2.45); 0.883
The respondent has been involved with more than 15 trials that had a DSMB monitoring the trial	1.73 (0.75, 4.00); 0.237	1.75 (0.48, 6.41); 0.362
The respondent has been involved with more than 15 trials that had some form of private industry sponsorship	1.48 (0.66, 3.32); 0.358	1.41 (0.58, 3.46); 0.438
Primary Profession by Training		
• Other (Reference Category)	1	1
• Mathematician/Statistician/Biostatistician	0.59 (0.22, 1.62); 0.305	0.67 (0.27, 1.65); 0.375
• Methodological Scientist/Research Methodologist	0.85 (0.23, 3.24); 0.830	0.85 (0.19, 3.69); 0.819
Usual Work Setting of Respondents		
• Other (Reference Category)	1	1
• University or Academic Institution	1.19 (0.55, 2.60); 0.694	0.93 (0.43, 1.98); 0.838
• Private/Contracted Research Company	0.50 (0.18, 1.39); 0.189	0.51 (0.19, 1.39); 0.186
UCP^A Hosmer and Lemeshow Test ($\chi^2 = 2.664$, D.F = 7, p = .914); [Coded as Yes, share the UCP (0), No, do not share UCP (1)] n=192		MI Sensitivity Analysis for UCP^B n=264
	Odds Ratio (95% CI); p-value	Odds Ratio (95% CI); p-value
The respondent has been involved with more than 15 trials	1.65 (0.69, 3.92); p=0.266	1.51 (0.63, 3.63); 0.350
The respondent has been involved with more than 15 trials that had a DSMB monitoring the trial	1.04 (0.46, 2.35); 0.937	1.01 (0.31, 3.32); 0.987
The respondent has been involved with more than 15 trials that had some form of private industry sponsorship	1.11 (0.52, 2.39); 0.798	1.06 (0.53, 2.15); 0.863
Primary Profession by Training		
• Other (Reference Category)	1	1
• Mathematician/Statistician/Biostatistician	0.60 (0.22, 1.62); 0.341	0.66 (0.29, 1.51); 0.326
• Methodological Scientist/Research Methodologist	0.28 (0.08, 0.99); 0.052	0.26 (0.074, 0.94); 0.039
Usual Work Setting of Respondents		
• Other (Reference Category)	1	1
• University or Academic Institution	1.28 (0.60, 2.71); 0.526	1.00 (0.43, 2.31); 0.995
• Private/Contracted Research Company	0.67 (0.25, 1.79); 0.416	0.68 (0.22, 2.09); 0.481
^A CIs and standard errors based on 1000 bootstrap samples with 95% bias corrected and accelerated CIs reported		
^B Results based on pooled results from sensitivity analysis with multiple imputation. The Hosmer Lemeshow Test is not provided for pooled results analysis.		
ACP (Adaptive Conditional Power), D.F. (Degrees of Freedom), CI (Confidence Interval), DSMB (Data Safety Monitoring Board), ICombinedER (Interim Combined Event Rate), IControlER (Interim Control Event Rate), UCP (Unconditional Conditional Power), MI (Multiple Imputation)		

Table 4: Multiple linear regressions of variables associated with the perceived usefulness with sharing the ICombinedER, IControlER, ACP or UCP	
	Estimated Coefficient (95% CI); p-value
ICombinedER^A (R ² = 0.11, p=0.11)	
The respondent has been involved with more than 15 trials	0.11 (-1.37, 1.42); 0.860
The respondent has been involved with more than 15 trials that had a DSMB monitoring the trial	0.69 (-0.29, 1.67); 0.230
The respondent has been involved with more than 15 trials that had some form of private industry sponsorship	-0.35 (-1.42, 0.77); 0.501
Primary Profession by Training	
• Other (Reference Category)	
• Mathematician/Statistician/Biostatistician	0.87 (-0.17, 2.06); 0.127
• Methodological Scientist/Research Methodologist	1.03 (-0.47, 2.47); 0.159
Usual Work Setting of Respondents	
• Other (Reference Category)	
• University or Academic Institution	-0.70 (-1.83, 0.45); 0.271
• Private/Contracted Research Company	-1.03 (-2.40, 0.40); 0.139
IControlER^B (R ² = 0.092, p= 0.64)	
The respondent has been involved with more than 15 trials	0.88 (-0.87, 2.60); 0.282
The respondent has been involved with more than 15 trials that had a DSMB monitoring the trial	-0.75 (-2.44, 0.84); 0.356
The respondent has been involved with more than 15 trials that had some form of private industry sponsorship	0.62 (-0.89, 1.78); 0.441
Primary Profession by Training	
• Other (Reference Category)	
• Mathematician/Statistician/Biostatistician	1.44 (-1.88, 5.67); 0.329
• Methodological Scientist/Research Methodologist	0.96 (-1.91, 4.64); 0.534
Usual Work Setting of Respondents	
• Other (Reference Category)	
• University or Academic Institution	0.27 (-1.72, 2.09); 0.762
• Private/Contracted Research Company	0.17 (-1.89, 2.61); 0.871
ACP^C (R ² =0.23, p=0.11)	
The respondent has been involved with more than 15 trials	-0.68 (-2.18, 0.67); 0.411
The respondent has been involved with more than 15 trials that had a DSMB monitoring the trial	-0.53 (-2.39, 1.35); 0.515
The respondent has been involved with more than 15 trials that had some form of private industry sponsorship	2.35 (0.45, 4.05); 0.017
Primary Profession by Training	
• Other (Reference Category)	
• Mathematician/Statistician/Biostatistician	0.52 (-1.35, 2.99); 0.614
• Methodological Scientist/Research Methodologist	1.64 (-0.80, 5.10); 0.279
Usual Work Setting of Respondents	
• Other (Reference Category)	
• University or Academic Institution	1.21 (-1.07, 4.32); 0.335
• Private/Contracted Research Company	0.44 (-2.07, 3.58); 0.779
UCP^B (R ² =0.051, p=0.90)	
The respondent has been involved with more than 15 trials	0.10 (-1.78, 2.02); 0.906
The respondent has been involved with more than 15 trials that had a DSMB monitoring the trial	-0.32 (-2.10, 1.48); 0.738
The respondent has been involved with more than 15 trials that had some form of private industry sponsorship	0.22 (-1.58, 1.88); 0.780
Primary Profession by Training	
• Other (Reference Category)	
• Mathematician/Statistician/Biostatistician	0.060 (-2.28, 2.29); 0.955
• Methodological Scientist/Research Methodologist	1.45 (-1.04, 4.26); 0.256
Usual Work Setting of Respondents	
• Other (Reference Category)	
• University or Academic Institution	1.00 (-1.21, 3.20); 0.405
• Private/Contracted Research Company	1.02 (-2.06, 4.34); 0.508
^A CIs and standard errors based on 1000 bootstrap samples with 95% bias corrected and accelerated CIs reported in brackets.	
^B CIs and standard errors based on 997 bootstrap samples with 95% bias corrected and accelerated CIs reported in brackets.	
^C CIs and standard errors based on 995 bootstrap samples with 95% bias corrected and accelerated CIs reported in brackets;	
Acronyms: ACP (Adaptive Conditional Power), DSMB (Data Safety Monitoring Board) CI (Confidence Interval), ICombinedER (Interim Combined Event Rate), IControlER (Interim Control Event Rate), UCP (Unconditional Conditional Power)	

Additional File 1: Definitions of interim results measures

Interim combined event rate (ICombinedER)	<p><i>“The total number of events observed at some planned interim point into the trial divided by the total number of participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial or after enrolling a certain number of participants).</i></p> <p><i>Example:</i></p> <ul style="list-style-type: none"> • <i>Total # of Deaths in both the placebo group and new intervention group, six months from the start of the trial = 80</i> • <i>Total # of Participants in both the placebo group and the new intervention group, six months from the start of the trial = 700</i> • <i>Calculation: $80/700 = 0.114$ or 11.4%</i> • <i>Therefore the Interim Combined Event Rate at the trial's interim analysis, six months from the start of the trial, is 11.4%” [1]</i>
Interim control event rate (IControlER)	<p>The number of events observed among control participants at some planned interim point into the trial divided by number of control participants admitted at that same planned interim point (e.g. a planned interim point can be six months from the start of the trial)</p> <p><i>Example:</i></p> <ul style="list-style-type: none"> • <i>Total # of Deaths in the placebo group, six months from the start of the trial = 15</i> • <i>Total # of Participants in the placebo group, six months from the start of the trial = 250</i> • <i>Calculation: $15/250 = 0.06$ or 6%</i> • <i>Therefore the Interim Control Event Rate at the trial's interim analysis, six months from the start of the trial, is 6%</i>

Adaptive conditional power (ACP)	<p><i>“The probability of rejecting the null hypothesis of no effect by the end of the trial (i.e. finding a statistically significant effect in favour of the intervention), at some predetermined interim point in the trial when the adaptive conditional power is scheduled to be calculated. The assumption made is that the observed interim effect (i.e. relative risk reduction) in the trial will remain the same until the end of the trial.</i></p> <p>Example statement:</p> <p><i>Given the interim data (data collected 2 years into the trial that is planned to last for 3 years), and assuming the observed interim effect (i.e. relative risk reduction) at the two year point to be the true effect for the remainder of the trial, the probability of rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 60%. The following pieces of information are used to calculate Adaptive Conditional Power at trial interim:</i></p> <ul style="list-style-type: none"> • <i>Control event rate and experimental event rate</i> • <i>Information Fraction; a ratio of the planned sample size and the number of patients recruited in trial at the interim analysis</i> • <i>Z score and B value at interim</i> • <i>Drift parameter” [1]</i>
Unconditional conditional power (UCP)	<p><i>“The <u>probability of correctly</u> 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 when indeed the alternative hypothesis is true, at some interim point in the trial.</i></p> <p><i>The following pieces of information are used to calculate Unconditional Conditional Power at interim:</i></p> <ol style="list-style-type: none"> 1. <i>The <u>hypothesized treatment effect at the design stage</u> (i.e. relative risk reduction) of the trial, assuming the hypothesized treatment effect at the design stage to be true and correct for the remainder of the trial;</i> 2. <i>The <u>sample size calculated at the design stage</u> for the trial AND;</i> 3. <i>The <u>combined event rate calculated at the trial’s interim</u>, assuming this rate to be true for the remainder of the trial.</i> <p>Example statement:</p> <p><i>Given the interim combined event rate and assuming the treatment effect (i.e. relative risk reduction) hypothesized at the design stage of the trial to be true for the remainder of</i></p>

	<p><i>the trial, the probability of correctly rejecting the null hypothesis of no effect (i.e. finding a statistically significant effect in favour of the intervention) at the end of the trial is 89%.” [1]</i></p>
<p>[1] V. Borg Debono, L. Mbuagbaw, J. Paul, N. Buckley, L. Thabane, Sharing some interim data in trial monitoring can mislead or unmask trial investigators: A scenario-based survey of trial experts, Contemporary Clinical Trials Communications 7 (2017) 81-85.</p>	

CHAPTER 6

CONCLUSION

The final chapter of this thesis will encapsulate the findings by first answering the questions in Chapter 1 that steered this research. Afterwards, we will summarise the implications and impact of the results generated from this thesis on interim result sharing practices by the DSMB with non-DSMB members.

Research questions addressed

1. What does the literature state about the current views and opinions on the issue of the DSMB sharing interim results during the conduct of a clinical trial, particularly phase III trials, with non-DSMB members, and what interim results should the DSMB share, if anything at all, with whom, and under what circumstances?

The findings from our narrative review inform trialists and those who put in place trial policies and guidelines, that there are mixed views on the DSMB sharing interim results with non-DSMB members [1]. Two categories of literature dominate (Category 1 and 2) but do not comprise the majority of the literature as separate groups. Category 1 is literature that is against sharing interim results and indicates that it should remain confidential with the DSMB. Category 2 shares the same sentiment as Category 1 but additionally acknowledges exceptions in that there are circumstances that may warrant the DSMB to share interim results with certain non-DSMB members. The exceptions include 11 possible circumstances as described in Table 2 of Chapter 2. What is shared with these various types of non-DSMB members depends on what the situation calls for and should be assessed by the DSMB using their expertise to balance risks with the potential benefits regarding participant safety and trial validity and integrity. Because of the limitations of the evidence found, collecting more empirical evidence through a survey of the clinical trial community, focused specifically on the issue of DSMB sharing interim

result measures, was needed to better understand and guide DSMB interim information sharing practices.

2. How useful is it for the DSMB to provide non-DSMB members three of the four main forms (ICombinedER, ACP, and UCP) of seemingly masked interim result measures and how are these measures interpreted?

The results of our first scenario question-based survey indicated that the ICombinedER, the ACP, and the UCP should not be shared. The ICombinedER and the ACP are well-understood measures. The ACP is unmasking of relative treatment effects at interim. The UCP, on the other hand, is misinterpreted most likely because the measure is unfamiliar. However, the ICombinedER can suggest any one of three plausible relative group effects at interim if shared making it a potentially useless and flawed measure to share as it invites guesswork about relative effects between comparison groups. There is a danger with the DSMB sharing any of these three measures with non-DSMB members as it may lead non-DSMB members to consciously or subconsciously alter their behaviour towards a trial, possibly introducing trial bias.

3. What are the professional opinions of those interested or involved in clinical trials on what interim information should be shared (including the following four main forms of seemingly masked interim result measures: ICombinedER, IControlER, ACP and UCP) with non-DSMB members at interim and if so, with whom and under what circumstance(s)?

The results from our second survey indicate that the ICombinedER is the only interim result measure where the majority of respondents think the DSMB for an RCT should share with non-DSMB members. As to who this measure can be shared with, the majority of respondents indicate that it could be shared specifically with the SC. However, they did not give the ICombinedER a very high score on usefulness. Their reasoning generally for sharing the ICombinedER is that it does not tell you anything about relative effects between comparison

groups in a trial so it does not do any harm in terms of unmasking interim results and keeps investigators informed about the trial's progress. They do indicate though that guesses can be made about effect sizes, as indicated above under question 2 and that the ICombinedER should not be shared if the IControlER is known, as having both can be unmasking of group effect sizes. Even though the majority of respondents indicated that the ICombinedER should be shared, we do not recommend sharing it. Evidence from Chapter 3 suggests that the ICombinedER is a flawed measure to share and rely on as it can be compatible with any of three types of interim results: 1) one group (e.g Drug X) is performing better than another (e.g. placebo), 2) one group is doing worse than another, or 3) both groups are performing the same. For instance, in Chapter 3 [2], respondents correctly pointed out that having been given the ICombinedER of 0.34 or 34% for mortality in a hypothetical interim trial scenario could mean a 25% relative risk reduction, 25% relative risk increase or about a 2% relative risk reduction (where both groups are performing about the same). This flaw in sharing this measure is also dangerous as non-DSMB members could make speculations about comparative effects between treatment groups at interim that could consciously or subconsciously alter their behaviour towards the trial, introducing bias. The results of this survey suggest that respondents from the trial community are not aware of this flaw with sharing the ICombinedER and may need to be educated on this issue.

Our results also empirically show that the IControlER, ACP, and UCP are measures where the majority of respondents think the DSMB for an RCT should not share with any non-DSMB member. The IControlER is likely unmasking of group effects as the ICombinedER is usually known by the SC and the ACP is unmasking of relative treatment effects at interim. The UCP, on the other hand, is a confusing interim result measure most likely because the measure is unfamiliar. Sharing any of these measures poses a danger in introducing trial bias by non-DSMB members as it could alter their behaviour towards the trial, consciously or subconsciously.

4. What demographic factors are associated with thinking certain interim result measures should or should not be shared, specifically the ICombinedER, IControlER, ACP and UCP, and what is the perceived usefulness of sharing any of this information?

Using the demographic information collected from the second survey, several regression analyses have provided empirical evidence to indicate the following: 1) An individual involved with greater than 15 trials that had some form of private industry sponsorship is a potential factor significantly associated with NOT sharing the IControlER and 2) An individual involved with greater than 15 trials that had some form of private industry sponsorship is a potential factor significantly associated with an increase in the perceived usefulness of sharing the ACP. This characteristic needs to be further evaluated to see if this subgroup of trialists has insight into interim trial management practices that protect a trial from bias.

No demographic factor seemed to be associated with sharing the ACP at interim. This finding was corroborated by a sensitivity analysis. Though some other demographic factors were found to predict sharing the ICombinedER and the UCP, they were sensitive to missing data upon our multiple imputation sensitivity analysis, thus caution should be exercised when interpreting the validity of those results and will require more exploration.

Findings compared to other studies

We found our review done in Chapter 2 to be unique in that it exclusively focuses on the issue of sharing interim results by the DSMB with non-DSMB members. However, another review found, done in 2005 [3] with the support of the National Health Services (NHS) in the UK, looks globally at many issues related to data monitoring and interim analysis. One of the questions they ask addresses in part the issue of DSMB confidentiality of interim data. They found within their literature review under “*Question 8: Should the DMC deliberations be open or closed (confidential or secret as opposed to publicly available)?*”, there to be close agreement that interim data and DSMB discussions should be confidential [3]. This supports what we found in our review within Category 1 literature that held a large percentage of the literature reviewed

(43.8%). Category 1 is the body of literature assessed as having the view against sharing interim results and that it should remain confidential with the DSMB. However, a sub-question to their Question 8, asked: *“Who outside the committee should see the interim analysis and how is this changed by whether the analyses were blinded or unblinded?”* [3] They indicate that some respondents have suggested that an independent unmasked statistician should see the interim analysis [3], which is what was found for Circumstance #2 described in Table 2 of Chapter 2. Their review also indicated that DSMBs may allow certain individuals such as the chair of the SC to become unmasked to certain interim results, especially if this is deemed by the DSMB of the trial to best serve patient/participant safety [3]. For circumstances #5 and #6 in Table 2 of Chapter 2, a severe trial safety issue was also found to be a potential driving factor to share unmasked interim safety results with non-DSMB members. Thus, their review [3] in part also supports what we found in Category 2 literature in Chapter 2, that even though interim results should remain confidential with the DSMB, there are circumstances the DSMB must consider that could warrant interim results to be shared with non-DSMB members. For our review in Chapter 2, Table 2 also uniquely goes into detail about other circumstances that may warrant sharing and we do our best to summarise where all the views on this issue rest. Our intent was to additionally discuss what to share and with whom in those circumstances and we found that it greatly depends on the trial circumstance in which the DSMB finds itself.

For the scenario question-based survey in Chapter 3, there were no other studies found that empirically evaluated how commonly generated pieces of interim results are interpreted by trial experts. This study is unique in its ability to evaluate how three interim results are interpreted by trial experts, through the use of a survey asking hypothetical scenario-based questions, using real interim trial information.

The study in Chapter 4, when compared to other studies, was also found to be unique in that no other study was found that empirically evaluated and focused on whether four main forms of interim result measures should be shared, with whom, and why from those involved or

interested in trials. Additionally, we evaluated the perceived usefulness of sharing a particular interim result measure. The scenario question-based survey from Chapter 3 asked trial experts how they interpreted the ICombinedER, ACP and UCP when shared in a hypothetical trial scenario. It was concluded from the results of the study in Chapter 3 that knowledge of these three interim measures should not be shared by the DSMB with non-DSMB members at interim as they may mislead or unmask interim results, potentially introducing trial bias [2]. This previous survey from Chapter 3 [2] corroborates our findings in Chapter 4 in that the majority of trial experts who responded to the latter survey also think the ACP and UPC should not be shared with non-DSMB members. It is important to note though that the majority of respondents from the survey in Chapter 4 thought that the ICombinedER should be shared because it is not directly unmasking of the event rate per group and keeps the SC informed about the trial's progress. However, respondents also indicated that guesses can be made about the effects between treatment groups when having the ICombinedER thus caution should be exercised when sharing this kind of information.

Six other surveys found dating from 1999 to 2011 did not specifically focus on the issue of the DSMB sharing interim results, and were very limited in regards to the amount of data they collected regarding what should be shared by the DSMB, with whom and why. These surveys globally looked at data monitoring practices and so each one does not provide a complete picture of the issue of the DSMB sharing interim results with non-DSMB members even when assessed as a group of articles. In general, 3 of the 6 surveys found [3-5] (1 qualitatively and 2 quantitatively reported) support the view that interim results should not be shared by the DSMB with non-DSMB members, particularly the study sponsor as was indicated in one of the surveys [5]. One of the 6 surveys [3] (quantitatively reported) supports that interim results should be not be shared by the DSMB except in particular circumstances, specifically when there is a safety concern. However, with whom to share was not specified. They also indicated that circumstances that come up should be discussed between SC and DSMB prior to sharing when

sharing interim data or results might be needed [3]. On the contrary, 2 of the 6 surveys [3, 6] (1 qualitatively and 1 quantitatively reported), showed support for the view that interim results should be shared by the DSMB and at least one type of non-DSMB member was indicated. These non-DSMB members included various individuals or groups, those being select institute staff [3, 6], everyone except the trial's participants, the trial statistician, and data centre personnel [3]. Reasons for sharing were not provided. Thus, overall, 4 out of these 6 surveys [3-5] in general seem to support not sharing interim results with 1 of these 4 indicating [3] that there may be a special circumstance that could warrant sharing, particularly when there is a safety concern. However, specifics on what interim results to share, with whom and why are not provided in any of them.

Key Limitations

One of the major limitations of the survey study done for Chapter 4 and 5 is a very low response rate despite best efforts to solicit and gather responses. Thus, we do not have a definitive way of knowing how our non-respondents were different from our respondents. We do know from our demographic information that the largest proportion of respondents self-identified as statisticians and about 54% were involved in at least one trial which reassured us that many of our respondents were most likely familiar with calculated interim result measures in a trial. Another limitation of our second survey is that there was missing data. Though we received 371 responses, 202 were complete responses, meaning they filled all the questions to our survey and 169 were partial or incomplete responses meaning that questions were either skipped or respondents left the entire survey blank after agreeing to participate. In many cases, especially with our demographic information, we had 40% or more missing information from respondents. Information regarding how respondents viewed sharing the four interim results measures had less missing data, most likely because these were questions situated at the beginning of the survey. However, in compensation for the missing data for Chapter 5, a sensitivity analysis was done using multiple imputation (MI) for the regression analyses which is the most robust form of

imputation for missing data, including survey data [7-9]. We then compared the regression results with the dataset we originally had versus the dataset with MI applied to see if the analysis was sensitive to data that was missing. If the results of the same analysis were different with the dataset we originally had versus the dataset with imputation, we exercised caution with interpreting the results. We also used bootstrapping with bias corrected and accelerated confidence intervals (CIs) for our regressions with the dataset we originally had to ensure robustness of the 95% CIs and significance values found. However, ideally one would like to have a complete data set or at least close to it and as high as a possible response rate.

Implication for Research

Our findings warrant more investigation into a subgroup of trialists who have substantial experience with trials with private industry sponsorship. We found that experience with greater than 15 trials with private industry sponsorship appears associated with NOT sharing the IControlER and an increase in perceived usefulness of the ACP. An important question related to practice stems from this finding: Does having more experience with private industry-sponsored trials provide trialists with a better understanding about the amount of information that the IControlER and ACP provide about treatment group effects and relative group effects respectively, at interim? More knowledge of this subgroup's experience can provide more insight into interim trial management practices, especially if this subgroup is already doing something preventatively to protect from trial bias. Though some other demographic factors were found to predict sharing the ICombinedER and the UCP, they were sensitive to missing data upon our MI sensitive analysis and will require more validation with larger surveys targeted at our sampling frame.

As mentioned before, major limitations with our second survey were a low response rate despite good follow-up practices and missing data. A lot of the times, response rate is an issue with surveys, especially with a population that is already under enormous time constraints. We recommend that other societies with an interest or focus in trial research may want to participate

and conduct convenient short in-person focus group meetings or surveys at their conferences about interim result sharing practices with members involved or interested in trials. This can provide a rich opportunity to have a more in-depth dialogue about interim result sharing practices, solicit views on the findings of this research and generate more data on what best practices should be that can be integrated into policies on DSMB stewardship. In-person interviews are likely to generate less missing data or information because anything left unanswered can be followed-up with at the moment the meeting is taking place.

Implications for Practice

Trials are susceptible to bias and it is important to have a protocol with safeguards in place to prevent the introduction of bias that could alter trial results generated, especially in phase III RCTs used to generate definitive results on efficacy and safety outcomes used for regulatory approval and clinical practice. As previously indicated in Chapter 2, there are some circumstances in the literature where certain interim results might be shared by and at the discretion of the DSMB with non-DSMB members and knowledge gained from our two surveys may have implications on what is shared in those circumstances.

Firstly, before the trial commences it is in the best interest of the trial and for those responsible for the conduct of the trial to have *a priori* plans in the protocol or DSMB charter for what interim result measure(s) will be shared, with whom and under what circumstance, with the option that sharing is still at the discretion of the DSMB. This option is important should the trial situation change and the DSMB deem sharing inappropriate. If information had to be shared with a particular non-DSMB member, safeguards should be in place that prevents other non-DSMB members directly responsible for the operation or conduct of the trial, or those participating in the trial in some way, from knowing such interim results.

Secondly, in cases where there may be a request from non-DSMB members to have certain interim result measures shared with them by the trial's DSMB, based on our survey's results, we do not recommend sharing the ICombinedER, IControlER, ACP or the UCP. The

ICombinedER is a well-understood measure and the majority of respondents in Chapter 3 correctly indicated that having it alone, without knowledge of the IControlER or the interim new intervention event rate, can be interpreted in any of three ways. Thus, this measure is of low usefulness, flawed to share, and could invite the mistaken opportunity for guesswork about comparative group effects. The results of the survey from Chapter 4 suggest that respondents from the trial community are not aware of this flaw with sharing the ICombinedER and may need to be educated on this issue. Sharing the ICombinedER becomes even more dangerous if there is good knowledge of the control rate in the literature or from some other sources. Further research on the lack of awareness of this issue with sharing the ICombinedER is needed. Knowledge of any of these four kinds of interim result measures may influence a change in behaviour in those responsible for the operation or conduct of the trial, or those who participate in the trial in some way and hence, may introduce trial bias. We should keep in mind that the DSMB needs to be trusted stewards of the trial and should be using discretion if there comes a time when sharing any of these four measures is needed or requested.

Implications for Guidelines

Future guidelines on DSMB operations should take into account the dangers of sharing these four forms of interim result measures, and explicitly state that sharing any type of interim result measure by the DSMB with a non-DSMB should be indicated *a priori* in the trial protocol or DSMB charter, as well as with whom and for what reason. Safeguards should also be indicated *a priori and* put in place to protect the trial from bias after sharing such information. There should also be allowance written in for the DSMB to use their discretion for sharing, even if sharing certain interim result measures are specified *a priori*. This allowance is important in case the trial situation changes or doing so may jeopardize patient safety and trial integrity.

Final Comments

This thesis has generated new empirical evidence via the use of survey methodology that has provided more clarity on the findings from our literature review from Chapter 2 regarding interim result sharing practices by the DSMB with non-DSMB members. We generated new knowledge suggesting what type of interim result measures should not be shared. We hope that this research provides insight for DSMB charters, trial protocols and guidelines on DSMB stewardship regarding best interim result sharing practices by the DSMB with non-DSMB members. Additionally, we hope it enforces the need to have *a priori* plans in place for sharing certain interim results when deemed appropriate, the importance of having safeguards in place to protect from trial bias, and an outline of the implications that sharing such information can have on trial integrity. Trials are complex studies and the DSMB, as stewards of the trial, should be given allowance to use their discretion regarding sharing interim results pending new circumstances and information, even when *a priori* plans are in place.

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