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Title:	Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) Randomized Controlled Trial
Protocol ID:	0796
Registration Number:	clinicaltrials.gov [NCT03005145]
Sponsor:	Sunnybrook Research Institute, Toronto, ON

BALANCE

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Data Monitoring Committee Charter

BALANCE Organization in Relation to Data Monitoring Committee:

The BALANCE Data Monitoring Committee (DMC) charter is based on the Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group charter, and draws heavily from the charter and experience of prior landmark Canadian Critical Care Trials Group studies.[1, 2] The BALANCE DMC charter outlines terms of reference for roles, responsibilities, and relationships of the DMC to the co-principal investigators (Dr. Rob Fowler, Dr. Nick Daneman), the study coordinator (Dr. Asgar Rishu), and the BALANCE steering committee (Dr. Rob Fowler, Dr. Nick Daneman, Dr. Asgar Rishu, Dr. Deborah Cook, Dr. Rick Hall, Dr. John Muscedere, Dr. Ruxandra Pinto, Dr. Steven Reynolds, Dr. Yaseen Arabi, Dr. Yahya Shehabi, Dr. Benjamin Rogers), the trial statistician (Dr. Ruxandra Pinto), investigators, trial participants, institutional research ethics boards (REBs), sponsor (the Canadian Critical Care Trials Group), and primary funding agency (The Canadian Institutes of Health Research (CIHR)).

Nominated Data Monitoring Committee Membership:

The BALANCE DMC has multidisciplinary expertise in infectious diseases, critical care, randomized clinical trial (RCT) design and conduct, clinical epidemiology, biostatistics, interim analyses and early stopping rules. The Nominated BALANCE DMC members include:

Name	Institution	Relevant Expertise
Dr. Roger Spragg	University of California, San Diego School of Medicine, San Diego, USA	Dr. Spragg has experience in the conduct and oversight of multicentre trials involving critically ill patients and will be the BALANCE DMC Chair
Dr. Taylor Thompson	Harvard University, Massachusetts General Hospital, Boston, USA	Dr. Thompson is the DMC critical care medicine content expert.
Dr. Steve Opal	Brown University, Rhode Island Hospital, Rhode Island, USA	Dr. Opal the DMC infectious diseases context expert.
Dr. David Schoenfeld	Harvard School of Public Health, Boston, USA	Dr. Schoenfeld biostatistician content expert.

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Overview of Data Monitoring Committee Responsibilities:

The primary ongoing responsibilities of the DMC will be independent review of reports received directly from the BALANCE Methods Center (Sunnybrook Research Institute in collaboration with CLARITY Research, McMaster University) regarding:

1. Recruitment rates
2. Adherence rates to treatment duration protocols
3. Data completeness, accuracy and timeliness
4. Serious adverse events
5. Outcomes event rates
6. Co-enrolment prevalence, noting specific trials in which more than 20 BALANCE patients are enrolled

Sample Size Calculation:

The primary analysis will assess whether 7 days of antibiotic treatment is associated with non-inferior 90-day survival rates in comparison to 14 days of antibiotic treatment for critically ill patients with bacteremia. We require 1,686 patients per arm to establish a non-inferiority margin of 4% absolute decrement in survival (baseline mortality 22%,[3] power 80%, alpha 0.025, one-sided equivalence test). We have inflated this to account for 5% loss-to-follow up, and early stopping rules (coefficient 1.024)[4, 5] for a total requirement of 3626. Recent landmark trials in critically ill patient populations with similar baseline mortality rates have used 4% as a non-inferiority margin;[6, 7] the U.S. FDA has recommended a similar margin for analogous industry-sponsored trials.[8] The PneumA study of 8 vs 15 day treatment for VAP used a non-inferiority margin of 10%,[9] but we believe this to be inappropriately high for the outcome of survival; a non-inferiority margin of <4% would render a trial unfeasible.[8] We will aim to enroll approximately 2/3 of these patients in Canadian intensive care units (ICUs), and the remaining 1/3 of patients in international ICUs.

Interim Analyses:

Three interim analyses are planned for BALANCE at one-sixth, one-third and two-thirds of projected total enrollment. Non-inferiority trials with mortality end-points have traditionally been less likely to establish "early stopping rules" than superiority trials. This is in part, due to concern that mortality-based margins of difference should be very low and that early stopping likely reduces confidence that an upper margin of difference has been excluded.[4, 5] However, we will consider stopping at the interim analysis for superiority, using the O'Brien-Fleming spending function to generate adjusted confidence intervals for the primary endpoint, splitting the type I error at $7x10^{-7}$, 0.0005, 0.0132 and 0.043, with 99.99%, 99.95% and 95.70% two-sided confidence intervals to give an overall type I error rate of 2.5%.[4, 5] We have inflated the sample size to account for these 3 analyses in addition to the final analysis. We will also consider stopping at

the interim analyses on the basis of inferiority or futility, and have provided guidance for the DMC (appendix).

After each interim analysis, the BALANCE DMC will recommend either:

1. To consider continuing patient enrolment, or
2. To consider suspending enrolment until careful review by the principal investigators and steering committee, or
3. To gather more information before a recommendation can be made, or
4. To consider terminating enrolment.

Responsibilities of the Data Monitoring Committee:

1. To advise the principal investigators and steering committee about the conduct of the trial and integrity of the data, so as to protect the validity of the trial.
2. To ensure the overall safety of trial patients by protecting them from avoidable harms. The DMC should not be expected or accountable for reviewing adverse events by routine real-time transmission.

Relationship of the Data Monitoring Committee to the Principal Investigators and Steering Committee:

1. The DMC is arms-length and independent of the principal investigators and steering committee in operating and formulating recommendations, but is supportive of the aims and methods of the trial.
2. The DMC serves in an advisory role to the principal investigators and steering committee.
3. The principal investigators and steering committee receive BALANCE DMC recommendations under advisement.
4. The DMC, principal investigators and steering committee work collaboratively to ensure rigorous, valid, safe and timely conduct of the trial.

Initial Responsibilities of the Data Monitoring Committee:

1. Review the BALANCE protocol and case report forms.
2. Review, discuss, debate and approve the Methods Center operations.
3. Review, discuss, debate and approve the mechanisms for transmitting serious adverse event information to the DMC.
4. Establish guidelines for calling emergency meetings of the DMC.
5. Propose a schedule for subsequent DMC meetings, acknowledging that the DMC Chair may call for a meeting of the DMC at any time, as may the principal investigators.
6. Approve or refine template tables provided by the principal investigators and trial statistician for future review at the interim analyses.

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7. Disclose any conflicts of interest such as: current honoraria or consultancies, involvement in regulatory issues relevant to the study drugs, investment in these or competing drugs, involvement with the sponsor, enrolment of patients in the trial, strong prior beliefs constituting intellectual conflict, other dual loyalties etc.

Ongoing Responsibilities of the Data Monitoring Committee:

The BALANCE DMC is responsible for helping to ensure that BALANCE patients are not exposed to unnecessary or unreasonable risks and that the trial is conducted according to the highest scientific and ethical standards.
Therefore, the BALANCE DMC will:

1. Review data from the 3 planned interim analyses provided by principal investigators and steering committee, via the Methods Centre.
2. Alert the principal investigators and steering committee about scientific, procedural or ethical concerns emerging from the interim analyses and/or final analyses.
3. Provide recommendations to facilitate rigorous, timely completion of the trial.
4. Comment on any new relevant external published data (provided by the principal investigators and steering committee) that may impact on patient safety or the efficacy of BALANCE.
5. Provide recommendations for adjustment of sample size or consideration of trial termination.
6. Read and provide suggestions for manuscript publications before submission.
7. Be acknowledged in the main report, unless requested otherwise.

Timing of Data Monitoring Committee Meetings:

The DMC will meet virtually, or if necessary in person:

1. Once initially to discuss the protocol and analysis plans, the DMC Charter, template tables, and to clarify any aspects with the principal investigators and steering committee.
2. At the first interim analysis.
3. At the second interim analysis.
4. At the third interim analysis.
5. At the end of the trial, to allow the DMC to discuss the final data with the principal investigators and steering committee to advise on data interpretation.
6. As needed, by teleconference.

Responsibilities of the Principal Investigator, Study Coordinator and Steering Committee to the Data Monitoring Committee:

1. The principal investigators and study coordinator will provide the protocol and CRFs to the DMC before their initial meeting.

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2. The principal investigators and study coordinator will provide preliminary template reports of site enrolment, patient recruitment rates, patient consent rates, treatment duration protocol adherence rates, data management templates (data completeness, accuracy, timeliness and query resolution), CIHR reports, 3 interim and final analyses (baseline characteristics, primary and secondary outcomes, and serious adverse events).
3. The principal investigators and study coordinator will modify these template reports if requested, and will use to create tables for the 3 interim analyses.
4. For baseline characteristics and outcomes, the (blinded) BALANCE statistician will provide to the (blinded) DMC, data according to group A and B, including baseline characteristics (age, sex, APACHE II score, source of bacteremia, etc.), primary and secondary outcomes and serious adverse events.
5. The principal investigators and study coordinator and biostatistician will ensure that DMC members remain blinded to allocation.
6. The principal investigators and study coordinator will provide the results of any new relevant external published data for DMC consideration.

Three-Part Structure of Data Monitoring Committee Meetings:

1. First, an open session will be held with the principal investigators and study coordinator and statistician. The purpose will be to review accrual, data timeliness and quality, completeness of follow-up and adjudication, serious adverse events, problems with centres, and any proposals for changes in the trial protocol or duration. In addition, the principal investigators will report any new external evidence (especially results from other relevant ongoing studies) that bear on the conduct of the trial.
2. Second, a partially closed session will be held between the DMC and the statistician to review the primary and secondary outcomes separated by group and presented in a blinded fashion (group A and group B). These data will not be available to the principal investigators, study coordinator, steering committee, or investigators except as authorized by the DMC Chair. The principal investigators will receive data in aggregate form.
3. Third, a totally closed session for just the DMC members will be held to discuss the current results, decide on recommendations, and draft comments and recommendations for 3 reports.

Potential Unblinding of the Data Monitoring Committee:

1. During the closed session, if the DMC deems it crucial to their interpretation of the data, the DMC will request unblinding themselves to group assignment without informing the investigative team of this need.
2. A request to unblind will be very unlikely because the general scientific philosophy of modern pragmatic trials is to not unblind until completion, and this is particularly true for BALANCE which involves different two durations of antibiotic treatment that are

both a component of contemporary clinical practice, and the specific antibiotic medications, dose and route of delivery are all chosen by the treating team.
3. The request to unblind would need to be extreme, unambiguous and unanimous. The signal would be need to derive from compelling trial results such as a significantly increased risk of mortality in one arm.
4. To achieve unblinding the database manager will be authorized to provide immediate unblinding information to the DMC chair, including during a DMC meeting. An independent statistician will redo analyses if requested. The principal investigators, study coordinator and statistician will not review unblinded results, and will not be informed of the DMC decision to unblind the results unless the DMC makes a recommendation to consider terminating enrolment at an interim analysis, or at the end of the study.

Discussions of the Data Monitoring Committee:

1. Efforts should be made for the DMC to reach unanimous recommendations.
2. The role of the Chair is to summarize discussions and encourage consensus.
3. Before making any recommendations, the DMC should consider the ethical, scientific, statistical, and practical implications for the trial.

Minutes of Data Monitoring Committee Meetings:

1. Within a week of each DMC meeting, the Chair, with administrative assistance provided, will generate minutes of the open and closed sessions of the meeting.
2. The minutes will contain the major points of discussion, recommendations made, and any additional information requested for future meetings.
3. Minutes of the open session of the meeting will be for the principal investigators and study coordinator.
4. Minutes of the closed session will be for the DMC members only (until the trial is complete).

Reports of the Data Monitoring Committee:

1. After each DMC meeting, the Chair will report to the principal investigators and study coordinator. Each meeting will be summarized in 2 reports (1 short report suitable for Investigators, the CCCTG, REBs and CIHR) and 1 more detailed report for the principal investigators, study coordinator and statistician).
2. The principal investigators will circulate the DMC's short and long reports to the appropriate individuals. It is the responsibility of the principal investigators to notify the investigators, the CCCTG and participating REBs of any recommendations about trial modification or enrolment suspension or termination.

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3. If the DMC recommends to continue enrolment in the trial following an interim analysis, no other information shall be provided to the principal investigators and study coordinator.
4. If the DMC recommends to consider suspending enrolment of the trial until careful review by the principal investigators and study coordinator; or whether more information is required before a recommendation can be made, or whether to consider terminating enrolment, the DMC will provide a full report of the rationale to the principal investigators, study coordinator and statistician.

Conflict Resolution:

1. DMC recommendations are advisory to the trial principal investigators, steering committee, and by extension other sponsors of the trial.
2. In the event that the principal investigators and/or study coordinator disagree with the DMC recommendation(s) to modify or to terminate the trial, a third party arbitrator may be called upon.
3. A third party arbitrator, selected by both parties, will be an individual possessing the requisite knowledge and experience (ideally both methodologic and clinical) to make a final decision.
4. The selection of the third party arbitrator will be made by mutual consent of both the principal investigators and the DMC Chair.

Confidentiality:

1. It is the duty of each member of the DMC to protect the confidentiality of the trial and the results of monitoring.
2. The members of the DMC acknowledge that the data emerging from this trial are the collective property of the principal investigators and study coordinator and investigators.
3. DMC members will not have the right to present or publish data or learnings from this trial anywhere without the explicit permission of the principal investigators and study coordinator, and not until after the trial is complete.

Reporting on the Data Monitoring Committee:

1. A brief summary of the roles, responsibilities, and recommendations of the DMC will be included in the trial manuscript.
2. DMC members will be invited to read and comment on the trial manuscript, including any statement related to the DMC.
3. DMC members will be named and their affiliations listed in the trial manuscript, unless requested otherwise.
4. Potential publications about research oversight coauthored by any of the DMC members will be deferred until the main manuscript is published.

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Appendix: **Contextual and Analytical Considerations for Stopping Considerations for each Interim Analysis of the Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) Randomized Clinical Trial.**

Stopping Guidelines for Inferiority

At each of three interim analyses (planned after 1/6, 1/3 and 2/3 of the patients have been enrolled) we explore the possible event rates for the 7-day group that will cause us to stop the trial for inferiority. We propose to stop the trial for inferiority of the 7-day group in comparison to the 14-day group, if the lower limit for a confidence interval for the difference between the 7-day and 14-day event rate is larger than 4% (the non-inferiority margin of error for the trial). To maintain and overall 5% type I error, at each interim analysis the confidence interval is based on the O'Brien-Fleming significance level α, corresponding to $z=Z_{OBF}*\text{sqrt}(N/n)$ where N=total sample size, n=sample size at the interim analysis, and $Z_{OBF}=2.024$

We varied the event rate in the 14-day group and used simulation to estimate the event rate in the 7-day group for which we would have enough power to determine that the event rate in the 7-day group is inferior to the 14-day group.

1. First we simulated data for the 7-day group and 14-day group from binomial distributions with event rates higher in the 7-day group.
2. Next, we calculated the confidence interval around the difference in the event rates in the 7- versus 14-day group
3. Then, we calculated the power as the proportion of simulations for which the lower confidence interval exceeded 4% (the non-inferiority margin of error for the trial).

The lowest event rate for which the power is at least 80% is the one that provides a guideline of when the trial would be stopped for inferiority.

The Figures operationalize the inferiority-based stopping guidelines for the trial at each of the three interim analyses. If the 7-day and 14-day mortality rates fall within the darkest grey shaded area, then we should consider stopping the trial for evidence of inferiority of the 7-day group.

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Stopping Guidelines for Superiority

At each of three interim analyses (planned after 1/6, 1/3 and 2/3 of the patients have been enrolled), we explored the possible event rates for the 7-day group that will cause us to stop the trial for superiority. This is similar to the approach taken for the inferiority-based stopping guidance. We propose to stop the trial for superiority of the 7-day group in comparison to the 14-day group, if the upper limit for a confidence interval for the difference between the 7-day and 14-day event rate is lower than 0% (no-difference). At each interim analysis the confidence interval is based on the O'Brien-Fleming significance level α, corresponding to $z=Z_{OBF}*\text{sqrt}(N/n)$ where N=total sample size, n=sample size at the interim analysis, and $Z_{OBF}=2.024$

We varied the event rate in the 14-day group and used simulation to estimate the event rate in the 7-day group for which we would have enough power to determine that the event rate in the 7-day group is superior to 14-day group.

1. First we simulated data for the 7-day group and 14-day group from binomial distributions with event rates lower in the 7-day group.
2. Next, we calculated the confidence interval around the difference in the event rates in the 7- versus 14-day group.
3. Then, we calculated the power as the proportion of simulations for which the upper confidence interval is lower than 0%.

The lowest event rate for which the power is at least 80% is the one that provides a guideline of when the trial would be stopped for superiority.

Figures 1-3 operationalize the superiority-based stopping guidance for the trial at each of the three interim analyses. If the 7-day and 14-day mortality rates fall within the light grey shaded area then we should consider stopping the trial for evidence of superiority of the 7-day group.

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Stopping Guidelines for Futility

At each of three interim analyses (planned after 1/6, 1/3 and 2/3 of the patients have been enrolled), we also explored the possible event rates for the 7-day group that will cause us to considering stopping the trial for futility, using the principle of conditional power. Conditional power is the probability that the final result will be statistically significant given the interim observed data, incorporating specific assumptions about the future data. Conditional Power was simulated for the three interim analyses under a range of conditions.

In the simulation, at the interim analysis, we assumed higher event rates (i.e. 90-day mortality) in the 7-day treatment group versus the 14-day group. For each of these event rates we can simulate samples for the remaining (future) data as follows:

1. The future event rate in the 14-day group was simulated with various scenarios:
    a. Default scenario: the same as assumed in the original sample size estimation (22% 90-day mortality); or,
    b. Alternative scenario: the same as observed at the interim analysis.
2. The future event rate in the 7-day group was simulated with various scenarios as well:
    a. Default scenario (least likely to stop early): the future event rate in the 7-day group will be the same as the future event rate in the 14-day group
    b. Alternative scenario (more likely to stop early): the future event rate in the 7-day group will be at the lower 95% confidence interval for the 7-day treatment group at the interim analysis.
    c. Alternative scenario (most likely to stop early): the future event rate in the 7-day group will be the same as the observed event rate at the interim analysis in the 7-day group.

Eventually, with a strong recommendation from the BALANCE Steering Committee and oversight of the Canadian Critical Care Trials' Group, we chose the most conservative scenario to consider for futility-based stopping considerations, namely when future data is simulated with an event rate that is the same for both groups and the same as in the original sample size calculation (1a and 2a above).

3. For each simulation, to maintain the overall type I error as stipulated by the O'Brien-Fleming stopping rule, a two-sided 95.7% confidence interval for the 7-day versus 14-day difference was calculated.
4. The conditional power is the percentage of simulations for which the upper limit of the confidence interval for the difference in 90-day mortality between 7-day group versus 14-day group is less than 4% (the non-inferiority margin of error for the trial).

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5. We specified a conditional power of ≤ 10% as a threshold for stopping the trial for futility, based on common and conservative practice from the existing medical literature.
6. We then calculated the event rate in the 7-day group at the interim analyses that will lead to a conditional power of 10% or less.

We repeated the above steps for each of the 3 interim analyses in order to derive futility stopping guidance graphs for the trial (Figures 1-3). If the event rates for the 14-day and 7-day treatment groups land in the medium grey shaded area, then the conditional power is ≤ 10%, and we should consider stopping the trial for futility. However, given that such an interim analysis finding does not lead to an interim conclusion of a high probability of better or worse outcomes for either treatment group, and that by enrolling a greater number of patients in a non-inferiority trial, generally greater certainty will emerge on treatment effects from each group, guidance from the DMC on the issue of stopping on the basis of futility should be only positioned a consideration, and not a strong recommendation.

This position is in distinction to guidance for stopping on the basis of inferiority or superiority - where there may be a substantial clinical and statistical inference that one treatment is inferior or superior to the other. Interim analysis results indicating that there is a chance of futility (in finding that 7-days treatment is non-inferior to 14-days) does not imply a benefit to one or the other treatment strategies. Stopping the trial with fewer enrolled patients will always be associated with greater uncertainty in any true treatment-related difference in mortality than if the trial continued. An argument can be made that non-inferiority trials should not be considered for stopping on the basis of futility as doing so may not allow for effective use of the data from contributions of those patients already enrolled in the trial, and be of least value to clinicians and future patients.

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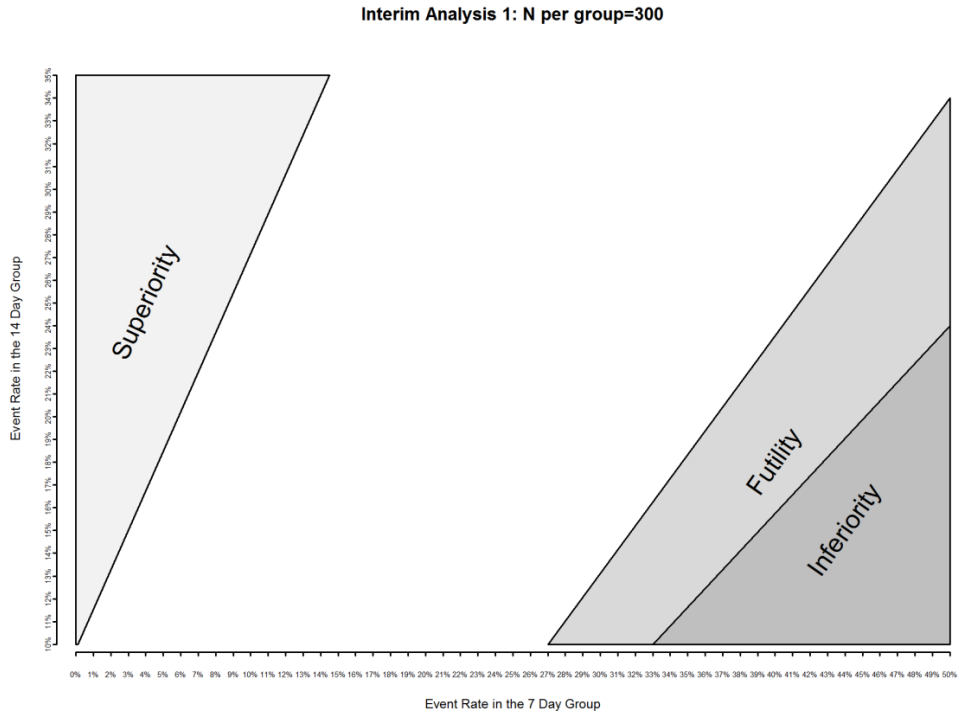
Figure 1. Operationalizing stopping guidelines for inferiority (dark grey shaded area), superiority (light grey shaded area) and futility (medium grey shaded area) with interim event rates when N per group = 300.



If the 7-day and 14-day mortality rates fall within the dark grey shaded area (inferiority) then we should consider stopping the trial for evidence of **inferiority** of the 7-day treatment.

If the 7-day and 14-day mortality rates fall within the light grey shaded area (superiority) then we should consider stopping the trial for evidence of **superiority** of the 7-day treatment.

If the event rates for the 7-day and 14-day treatment groups land in the medium grey shaded area, then the conditional power is ≤ 10%, and we should consider stopping the trial for **futility**.

If the event rates for the 7-day and 14-day treatment groups fall within the white portion of the graph, then the trial should be continued.

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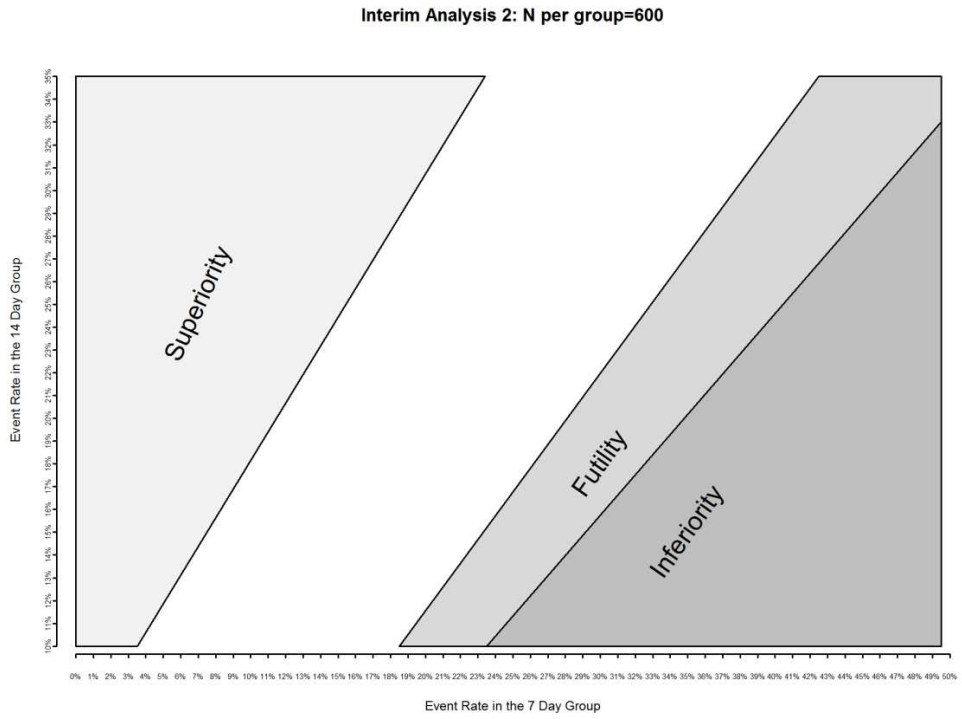
Figure 2: Operationalizing stopping guidelines for inferiority (dark grey shaded area), superiority (light grey shaded area) and futility (medium grey shaded area) with interim event rates when N per group = 600



If the 7-day and 14-day mortality rates fall within the dark grey shaded area (inferiority) then we should consider stopping the trial for evidence of **inferiority** of the 7-day treatment.

If the 7-day and 14-day mortality rates fall within the light grey shaded area (superiority) then we should consider stopping the trial for evidence of **superiority** of the 7-day treatment.

If the event rates for the 7-day and 14-day treatment groups land in the medium grey shaded area, then the conditional power is ≤ 10%, and we should consider stopping the trial for **futility**.

If the event rates for the 7-day and 14-day treatment groups fall within the white portion of the graph, then the trial should be continued.

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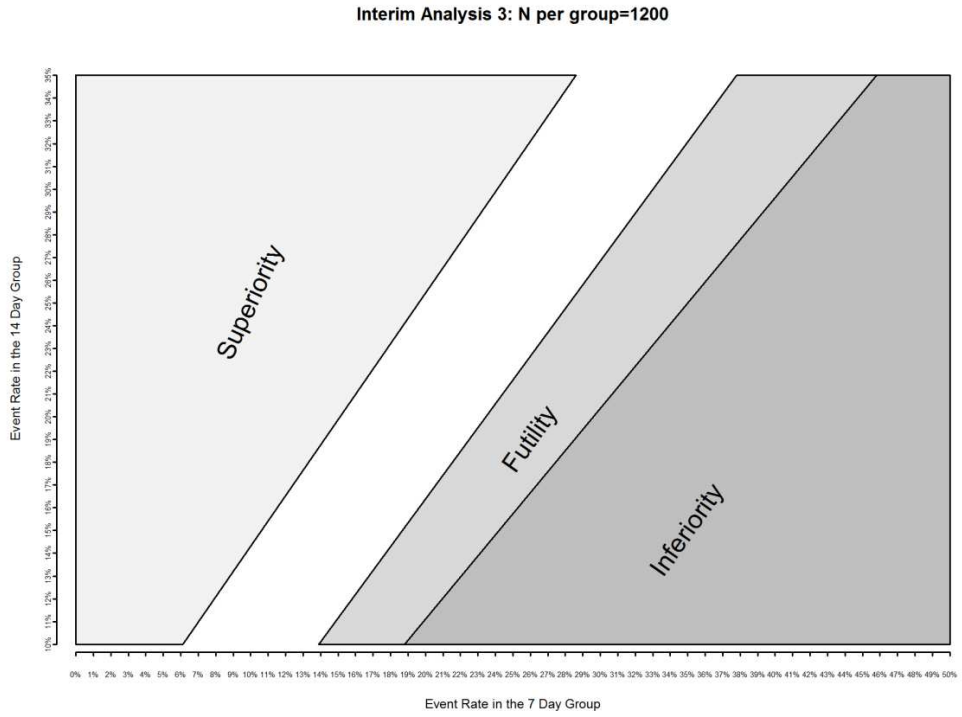
Figure 3: Operationalizing stopping guidelines for inferiority (dark grey shaded area), superiority (light grey shaded area) and futility (medium grey shaded area) with interim event rates when N per group = 1200



If the 7-day and 14-day mortality rates fall within the dark grey shaded area (inferiority) then we should consider stopping the trial for evidence of **inferiority** of the 7-day treatment.

If the 7-day and 14-day mortality rates fall within the light grey shaded area (superiority) then we should consider stopping the trial for evidence of **superiority** of the 7-day treatment.

If the event rates for the 7-day and 14-day treatment groups land in the medium grey shaded area, then the conditional power is ≤ 10%, and we should consider stopping the trial for **futility**.

If the event rates for the 7-day and 14-day treatment groups fall within the white portion of the graph, then the trial should be continued.

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