DRAFT CYCLE Data Monitoring Committee Charter
February 27, 2018

CYCLE Organization in Relation to Data Monitoring Committee:

The CYCLE Data Monitoring Committee (DMC) charter is based in part on the Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group charter[1]. This DMC Charter outlines terms of reference for roles, responsibilities, and relationships of the DMC to the Principal Investigator (PI) [Michelle Kho], Project Coordinator (PC) [Alexander Molloy], Trial Analyst [Diane Heels-Ansdell], International Management Committee (IMG) (To be confirmed), Trial Investigators, Trial Participants, Institutional Research Ethics Boards (REBs), and the Canadian Critical Care Trials Group (CCCTG).

Data Monitoring Committee Membership:

The DMC is independent from other persons involved in CYCLE, and has the requisite expertise in randomized clinical trial design, epidemiology, biostatistics, warning guides/stopping rules, critical care, and physical rehabilitation with critically ill patients. Dr. **XXX** (University, City, Country) is a biostatistician and epidemiologist with research expertise in trial conduct and monitoring. Dr. **XXX** (University, City, Country)is an intensivist with clinical expertise in critical care rehabilitation, and research experience in trials. Dr. **XXX** (University, City, Country) is an intensivist with extensive research experience in outcomes of critically ill patients.

Overview of Data Monitoring Committee Responsibilities:

The primary ongoing responsibilities of the DMC will be to independently review reports received directly from the Methods Center at the time of the one blinded interim analysis and final analysis. These will focus on: 1) recruitment (center and patient) and screening, consent and coenrolment rates; 2) protocol procedures (randomization, stratification, protocol adherence including maintaining blinding); 3), data management tables (overall event rates for primary outcome); and 4) baseline characteristics, primary and secondary outcomes, adverse events, serious adverse events, errors in eligibility assessment or randomization, and consent withdrawals. The DMC will monitor performance and make suggestions at their discretion. The DMC will receive all serious adverse events at the time of the interim analysis, and will evaluate these in their formal report.

Overview of Sample Size Calculation and Analysis:

CYCLE is a randomized concealed blinded stratified parallel group international trial, the rationale for which we have outlined. The primary objective of this trial is to determine the effect of early in-bed cycling and routine physiotherapy interventions on the Physical Function ICU Test (PFIT-s)[2] 3 days post-ICU discharge compared to routing physiotherapy interventions among mechanically ventilated critically ill patients. The allocation ratio is set at 1:1. Secondary outcomes include strength, physical function, frailty, psychological distress, quality of life, mortality, and healthcare utilization.

The total sample size for CYCLE to determine the effects of early in-bed cycling is 360 patients. The key outcome is physical function 3 days post-ICU discharge, which formed the sample size calculation. Our sample size of 360 patients is based on identifying a 1.0 point mean difference[3] between the Cycling and Routine groups for the PFIT-s 3 days after ICU discharge. Psychometric studies of the PFIT identified the minimal clinically important difference was 1.0 points.[2,4] By logistic regression, our analysis of patients enrolled in TryCYCLE and CYCLE pilot studies identified that each 1.0 point increase in PFIT-s at ICU discharge (representing better function) was associated with a 40% reduction in the composite outcome of death, readmission to ICU, or need for paid assistance after hospital discharge.[3] Based on a standard deviation of 2.5 points at ICU discharge[5,6] (from our CYCLE pilot RCT, since we do not have data at 3 days after ICU), a 1.0 point difference between groups,[2-4] and 90% power (0.05 alpha), we need to randomize and analyze 266 patients (133 per group). Based on pilot data, we anticipate approximately 35% total attrition, and will recruit 360 patients overall.

Enrolment:

We will enrol ~180 patients/arm in ~17 centers over ~3 years. However, we anticipate randomizing ~370 patients to account for any potential errors in eligibility assessment or randomization, and consent withdrawals. In the final analysis, patients will be analyzed in a blinded manner and according to the intention to treat principle, as well as per protocol.

Overview of Warning Guides for the Interim Analyses:

To avoid overestimates that would distort subsequent clinical decision-making, and to ensure optimal precision for our primary key outcome (PFIT-s), we will conduct only a single interim analysis[7,8] after half of the planned patients have been enrolled, for review by the independent DMC. To maintain the overall type-I error rate (i.e., α), we will evaluate the primary endpoint using a fixed simple conservative α=0.001 for the interim analyses[9,10] when 180 patients (50% of patients) have reached Day 90 follow-up, and α=0.05 for the final analysis.

We hypothesize that those randomized to early in-bed cycling will have better physical function at 3 days post-ICU discharge. The DMC has the option of recommending early stopping of the trial if there is unequivocal net benefit or net harm, thinking both statistically and clinically with respect to the a) the importance of the outcome(s) and b) the magnitude of effect.

Other considerations may influence DMC recommendations to suspend or terminate enrolment rather than continue enrolment may be related methodologic considerations, implementation concerns, or compelling external evidence.

Importantly, we are wary of the increasing number of trials (particularly in cardiology and, disproportionately, in critical care medicine) stopped early for benefit, harm or futility. Acknowledging the ethical obligation to not just those in the trial, but future patients who will need, and whose clinicians will need precise and accurate data, we are mindful of the problematic inferences that may arise from truncated RCTs[7,11,12].

The DMC will inform the IMC if, in their view, major issues have arisen that are likely to convince a broad range of clinicians and the general clinical community, that on balance, it is clear that there is net benefit of early in-bed cycling.

After the interim analysis, the DMC will:

1. Recommend whether to continue patient enrolment;
2. Recommend whether more information is required before a recommendation can be made;
3. Recommend whether to suspend enrolment until careful review by the IMC;
4. Recommend whether to terminate enrolment.

Specific Responsibilities of the Data Monitoring Committee:

1. To aid the IMC by providing advice about the conduct of the trial and integrity of the data, so as to protect the validity of the trial, current and future patients.
2. To ensure the overall safety of trial patients by protecting them from avoidable harm.

Relationship of the Data Monitoring Committee to the International Management Committee:

1. The DMC is independent of the IMC but is supportive of the aims and methods of the trial.
2. The DMC serves in an advisory role to the IMC.
3. The IMC receives recommendations from the DMC under advisement.
4. The DMC and IMC work collaboratively to ensure rigorous, safe and timely conduct of the trial.

Initial Responsibilities of the Data Monitoring Committee:

1. Review the protocol and case report forms (CRFs) to become familiar with the trial design.
2. Review the DMC Terms of Reference, and suggest changes as desirable.
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 Chair may call for a meeting of the DMC at any time, as may the IMC.
6. Approve or refine template tables provided by the IMC and Trial Statistician for future review at the interim analyses.
7. Disclose any conflicts of interest such as: current honoraria or consultancies, involvement in regulatory issues relevant to the study product, investment in these or competing agents, involvement with any funders, enrolment of patients in the trial, strong prior beliefs constituting intellectual conflict, other conflicts of interest or competing loyalties, etc. Decisions concerning whether an individual with a real or perceived conflict of interest may participate on the DMC will be made by the DMC Chair and IMC.

Ongoing Responsibilities of the Data Monitoring Committee:

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

1. Review data from the blinded planned interim analyses provided by the IMC[13].
2. Alert the IMC about scientific, procedural or ethical concerns emerging from the interim analyses and from the final trial results.
3. Provide recommendations to facilitate rigorous, timely completion of the trial.
4. Comment on any new relevant external published data that may impact on safety or efficacy.
5. Provide recommendations for adjustment of sample size or enrolment suspension or 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, largely by teleconference:

1. Once initially to discuss the protocol, interim analysis plans, the DMC Charter, and to clarify any roles and responsibilities with the IMC.
2. At the time of the interim analysis.
3. At the end of the trial to allow the DMC to discuss the final data with the IMC.
4. As needed.

Responsibilities of the Principal Investigator, Project Coordinator and International Management Committee to the Data Monitoring Committee:

1. The PC will provide the CYCLE protocol, CRFs and DMC Charter.
2. All documents will be discussed at the first meeting of the DMC.
3. The PI and PC will provide template reports of 1) recruitment (center and patient) and screening, consent and coenrolment rates; 2) protocol procedures (randomization and stratification, protocol adherence including maintaining blinding); 3) data management tables (data completeness and timeliness, overall event rates by center); 4) one blinded interim analysis (baseline characteristics, primary and secondary outcomes, adverse events, serious adverse events, errors in eligibility assessment or randomization, and consent withdrawals).
4. When completed, the Statistical Analysis Plan will also be shared.
5. The PI and IMC will modify the template reports if requested for the interim analysis.
6. For baseline characteristics and outcomes, the blinded Trial Statistician will provide to the initally blinded DMC, data according to group A and B, including baseline characteristics (age, sex, APACHE II score, medical vs surgical, etc.), primary and secondary outcomes, adverse events and serious adverse events.
7. The Trial Statistician will thus remain blinded to allocation.
8. The PI and IMC will remain blinded.
9. The PI and IMC will provide any new relevant external published data for DMC consideration. This evidence will be shared at the time of any DMC meetings, and at the discretion of the

IMC if important evidence has emerged at other times that may influence the conduct of the trial.

Three-Part Structure of Data Monitoring Committee Meetings:

1. First, an 'open' session will be held with the PI, IMC and Trial Statistician. The purpose will be to review accrual, data timeliness, completeness of follow-up and adjudication, serious adverse events, problems with specific centers, and any proposals for changes in the trial protocol or duration. In addition, the PI will report any new external evidence (especially results from other relevant studies) that may influence the conduct of the trial. In the open session, the primary and secondary outcomes for the whole group (not divided by randomized group) will be shared with the PI.
2. Second, a 'partially closed' session between the DMC and the Trial 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 PI, PC, IMC, or Investigators except as authorized by the DMC Chair. The PI and IMC will receive data only in aggregate form.
3. Third, a 'totally closed' (executive) session for just the DMC members. In this totally closed session, the DMC will discuss the emerging results, decide on recommendations, and draft comments and recommendations for their report (*vide infra*).

Discussions of the Data Monitoring Committee:

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

Minutes of Data Monitoring Committee Meetings:

1. Within one week of each DMC meeting, the DMC Chair 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 made available to the PI, PC and IMC.
4. Minutes of the closed session will be available to the DMC members only, until the trial is completed.

Reports of the Data Monitoring Committee:

1. After each DMC meeting, the Chair will report to the PI and IMC. Each meeting will be summarized in 2 reports: 1 short report suitable for Investigators, the CCCTG, REBs etc., and 1 more detailed report for the PI, PC and IMC.
2. If accepted by the IMC, the PI will circulate the DMC's short and long reports to the appropriate personnel.
3. If the DMC recommends continuing enrolment in the trial following an interim analysis, no other information shall be provided to the PI and IMC.
4. If the DMC recommends suspending enrolment of the trial until careful review by the PI and IMC, or if the DMC recommends that more information is required before a recommendation can be made, or if the DMC recommends terminating enrolment, the DMC will provide a full report of the rationale to the PI, PC and IMC.

Conflict Resolution:

1. In the event that the PI and/or the IMC disagree with the DMC recommendation(s) to modify or to terminate the trial, a third-party arbitrator may be called upon.
2. A third-party arbitrator, selected by both parties, will be an individual possessing the requisite knowledge and experience (both methodological and clinical), to make a final decision.
3. The selection of the third-party arbitrator will be made by mutual consent of both the PI and the DMC Chair.

4. It is the responsibility of the PI to notify the Investigators, the CCCTG, and REBs of recommendations about trial modification or enrolment suspension or termination.

Confidentiality:

1. Each member of the DMC is to protect the confidentiality of the trial and its monitoring.
2. Each member of the DMC acknowledges that the data emerging from the trial are the collective property of the PI, IMC and Investigators.
3. DMC members will not have the right to present or publish data from this trial anywhere without the explicit permission of the PI and IMC, and not until after the trial is complete.
4. DMC members will keep their knowledge of the trial results confidential.

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.

References

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