Analytical Plan for ABC-PICU

Developed by Dean Fergusson and Elham Sabri for the ABC-PICU Investigators. The analytical plan represents the operationalization of the statistical plan of the ABC-PICU Protocol.

Overall Approach to Analysis: All statistical analyses will be based on an intention-to-treat (ITT) approach, in which participants will be analyzed according to the intervention to which they were randomized. All p values will be reported as two-sided. Hypothesis testing for the primary analysis will be carried out with an overall level of significance set using a p value < 0.05.

Descriptive Statistics for Baseline and Post-randomization Characteristics: Baseline characteristics of patients in both study arms will be assessed using frequency distributions and univariate descriptive statistics including measures of central tendency and dispersion. Means (± standard deviation) will be used to report central tendencies of data that can be reasonably approximated using a normal distribution, whereas medians (inter quartile ranges) will be used to report data with non-normal distributions. Percentages will be reported for categorical data. Post-randomization characteristics of our intervention (short storage vs standard issue RBC units) and major co-interventions in the two treatment arms will be presented using measures of central tendency and dispersion for continuous data and percentages for dichotomous data. Wilcoxon-Rank Sum tests will be used for difference in continuous data and Chi-Square tests for dichotomous data.

Primary Analysis of Primary Outcome: The analysis of the primary outcome measure will be conducted on an "intent-to-treat" basis with all patients randomized in the ABC PICU Trial. The principal analysis, i.e. the influence of treatment groups ("short storage" versus standard issue) on the primary outcome, will be compared using an absolute risk reduction with 95% confidence intervals and a Chi-Square test to compare the proportions.

Secondary Analyses of Primary Outcome: Secondary analyses of the primary outcome include a logistic regression model to further elucidate the measure of effect while adjusting for known prognostic risk factors. For adjusted model, risk factors such as site, age, gender, co-morbid illnesses, and severity of illness scores will be added to logistic model based on clinical (not statistical) rationale. Continuous risk factors (e.g. PRISM III, number of transfusions per patient) will be entered into the models as a continuous measure rather than categorical to improve statistical efficiency. Regression diagnostics will be performed on adjusted model. The treatment effect will express as an adjusted risk reduction with 95% confidence intervals. We will also compare Kaplan-Meier curves using a log rank test followed by proportional hazards

modeling for NPMODS rates: this analysis will compare the length of time between randomization and appearance of NPMODS.

Analyses of Secondary Outcomes: All secondary outcome measures will also be analyzed by an "intent-to-treat" approach. The effect of treatment on dichotomous secondary outcomes will be compared by calculating absolute risk difference with 95% confidence intervals and Chi-Square tests to compare proportions. Continuous outcome measures will be analyzed using either parametric procedures (independent t test) or non-parametric procedures (Wilcoxon Rank Sum). Difference in means with 95% confidence intervals will be reported. No adjustment for multiple testing will be done for secondary outcomes.

Major Subgroup Analyses of Primary Outcome: Subgroup analyses of the primary outcome will be performed for the following subgroups of patients: age, country, type of ICU admission, PRISM IIII score at ICU admission, volume of red cells transfused per kg. The analysis of the primary outcome will be repeated for each subgroups of patients.

Sensitivity Analyses of Primary Outcome: The analysis of the primary outcome will also be repeated using per-protocol populations consisting of patients who exclusively receive red cells $\leq$ 7 days in the fresh red cell group and all patients in the standard-issue group. A sensitivity analysis will also compare patients who exclusively receive red cells $\leq$ 7 days in the fresh-blood group to patients who only receive red cells > 7 days of storage.

Data Source and Analysis Set: Data will be collected using Web-based application produced by the data coordinating center. Data source will be SQL Server 10.5 (64 bit) database. Daily back-ups of the full database will be made and stored at 2 different locations. Data will be extracted via XML to an Excel file for statistical analysis.

Programming Plans: All data manipulations and statistical analyses will be performed using Statistical Analysis System, Version 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

Handling of Missing Values: Attempts will be made to capture all missing values by regular querying to study coordinating centers. Any remaining missing data will be left as missing for the data analyses and no data imputation will be performed.

Quality Control: Quality assurance will be maintained with field validation during data entry, a query system to request clarification and correction on data entry errors, and a Memo-to-File system for direct database changes.