Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.


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Supplementary Appendix – ROC PRIMED Analyze Early versus Later Trial

Supplement to: Stiell IG, Nichol G, Leroux BG, et al. Early versus Later Rhythm Analysis in Out-of-Hospital Cardiac Arrest

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Appendix Figure 1: Patient Flow Chart

Screened: includes treated cardiac arrests and cases with ITD opened; EMS Wit: witnessed by Emergency Medical Services personnel; DNR: do not resuscitate orders; Non-ROC: treatment by non-ROC agency; DSE: drowning, strangulation, electrocution
Appendix Figure 2: Distribution of cases by actual time to analysis for the Analyze Early (solid line) and Analyze Later (dashed line) study groups
**Appendix Figure 3:** This graph plots each site’s treatment effect (difference in probability of survival to discharge with MRS 3 or less) versus the overall site-specific probability of survival with MRS 3 or less (average two treatment arms).
2) Explanation of Relationship with ITD Trial

The ROC PRIMED Impedance Threshold Device (ITD) trial was conducted simultaneously with the ROC PRIMED Analyze Early versus Later (AEvsAL) trial, thus halving the cost and time required to conduct these two trials. Furthermore, although no substantial interactive effect between the two interventions was anticipated, simultaneous implementation allowed assessment of the ITD under the early and later strategies for rhythm analysis, both of which were in common use. Potential difficulties caused by simultaneous implementation of two protocols were mitigated by not requiring EMS and fire personnel to actively perform randomization, which was accomplished by pre-determined cluster randomization or pre-randomized ITD kits. A full factorial design was not possible because not all agencies participated in both trials (one did not participate in the AEvsAL trial and another in Oregon did not participate in the ITD trial) and inclusion criteria for the two trials differed. In particular, EMS-witnessed cases were not eligible for the ALvsAE trial whereas enrolment in the ITD trial required opening the ITD kit which was not done in approximately 28% of cases (e.g., due to adverse scene conditions or early ROSC). Of the 12,090 patients enrolled in at least one trial, 7283 (60%) were enrolled in both trials, 2870 (24%) were enrolled only in the AEvsAL trial, and 1937 (16%) were enrolled only in the ITD trial.
a) **RUN-IN PERIOD:**

i) **Regulatory** The following documents were required from sites prior to starting the run-in period:
1) IRB/Ethics Board approval and approved consents from the site’s institution.
2) Completion of community consultation (US sites): Consultation plan including the date of the events, surveys, press releases and ads, the number of attendees at meetings and the number of responses to any of the consultation methods, percentage of attendees/responders who approved.
3) IRB approval of above completed community consultation/notification.
4) IRB/Ethics approval (or institutional approval if the hospital does not have an IRB) at receiving hospitals for participating agencies.
5) EMS agencies FWAs
6) PI Letter of agreement
7) Any other required regulatory documents

ii) **ECGs**
1) Successful sample transmission of ECGs from each EMS agency to site.
2) Successful sample transmission of an ECG from each type of device used at the site (Medtronic, Philips and ZOLL) to the CTC (and any other ECG devices used at the site).
3) Successful completion of 10 complete Epistry CPR Process forms per site. If the site is using devices from multiple companies, they should submit at least 2 from each device manufacturer. A reminder that the EMS Medtronic LP12 must be in the paddle mode to obtain the impedance. Also, Philips devices must be used in the “defib” mode.

iii) **Epistry Data**
1) Successful completion of a treated Epistry episode (cardiac or trauma) from each EMS agency participating in the cardiac study, including a PCR or trauma/cardiac arrest supplemental form.
2) Successful completion of at least 10 Epistry treated cardiac arrests, 5 with data through hospital discharge per site. These may be the same as the episodes in item 1.
3) Outcome data obtained on at least 95% of cardiac Epistry patients.

iv) **ROC PRIMED Data Necessary for Starting Run-In Period**
1) Practice completion of all data forms on 2 patients and submit to the CTC.
2) Names of the site coordinators who will be notifying/consenting patients, doing patient follow-up, and collecting and entering data on the ROC PRIMED data forms.

v) **Site Plans**
1) Final cardiac compliance monitoring plan
2) Distribution of Cardiac Arrest Treatment Guidelines to receiving hospitals (Appendix 3 in the ROC PRIMED protocol).
vi) EMS Training
A total of 90% of active EMS providers within a ROC agency should be trained before that agency can begin to enroll patients in the run-in period. A letter/memo from the site PI will be submitted to the CTC stating that the agency(s) have been adequately trained and the medical director/training director is in agreement will be submitted to the CTC before an agency can begin the run-in period.

vii) EMS Provider Performance Monitoring
ECGs will be reviewed for EMS provider compliance with the CPR process prior to starting the run-in period. It is understood that some agencies may not have a large amount of CPR process data for review depending on when they began using the new AED/defibrillators and this will be taken into consideration when reviewing agency data.

* There will be a staged run-in period for agencies as they complete training, have successfully transmitted data and ECGs and IRB/REB approval has been obtained for their receiving hospitals. In other words, one or more agencies at a site may start the run-in period rather than having to wait until all agencies are ready to begin. For those agencies adopting a cluster design throughout the entire agency the CTC may need to request that 2 agencies start together to balance the recruitment of cases in the treatment arms.

b) PROGRESSION TO EVALUABLE DATA PHASE:

The following goals for EMS agency and clinical site performance will be used as guidelines by the Study Monitoring Committee when deciding whether an agency may proceed to the evaluable data phase of the ROC PRIMED study. The requirements listed for starting the run-in phase will continue to be required for progression from the run-in to the evaluable data phase, in addition to those below.

1) EMS providers notify site of episode within 48 hours of event in 90% of CAs and sites in turn will submit the web Enrollment form within 72 hours of the episode. This will be evaluated per agency.

2) Submission of PCR and ECG data to the CTC will be required on a sample of episodes sufficient to evaluate the quality of protocol performance in a timely manner.

3) ECGs and PCR data during the run-in period will be assessed for EMS provider compliance with the protocol (with the cluster arm). This will be evaluated per agency (may consider waiving if it is a small agency and no cases were submitted). The following are guidelines for benchmarks to be obtained prior to moving to the evaluable data phase.

4) Analyze Early / Analyze Late Protocol Implementation
Interval from 1st EMS CPR to 1st Analysis should be estimated as well as feasible by the local data abstractors. As appropriate to the local practice, this interval might be based on time that defibrillator is turned on, time pads are placed, time that unit arrives on-scene, and paramedic report of antecedent CPR. Sites will be encouraged to use a consistent data abstraction method taking into consideration the local EMS protocol.
• Interval from 1st EMS CPR to 1st Analysis should be <60 seconds in 90% of analyzable cases for Analyze Early
• Interval from 1st EMS CPR to 1st Analysis should be 150–210 seconds in 90% of analyzable cases for Analyze Late
• Extreme outliers should have sufficient explanation of circumstances to assure that there are not problems with protocol adherence. (This might include near simultaneous arrival of a second unit that takes command of the scene.)

5) Inclusion / Exclusion Criteria
• All protocol deviations should be considered individually
• There should be no inappropriate enrollment of subjects (e.g. known pregnancy) or inappropriate treatment of cases (e.g. Analyze Late strategy used on an EMS-witnessed case)

6) ECGs will be reviewed for EMS provider compliance with the intended CPR process. This will be evaluated per agency. In order for any cluster to progress to the evaluable data phase, all agencies within that cluster must be able to progress. The CPR Performance Standards are listed in the Appendix 4 of the protocol, pg. 8.

7) Coordinators will be trained in administering the follow-up quality of life forms. The training will include mock interviews using the follow-up data forms either at a ROC SC meeting or by web-ex.
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