ROC PRIMED Questions and Answers

1) What is the ROC PRIMED study?

ROC PRIMED stands for the Resuscitation Outcomes Consortium **P**rehospital **R**esuscitation using an **IM**pedance valve and **E**arly versus **D**elayed (ROC PRIMED) study. This clinical trial examined the usefulness of two resuscitation strategies for patients who suffer cardiac arrest, when the heart abruptly stops, outside of a hospital setting. The study involved emergency medical services (EMS) providers at locations across the United States and Canada. The goal of the study was to increase the number of neurologically intact patients, who can still function independently, that survive cardiac arrest outside of a hospital setting. ROC is the largest clinical research network to study prehospital treatments for cardiac arrest in the United States and Canada and is composed of 10 clinical centers and a data coordinating center.

One strategy looked at when to analyze the patient's heart rhythm to determine whether defibrillation is needed, methods known as Analyze Early and Analyze Later. Some EMS providers perform cardiopulmonary resuscitation (CPR) for 30-90 seconds before analyzing the heart's rhythm, and, if necessary, defibrillate to restore the heart to its normal rhythm (Analyze Early). Other EMS providers perform CPR for three minutes before analyzing the heart rhythm (Analyze Later) and defibrillate if necessary. There is evidence that the longer CPR duration helps oxygenated blood circulate more, which may prime the heart to receive the most benefit from defibrillation. Other studies suggest that delivering defibrillation sooner might be more helpful. The ROC PRIMED study found both to be equally beneficial, with no improvement or decline in patient survival rates.

The other strategy in ROC PRIMED looked at the use of an impedance threshold device (ITD), to help improve blood flow during CPR given by EMS providers. An ITD, also known as an impedance valve, is a small, hard plastic device about the size of a fist that is attached to the face mask or breathing tube during CPR administered by EMS providers. Although the device is attached to the face mask or breathing tube during CPR, it is not intended to help with breathing. Instead, it is designed to increase the degree of negative intrathoracic pressure during decompression of the chest. Some previous smaller studies on humans and in animal models showed short-term improvement in blood flow in patients who went into cardiac arrest. However, in this study, the use of the device did not appear to improve or decrease patient survival rates.

2) Where was ROC PRIMED conducted?

The study took place at 10 locations across the U.S. and Canada. Approximately 150 EMS and fire services organizations, involving more than 20,000 EMS providers who serve a combined population of nearly 15 million people from diverse urban, suburban, and rural regions participated in ROC PRIMED.

3) Why was the ROC PRIMED study enrollment stopped?

The study's independent safety oversight panel, the Data and Safety Monitoring Board (DSMB) recommended that the study end enrollment early because adding more patients appeared unlikely to

alter the outcome. Preliminary results from the Analyze Early, Analyze Later testing indicate that neither strategy improved or decreased patient survival rates. Both methods appear to be equally helpful for patients. The testing of the ITDs, which are relatively new devices not yet widely used, showed no improvement or decrease in patient survival rates, according to preliminary results. Further analysis may yield additional insights. In both circumstances, there were no patient safety concerns.

4) When did the study stop enrollment?

Investigators could continue to enroll new patients until Nov. 6, 2009. The DSMB made their recommendation to stop the study on Oct. 23, 2009 after reviewing interim data analyses. Researchers began ending enrollment on Oct. 28, 2009.

5) How many patients were enrolled?

Approximately 11,500 patients were enrolled in ROC PRIMED. The first ROC PRIMED patient was enrolled June 7, 2007, and Nov. 6, 2009 was the last day investigators could enroll new patients.

6) What does neurologically intact survival mean?

Patients with preserved neurologic function are able to carry out activities of daily living. In contrast, patients who suffer neurological damage following cardiac arrest may no longer be able to care for themselves due to injury to parts of the brain.

7) Were there any deaths as a result of study participation?

Some cardiac arrest patients died before reaching the hospital or at the hospital, but there is no evidence that anyone died because they were part of the study. All participants received standard emergency care from EMS providers, with some patients randomly selected to also receive the intervention to be tested. Part of the reason for the study is that most patients (90 to 95 percent) who suffer cardiac arrest outside of a hospital setting do not survive. Researchers are seeking interventions that could improve survival rates.

8) What do the results of the study mean?

The preliminary results of the study indicate that a small amount of CPR (30-90 seconds) is just as effective as a longer period of CPR (approximately three minutes) before EMS providers analyze heart rhythm to determine the need for defibrillation when performing CPR. The method of analyzing heart rhythm after 30-90 seconds of CPR is just as beneficial as performing CPR for up to three minutes before analyzing heart rhythm. Both methods are in widespread use depending on the common practice of individual organizations. Use of the ITD did not improve or decrease survival rates of study participants. The novel device is not yet in widespread use.

9) When will the final study results be available?

ROC PRIMED investigators are analyzing the data and will prepare a report for publication to be submitted for peer review. We hope to have the final results published in the coming months. Some

study participants may be followed for up to 6 months following their enrollment in the study, if they agree to be monitored. This data would be included in the final study results.

10) What is an ITD?

An impedance threshold device is a small, hard plastic device about the size of a fist that is attached to the face mask or breathing tube during CPR by EMS providers. The ITD has been shown to increase blood flow and thus potentially improve CPR, which provides only about a quarter of normal blood flow when performed using standard methods. While the impedance device goes over the patient's mouth, it is not a breathing aid. Instead, the device increases the normal pressures created when the chest decompresses to improve blood flow to vital organs.

In animal and smaller human research studies, the device has been shown to markedly increase blood flow during CPR and raise blood pressure. Human studies showed a tendency toward improved short-term outcomes without adverse effects. However, a large human study, such as ROC PRIMED, was needed to show whether the device significantly improves survival without neurological damage.

A modified version of the ITD is approved by the U.S. Food and Drug Administration (FDA) for use in low blood flow conditions other than cardiac arrest.

11) What have other studies of ITD shown?

Smaller published studies in humans suggested that the ITD improves blood circulation and short-term outcomes, such as increased blood pressure. However the total number of patients enrolled was small. Although there was some evidence in these earlier studies favoring use of an ITD, the lack of demonstrated benefit in survival convinced the NHLBI and the ROC investigators that a larger randomized trial was needed to test whether an active ITD is better than a non-functional ITD.

12) What have other studies of Analyze Late versus Analyze Early shown?

Smaller published studies in humans suggested that CPR before defibrillation may increase survival but the results to date were inconclusive. Although there was some evidence in these earlier studies favoring immediate defibrillation (30 to 90 seconds) in cases where the response time is less than two minutes, such response times are rare and the frequent delay in recognition of the out-of-hospital cardiac arrest and calling 911, as well as the complexity of the resuscitation protocol, convinced the ROC investigators that a randomized trial was necessary to test whether Analyze Later is better than Analyze Early.

13) How did patients indicate they would participate in this study?

In most cases, the participant or their representative could not provide informed consent prior to treatment, as is done in most clinical trials. Because of the nature of the research, participants will either be in a semi-conscious or unconscious state when they are enrolled in ROC studies. Life-supporting interventions must be given immediately in the field to save their life. Patients are too sick to consent to immediate treatment. Surviving patients and/or their authorized representatives are informed about

the trial as soon as feasible after the intervention has been given. Instead, the ROC research studies were conducted under federal regulations that allow an exception from explicit informed consent.

Before any patients were enrolled, communities were consulted about participation and made aware that informed consent will not be obtained for most study participants, as required by law. ROC PRIMED also includes follow-up telephone calls with survivors who are required to provide consent for this part of the study.

14) What is an exception from informed consent?

In 1996, the FDA developed specific regulations to permit research without prospective consent under carefully controlled circumstances. This is in recognition of the unique nature of emergency medical situations in which patients or family members cannot give informed consent before treatment as well as the need to allow emergency care to advance through research.

According to FDA regulations, to qualify for an exception from informed consent, the research study must involve participants suffering from a life-threatening disease process or injury for which the current standard of care is associated with a very high failure or mortality rate. In addition, there must be reasonable evidence that the research has the potential to provide real and direct benefit to the patient. Furthermore, studies must be held to the highest ethical standards. The ROC trials have undergone multiple independent rigorous reviews to ensure that they meet these standards.

The use of a randomized clinical trial is the "gold standard" for determining what works best for people. For treatments that must be given immediately to be effective, exception from informed consent research is considered appropriate by federal regulatory bodies and many ethicists who study this field. The obligation to improve standard treatments that yield poor results in life-threatening conditions is also considered an ethical imperative, as is maintaining individual rights of citizens. In waiver of consent trials, citizens receive standard treatment in addition to research treatment. To be tested in this fashion, the research treatment has to have shown promise in earlier or smaller studies.

15) Would you let a family member be enrolled in a future study like this?

Yes, absolutely. Randomized trials are the best way for us to learn how to treat patients with acute life-threatening conditions like cardiac arrest. It is critical that we understand how to effectively treat patients with out-of-hospital cardiac arrest as it remains a significant and serious public health issue.

16) Should public bystanders be performing full CPR, with breathing and chest compressions, or using the "Hands Only" method that was introduced last year?

The ROC PRIMED study did not explore this issue, however, the American Heart Association (AHA) in 2008 put out a science advisory to encourage the general public to skip the ventilation step in CPR and focus only on continuous chest compressions and having someone call 911. Chest compressions should be delivered until professional assistance arrives. The AHA last issued revised guidelines in 2005. In the 2005 version, it was recommended that trained emergency medical service providers use a combination

of ventilation and chest compressions, with a greater emphasis placed on chest compressions. The next AHA guidelines are scheduled to come out in October 2010.

More information:

- Resuscitation Outcomes Consortium: https://roc.uwctc.org/tiki/tiki-index.php

- Sudden Cardiac Arrest: http://www.nhlbi.nih.gov/health/dci/Diseases/scda/scda_whatis.html

Created November 6, 2009