Frequently Asked Questions for patients, relatives or public:

1. Why has this trial come about?

Around 60,000 people sustain sudden cessation of heart function (cardiac arrest) each year in the UK. Initial resuscitation efforts are effective in restarting the heart in about 1 in 4 cases (25%), but over half of these patients subsequently die in intensive care as a consequence of severe brain damage. These dire outcomes are costly to patients and their families many of whom either lose a loved one or are burdened with providing on-going care. Despite the major burden on NHS resources to treat this condition (e.g. provision of intensive care, cardiac catheterisation, therapeutic cooling), there are relatively few trials to inform treatment guidelines compared to other conditions (e.g. cancer, heart disease).

Adrenaline is a drug that is used as part of the treatment for cardiac arrest. Adrenaline has never been formally tested in humans with sufficient numbers to inform us reliably whether it is helpful or harmful. Recent studies have created substantial concern amongst doctors, nurses, paramedics and patients that adrenaline may be harmful when used as a treatment for cardiac arrest. Specifically, recent research has shown that adrenaline reduces blood supply to the brain which can lead to severe brain damage and death. This concern has led to the International Liaison Committee for Resuscitation, a worldwide collaboration of resuscitation experts and scientists, calling for urgent studies to find out the effects of adrenaline in cardiac arrest.

There are several precedents where treatments have been evaluated after years or decades of use and have been found to be ineffective or harmful. It is possible that adrenaline for cardiac arrest may be a similar case. A very high profile example is Thalidomide which was given in the 1960's as a treatment for morning sickness but resulted in infants being born with malformation of the limbs and a dramatically reduced life expectancy.

The need for this trial has also been recognised by the National Institute for Health Research who has provided the funding for this study. As part of the funding process they carefully appraised the need for the study.

The need to do this research is underpinned by a serious concern that although using adrenaline might help restart the heart in the short term, it causes severe brain damage leading to death a few hours or days later. We want the best possible outcomes for all people who have a cardiac arrest, both now and in the future.

2. Is experimenting like this on humans allowed? Is it legal to do this?

The legal basis for entering a patient into the trial prior to informed consent in an emergency situation is set out in Statutory Instrument 2006 No. 2984, The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006. A member of the research team will seek consent to continue in the study as soon as possible once the initial emergency has passed. People who do not want to be part of the trial may opt out in advance by contacting the University Trial Team (see question 13).

Particular care has been taken to ensure this project meets all legal and regulatory requirements.

The trial protocol and supporting documents have been reviewed and approved by the funding body, the National Institute for Health Research (NIHR); by a Research Ethics Committee (REC) who

consider the need for the research and weigh up the risk and benefit for patients; the Medicines and Healthcare Regulatory Authority (MHRA) who review the application with regard to Good Clinical Practice and the Confidentiality Advisory Group (CAG) who review applications for research where consent from the patient cannot be obtained.

3. What is the ethical justification for the trial?

Adrenaline has never been formally tested as a treatment for cardiac arrest. Recent studies have created substantial concern amongst doctors, nurses, paramedics and patients that adrenaline may be harmful when used as a treatment for cardiac arrest. Specifically recent research has shown that adrenaline reduces blood supply to the brain which can lead to severe brain damage and death. This concern has led to the International Liaison Committee for Resuscitation calling for urgent studies to find out the effects of adrenaline in cardiac arrest.

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4. Has the study received ethical approval?

The PARAMEDIC-2 trial was reviewed and approved by the South Central Oxford C Research Ethics Committee.

All research studies run in the NHS are conducted in accordance with the Research Governance Framework and relevant legislation. The Health Research Authority provides robust, ethical review of proposed research via independent Research Ethics Committees (RECs) who scrutinise applications and put the rights, safety, dignity and well-being of research participants at the centre of their decision making.

NHS Research Ethics Committees consist of 12 members, a third of whom are lay (broadly, this means their main professional interest is not in a research area, nor are they a registered healthcare professional).

They safeguard the rights, safety, dignity and well-being of research participants, independently of research sponsors. They review applications for research and give an opinion about the proposed participant involvement and whether the research is ethical. RECs are entirely independent of research sponsors (that is, the organisations which are responsible for the management and conduct of the research), funders and investigators.

5. How will consent be obtained?

It is not possible to obtain consent in the immediate emergency situation as resuscitation must be started without delay. A member of the research team will seek consent to continue in the study as soon as possible once the initial emergency has passed.

6. Why can't you compare data on patients who currently have adrenaline and those who don't?

The only way to measure the effectiveness of adrenaline is to create two arms where patients in one arm is randomised to receive a placebo (salt water) injection and patients in the other arm receive adrenaline, allowing the two 'treatments' to be compared in the same type of patient with similar characteristics (age, sex, medical history etc.). If we were to simply compare current data from everyday records, some patients may not have been given adrenaline because they got a pulse back quickly (for example after early defibrillation), so the data would show more survival in the group who did not receive adrenaline: this would not be a 'fair test' of adrenaline treatment.

7. Why was my relative entered into this trial without anyone's permission or knowledge?

We are aware of the sensitive nature of the circumstances in which patients will be part of the trial, and of distress that relatives will be in at such a difficult time. We have given careful consideration to the need for a compassionate approach to relatives, to reduce further distress, and have discussed this in detail with both the Ethics Committee and with our patient/service user advisers for the trial. The trial has been designed, and will be conducted, according to the legal and ethical requirements, and will be independently monitored to ensure that patients' rights, dignity and safety are paramount.

When a person is unconscious due to their cardiac arrest we can't ask permission about their treatment. Due to the urgent need for treatment we are not able to ask a relative or friend, should there be anyone else on scene. Research like this is considered lawful and ethical, provided it has been scrutinised and rigorously reviewed by several regulatory organisations including an ethics committee (which is a panel of medical, scientific and legal experts as well as representatives of the public) who review the research in terms of its importance to clinical practice and assess the risk and benefits of doing such a trial. The trial is reviewed regularly by two independent monitoring committees, made up of representatives of the public and very experienced medical and scientific experts in the field.

The research team, headed by an intensive care Consultant who works in NHS hospitals as well as being a Professor at the University Clinical Trials Unit, and other doctors, nurses, paramedics and scientists, are required to keep these organisations informed of progress with the trial, and to report to an independent monitoring committee who have the authority to stop the research if there are major concerns about patient safety. Without research like this we would not be able to make improvements in patient care in the emergency setting.

8. My relative died after being enrolled in this trial. I want to know what treatment my relative had.

When someone is in cardiac arrest their heart has stopped and they are clinically deceased. This may be due to one of several causes, for example heart disease, overdose, drowning etc. A person who has a cardiac arrest in the community rather than in hospital has less than 10% chance of surviving. Current treatments for cardiac arrest include basic life support (particularly chest compressions), defibrillation (an electric shock) and a range of medicines such as adrenaline. Of these treatments, good evidence of benefit exists only for basic life support and defibrillation. Adrenaline has never been formally tested in humans with sufficient numbers to inform us reliably whether it is helpful or

harmful, and recent studies have created substantial concern amongst doctors, nurses, paramedics and patients that adrenaline may be harmful when used as a treatment for cardiac arrest. Specifically, recent research has shown that adrenaline reduces blood supply to the brain which can lead to severe brain damage and death. This concern has led to the International Liaison Committee for Resuscitation, a worldwide collaboration of resuscitation experts and scientists, calling for urgent studies to find out the effects of adrenaline in cardiac arrest.

To look at the effectiveness of adrenaline we need to collect data on 8000 patients. It is very difficult look at an individual patient's treatment and decide if part of the treatment lead to the death.

If you decide you do want to know about the treatment your relative received we can tell you this, but we would like to meet with you to do this to be able to explain fully what the information means in order for it to be of help to you, and to offer you support at what we recognise will be a difficult time for you.

9. Adrenaline naturally occurs in the body so how can it be harmful?

Adrenaline is secreted from the adrenal glands during what is known as the "fight or flight response". A much smaller amount is secreted in the body naturally compared to what is injected during cardiac arrest. There is some evidence and theories that people who are very stressed and may be subjected to higher levels of adrenaline are more likely to suffer with stress related illnesses.

10. What if adrenaline turns out to be effective and you denied 4,000 people this life saving drug?

The reason for the trial is that there is a growing body of evidence that adrenaline may not be effective, and may even be harmful. The trial data will be monitored at frequent intervals during recruitment by an independent group of doctors and statisticians (called the Data Monitoring Committee), and if they find that adrenaline or placebo is clearly superior, the trial will be halted. In this way we will make sure that as soon as a result is known, no further trial patients will receive an inferior treatment.

11. What if the hospital staff give adrenaline? Is there any point changing the out of hospital treatment?

Because the concerns are about the effects and safety of adrenaline in patients with out of hospital cardiac arrest, our focus is on patients treated by the ambulance service before reaching hospital. This is because the first treatments given to patients are the most important in determining survival. We will, however, be collecting some data on treatments given in hospital so that we can ensure that we make a fair comparison of patients in each arm of the trial.

12. What if I need adrenaline because of an allergic reaction or anaphylaxis?

The trial will focus on patients in cardiac arrest, and will specifically exclude patients with, or suspected of having, an anaphylactic reaction, as adrenaline is recommended for these patients. The trial is based on concerns about adrenaline in patients with cardiac arrest, where the doses of adrenaline that are given are larger than would be given for anaphylactic shock.

Ambulances will carry standard adrenaline as well as trial drug packs (which will contain either adrenaline or placebo), and this will be used for patients who are not recruited to the trial but require adrenaline.

13. What will be the system to opt out of the Trial?

We respect the wishes of members of the public who do not wish to be enrolled in the PARAMEDIC 2 trial.

If you would NOT wish to be enrolled in the PARAMEDIC 2 trial, in the event that you have a cardiac arrest, you can opt-out by requesting a stainless steel bracelet which has the words 'NO STUDY' engraved on it by completing a form on the trial website www.warwick.ac.uk/paramedic2 or contacting the trial team directly by phone 024 76151164 or email paramedictrial@warwick.ac.uk.

Local paramedics have been trained to look for these bracelets in the same way they do for other medical ID bands. This means that, in the event that you have a cardiac arrest, you will receive standard treatment which may include adrenaline. This system is used successfully in North America for a number of trials.

14. With salt water used in place of adrenaline what effect could this have on patients, despite the low chance of survival out of hospital could this not put lives further in danger?

All patients will receive the treatment that is proven to improve survival from cardiac arrest – these are cardiopulmonary resuscitation (CPR) and defibrillation (electric shocks). Adrenaline is an unproven treatment for cardiac arrest, which is why there is a need for this study

In the volume delivered as a placebo, salt water (saline) will have no significant effect, i.e. it will be neither helpful nor harmful.