



**The Adrenaline Trial**

# **Study Guide for Emergency Care Clinicians**

(Version 1.2 26/09/2014)

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**NHS**

*National Institute for  
Health Research*

## Notes

1. These learning materials are aimed primarily at paramedics, ambulance nurses, emergency care practitioners and doctors recruiting patients in the pre-hospital setting for the PARAMEDIC-2 Trial. They may also be of use to ambulance technicians and emergency care assistants, who may be called upon to assist participating paramedics in the management of patients in the PARAMEDIC-2 Trial.
2. Whenever this guide refers to paramedics, it is assumed other health professionals are included.

## Learning outcomes

After studying these learning materials and further practical training, the student should be able to:

- ✓ Describe the characteristics of a Randomised Controlled Trial (RCT)
- ✓ Discuss key ethical and legal requirements and the principles of research in emergency situations
- ✓ Describe the trial procedures in relation to the trial timeline and data to be collected

Completion of the training and studying learning materials, complemented with an account of your own learning or a written reflective account based in practice, may assist in providing evidence of CPD.



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Also enclosed in training pack:

- ✓ The trial protocol
- ✓ Frequently Asked Questions (FAQs)
- ✓ Summary of evidence on adrenaline studies (BMJ paper)
- ✓ Local trial procedures
- ✓ Copy of training slides
- ✓ Statement from the HCPC

## What is a Randomised Controlled Trial?

Randomised controlled trials (RCTs) are a research design used primarily to test if treatments are safe and effective. As their name suggests, RCTs involve the **random** allocation of different interventions (treatments) to patients. This helps to balance any potential **confounding factors** (see below) between treatment and control groups: thus, an RCT is a 'fair' test of one intervention compared to another.

RCTs are the most **rigorous** way of determining whether there is a relationship between the intervention and the patient outcome and to be effective in answering a research question they must have several important procedures in place.

- The patient must have the intervention at random (pure chance) and not be pre selected in any way that might introduce bias.
- Both groups of patients (Intervention and Control) must be treated identically except for the experimental treatment.
- Potential biases (see below) must be eliminated.

### **Confounding factors explained:**

*Factors that can mask the effect of the treatment under investigation, e.g. clinical factors.*

### **Bias explained:**

*When someone has a preference towards a result i.e wanting to see that adrenaline is affective. The means someone is no longer impartial.*

***Example of potential bias AND a confounding factor in the PARAMEDIC-2 study would be if paramedics chose only to use the trial drug packs on patients that were more likely to die and use regular adrenaline for those likely to survive. This would introduce a confounding factor where by paramedic choice in treatment affects the study results and the bias of the paramedic's opinion on the drug pack affects the results of the study. This would seriously jeopardise the integrity of the trial and we would not be able to answer the research question and therefore a lot of time, effort and money would be wasted.***



## What is Good Clinical Practice (GCP)?

GCP is an international quality standard for the design, conduct and reporting of research involving humans. It is comprised of 13 core principles, which apply to all clinical investigations that could affect the safety and well-being of human participants (in particular, clinical studies of medicinal products).

*The 13 principles of Good Clinical Practice are as follows:*

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior ethical approval or favourable opinion by institutional review board (IRB)/independent ethics committee (IEC).
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a relevant qualified medical person.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.



GCP was developed by the regulatory authorities of the EU, Japan and USA in a steering group termed the Tripartite International Conference on Harmonisation (ICH) and provides international assurance that:

- Data and reported results of clinical investigations are credible and accurate, and
- Rights, safety and confidentiality of participants in clinical research are respected and protected

Compliance with GCP is a **legal obligation** in the UK/Europe for all studies of investigational medicinal products ('drug trials'). Thus, PARAMEDIC-2 falls within the remit of GCP requirements.

We have written a slide set to describe how the principles of GCP apply to the PARAMEDIC-2 trial. Visit our website [www.warwick.ac.uk/PARAMEDIC2](http://www.warwick.ac.uk/PARAMEDIC2) for more information.

### Available GCP Courses:

*Paramedics are not required to undertake full GCP training for the PARAMEDIC-2 trial, but we recommend you should read information provided and understand the principles*

The College of Emergency Medicine provide further information on GCP on their website with the facility to complete a self assessment and print a CPD certificate:

<http://www.collemergencymed.ac.uk/Shop-Floor/Research/GCP%20training%20and%20key%20documents/>

Because PARAMEDIC-2 is funded by the National Institute for Health Research (NIHR), further information and training (over and above that contained in this booklet and delivered as part of the trial training) is available for free via the NIHR Clinical Research Networks.

<http://www.crn.nihr.ac.uk/learning-development/good-clinical-practice/>



## Consent and Ethics (A summary of section 2.6 of the protocol)

Due to the nature of research in the emergency setting and the need for urgent intervention to treat cardiac arrest, informed consent cannot be obtained from the patient at the time of recruitment.

This trial has been reviewed and approved by the **Oxford Research Ethics Committee** [14/SC/0157] in accordance with the **Medicines for Human Use (Clinical Trials) Amendment (no.2) Regulations 2006**. This means that authority has been given to allow us to recruit patients without obtaining consent at the time of enrolment into the trial. The authority has been given with several conditions which include having a communication strategy to ensure we inform the general public about the trial and having a strategy for handling any queries from the general public.

We also have approval from the **Medicines for Healthcare and Research Authority (MHRA)** (who regulate medicines in the UK and can inspect the trial documentation for compliance with good clinical practice) and the **Confidentiality Advisory Group (CAG)** (who give recommendations to the ethics committee about holding data without consent, see). For more information go to:

<http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials>

<http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/what-is-section-251/>

If patients survive to be admitted to a hospital ward, the research paramedics employed for the trial will make contact with the patients (or their personal or legal representatives) and seek informed consent to participate in the follow-up of the study, which involves completing quality of life questionnaires (see section “Hospital Involvement” in this document for more information).

## Declaration of Helsinki (1964)

For more information on ethical aspects of clinical research, paramedics are encouraged to read the Declaration of Helsinki (1964, see link below) which details the ethical principles to which research should be conducted. Some key quotes from the Declaration include:

*“The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease”.*

*“Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects”.*

<http://www.wma.net/en/30publications/10policies/b3/>



## Randomisation for PARAMEDIC-2 (Section 2.7 of the protocol explained)

For PARAMEDIC-2, the trial drug packs will consist of a plastic bag holding either 10 syringes containing adrenaline (1mg in 3ml) or 10 syringes containing placebo (water for injection). There will be no way for the paramedic or other health professionals to know what is in the pack (adrenaline or placebo).

Ambulance service vehicles will carry the trial packs.

Randomisation will occur by opening the pack.

It is vital to the scientific integrity of the trial that only **1 pack per patient** is used and any **unused syringes are not used** on another patient.

It is also vital that if a trial drug pack is used on a patient that **'standard' adrenaline is NOT used on that patient in the pre-hospital setting.**

It is **essential** to the trial that local procedures (enclosed) are followed and the reporting of the enrolment of a trial patient is carried out in timely fashion so that the trial team know a patient is in the trial and the team can begin to track the patient through the hospital and make contact if appropriate.





## More about PARAMEDIC-2

### Data Collection for the Trial:

We plan to recruit patients and collect data from Autumn 2014 until August 2017.

If you open a trial drug pack the patient will be enrolled. You do not have to complete any additional forms but you will need to follow your local procedures for reporting the enrolment of a patient, please read the enclosed local procedures for your ambulance service. It is very important that we know about any enrolled patients as quickly as possible so that we can follow them up in hospital and notify surviving patients of their enrolment and discuss consent to continue in the trial. Data will be collected by the WCTU in collaboration with the Ambulance Service Audit department. The table below shows the data that will be collected.

You will not be asked to report any data other than the initial enrolment of the patient. Ambulance staff (other than the Research Fellows) will be responsible for collecting the data for Day 0 only.

|  | Day 0<br>Cardiac<br>Arrest | Hospital | Day 30 | Week 6<br>Letter to<br>Patient (if<br>missed in<br>hospital) | Month 3<br>(2-4)<br>Follow up<br>visit | Month 6<br>(5-10)<br>Postal | Month 12<br>(12) |
|--|----------------------------|----------|--------|--|--|-----------------------------|------------------|
| Inclusion/<br>Exclusion Criteria,<br>Cardiac Arrest Data           | ✓                          | x        | x      | x  | x                                      | x                           | x                |
| Patient Identifiers (if<br>applicable), Adverse<br>Event Reporting | ✓                          | ✓        | x      | x  | x                                      | x                           | x                |
| Survival Status  | ✓                          | ✓        | ✓      | x  | ✓                                      | ✓                           | ✓                |
| Neurological<br>Outcome, <u>QoL</u>                                | x                          | ✓        | x      | x  | ✓                                      | ✓                           | x                |
| Patient contact,<br>Consent  | x                          | ✓        | x      | ✓  | x                                      | x                           | x                |
| Functional outcomes  | x                          | x        | x      | x  | ✓                                      | x                           | x                |



## **Adverse Events - section 4 of protocol explained:**

**A serious adverse event (SAE) or serious adverse drug reaction (SAR) or unexpected serious adverse reaction (SUSAR):** any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- (a) results in death
- (b) is life-threatening
- (c) requires hospitalisation or prolongation of existing hospitalisation
- (d) results in persistent or significant disability or incapacity
- (e) consists of a congenital anomaly or birth defect.

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

## **Reporting a problem**

To ensure patient safety and comply with GCP we must collect, review and report SAE's/SARs quickly (ambulance service to report to WCTU within 24 hours).

**However for PARAMEDIC-2 all patients will be transported to hospital or die therefore we do not want these events reporting at as SAEs.**

DO NOT report the following events:

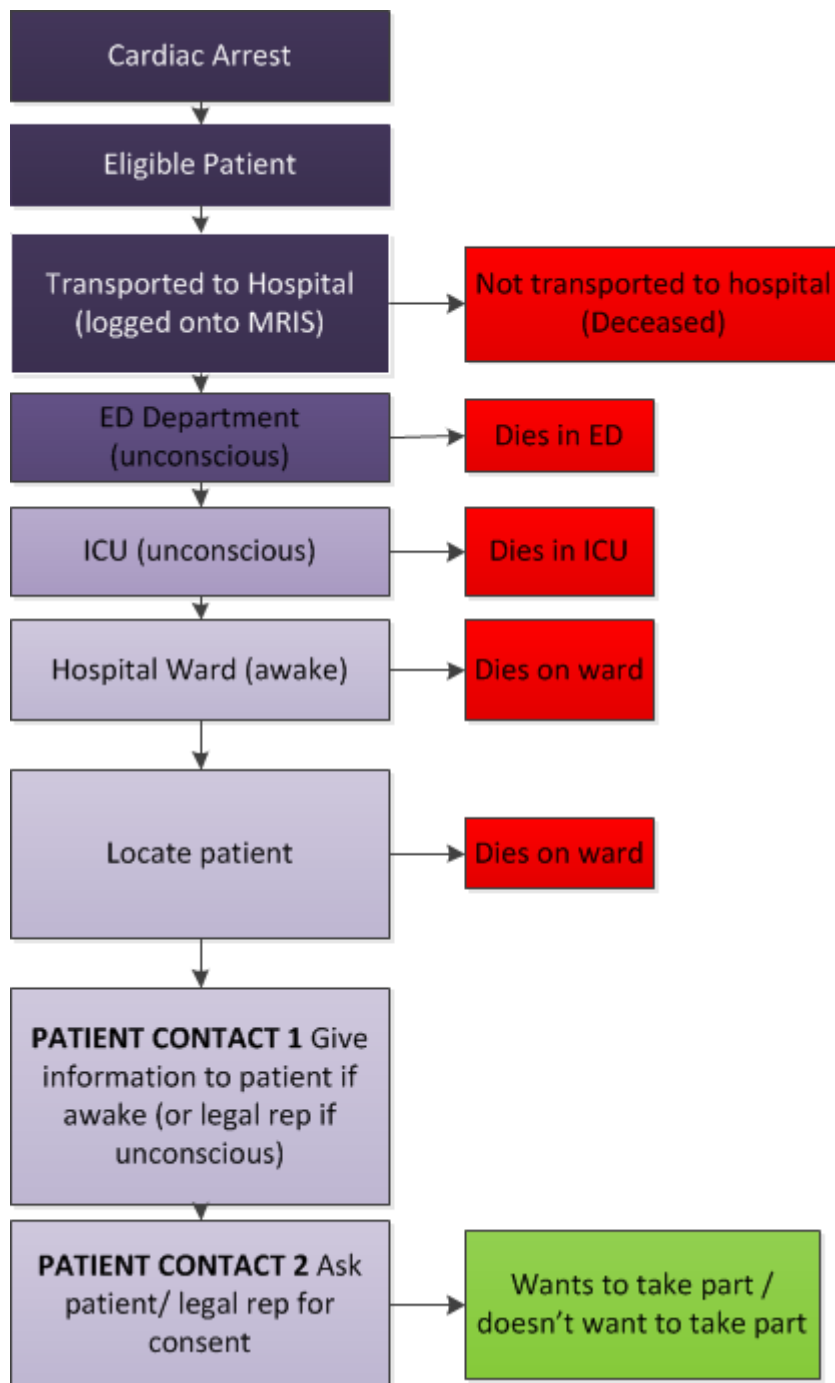
- Death
- Hospitalisation
- Persistent or significant disability or incapacity
- Organ failure

Because these are all associated with cardiac arrest anyway.

**Please report anything else that is unusual or of concern to your local Research Fellow immediately.**

## What happens when the patient goes into hospital?

The flow chart below shows the steps that will occur. We (the Trial Team) will track the patient in hospital and check what their outcome is. If they survive to hospital ward (where they are more likely to be conscious) the trial Research Paramedics will liaise with the hospital care team about the appropriateness of approaching the patient or their family (if the patient lacks capacity) to explain the trial and discuss consent to continue in the trial.





If the patient agrees to continue we will arrange for a Research paramedic to visit the patient at home approximately 3 months after the cardiac arrest to complete questionnaires about their health, recovery and quality of life. We will also post out questionnaires at approximately 6 months post cardiac arrest and track survival to 12 months post cardiac arrest.

### Trial Timeline:

The table below shows the trial management plan approved by the National Institute for Health Research Health Technology Assessment (NIHR HTA) who have funded the trial. The trial funding started in March 2014 and will end in August 2018. We need to have recruited 8,000 patients by end of August 2017 and aim to have results in 2018.

|                        | YEAR 1 |        |        | YEAR 2 |        |        |        | YEAR 3      |        |        |        | YEAR 4    |        |        | YEAR 5   |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
|------------------------|--------|--------|--------|--------|--------|--------|--------|-------------|--------|--------|--------|-----------|--------|--------|----------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
|                        | SET UP |        |        | PILOT  |        |        |        | RECRUITMENT |        |        |        | FOLLOW UP |        |        | ANALYSIS |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
|                        | Mar-14 | Apr-14 | May-14 | Jun-14 | Jul-14 | Aug-14 | Sep-14 | Oct-14      | Nov-14 | Dec-14 | Jan-15 | Feb-15    | Mar-15 | Apr-15 | May-15   | Jun-15 | Jul-15 | Aug-15 | Sep-15 | Oct-15 | Nov-15 | Dec-15 | Jan-16 | Feb-16 | Mar-16 | Apr-16 | May-16 | Jun-16 | Jul-16 | Aug-16 | Sep-16 | Oct-16 | Nov-16 | Dec-16 | Jan-17 | Feb-17 | Mar-17 | Apr-17 | May-17 | Jun-17 | Jul-17 | Aug-17 | Sep-17 | Oct-17 | Nov-17 | Dec-17 | Jan-18 | Feb-18 | Mar-18 | Apr-18 | May-18 | Jun-18 | Jul-18 | Aug-18 |
| Set up & approvals     | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black       | Black  | Black  | Black  | Black     | Black  | Black  | Black    | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  |        |        |
| Recruitment & Training | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black       | Black  | Black  | Black  | Black     | Black  | Black  | Black    | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  |        |        |
| Follow up              | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black       | Black  | Black  | Black  | Black     | Black  | Black  | Black    | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  |        |        |
| Analysis & Results     | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black       | Black  | Black  | Black  | Black     | Black  | Black  | Black    | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  |        |        |
| Final report to funder | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black       | Black  | Black  | Black  | Black     | Black  | Black  | Black    | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  | Black  |        |        |

### Your Responsibilities:

Follow the trial protocol:

- Include the right patients
- Give the assigned drug from the trial pack
- Complete the study documentation (local guidance)
- Report any serious adverse events

**Ask if you are unsure**