Emergency Code Break in Clinical Trials.

POLICY DETAILS	
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Superseded documents	Final v5.1 24/Oct/2018
Relevant regulations/legislation/guidelines	Statutory Instrument 2004 no 1031 Statutory Instrument 2006 no 1928 (*as amended from time to time)*

CHANGE HISTORY			
Date	Version Number	Change details	Approved by
11/11/2013	2.0	Scheduled Review and change of branding from JCTO to KHP-CTO and ESMS to MTIS	Jackie Powell
17/03/2015	3.0	Clarification of the scope of this SOP. This SOP is only mandatory for those trials choosing to use MTIS.	Jackie Pullen
28/04/2017	4.0	Scheduled review and change of name from MTIS to ESMS Global Ltd. Update to glossary section and ESMS setup procedure.	Jackie Pullen
21/08/2018	5.0	Procedure updated to include trials not using ESMS for the provision of	Jackie Pullen

		emergency code break services. Information added regarding how the randomisation data would be obtained and securely delivered to ESMS.	
24/10/2018	5.1	Minor amendment to include trials managed by KHP-CTO	Jackie Pullen
13/10/2021	5.2	Minor amendment to ESMS processes	Jackie Pullen

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1.0 GLOSSARY

Blinding - A procedure in which one or more parties involved in the conduct of a clinical trial are unaware of the treatment assignment(s).

Chief Investigator (CI) - A Registered Physician, Dentist, Pharmacist or Registered Nurse who has overall responsibility for the conduct of the trial.

Clinical Research Associates – (CRAs) – Part of the KHP-CTO Quality Team. Ensure compliance with the Regulations, GCP and SOPs, by monitoring clinical trials.

Clinical Trial - Any investigation in human participants, other than a non-interventional trial, intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal product and/or to identify any adverse reactions to one or more such products and/or to study absorption, distribution, metabolism and excretion of one or more such products with the object of ascertaining the safety and/or efficacy.

Code Break - breaking the blind. This is the mechanism that permits the rapid identification of the trial treatment in case of a medical emergency, but does not permit undetectable breaks of the blinding.

Emergency Scientific and Medical Services Global Ltd. (ESMS) – an independent provider of emergency code break and medical information.

Investigational Medicinal Products (IMP) - means a pharmaceutical form of an active substance or placebo being tested, or used as a reference in a clinical trial. This includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial –

- **(a)** used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation,
- **(b)** used for an indication not included in the summary of product characteristics (or equivalent document) under the authorisation for that product, or
- **(c)** used to gain further information about the form of that product as authorised under the authorisation

King's Health Partners (KHP) - King's Health Partners Academic Health Science Center is a pioneering collaboration between one of the King's College London (University) and three of London's most successful NHS Foundation Trusts – Guy's & St Thomas', King's College Hospital and the South London & Maudsley.

King's Health Partners Clinical Trials Office (KHP-CTO) - Established in 2006 by King's College London, Guy's & St Thomas' NHS Foundation Trust, South London and Maudsley NHS Foundation Trust and King's College Hospital Foundation Trust to provide a streamlined approach for all aspects of trial administration.

KHP-CTO Quality Team – Comprises the Clinical Quality Manager, Clinical Research Associate(s), Clinical Trial Administrator(s), Systems Executive and Training Executive(s).

MATTS – MedSciNet's Active Trial Tracking System. An electronic Clinical Trial Portfolio Management System.

Medicines & Healthcare products Regulatory Agency (MHRA) - UK competent authority responsible for regulation of clinical trials.

Principal Investigator (PI) - A Registered Physician, Dentist, Pharmacist or Registered Nurse who has responsibility for the conduct of the trial at a host site.

Standard Operating Procedures (SOPs) - "detailed, written instructions to achieve uniformity of the performance of a specific function," SOPs are the base on which Quality Systems and Processes are conducted and monitored against.

The Regulations - The Medicines for Human Use (Clinical Trials) Regulations 2004, transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 1031. This became effective on the 1st May 2004. An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928. As amended from time to time.

2.0 BACKGROUND AND PURPOSE

The investigator site should have the ability to unblind a subject immediately in the case of a medical emergency. The purpose of this SOP is to describe the process for emergency code break (unblinding) of treatment within clinical trials of IMPs sponsored or co-sponsored by King's Health Partner Organisations.

3.0 SCOPE

Clinical trials of IMPs sponsored by one or more of King's Health Partner Organisations, or clinical trials where the sponsor responsibilities are managed by the KHP-CTO, where one or more parties involved in the trial is unaware of the treatment assignments (blinded).

4.0 AUTHORISED USERS

- The only people authorised to perform emergency unblinding are healthcare professionals who have direct responsibility for the care of the trial subject concerned. Clinical Trial Investigators, or pharmacists calling on their behalf, are also recognised as authorised users. KHP-CTO staff are authorised to request unblinding for expedited reporting of SUSARs.
- The subject themselves, their relatives, or other members of the public are not authorised users and an emergency unblinding cannot be performed upon their request. If such a request is made the caller will be referred to their Clinical Trial Investigator, GP or their nearest A&E Department, as appropriate.
- During normal office hours, requests for information about the trial (e.g. study visits/appointments medication queries etc.) should be referred to the local site Investigator Team: contact details supplied upon set-up.
- Members of the public will not be referred to the KHP-CTO.
- In extraordinary circumstances or incidents where there may be a public health concern, other professional individuals, e.g. police, teacher, may need to be authorised to request emergency unblinding by King's Health Partner Organisation Communications Departments.

5.0 PROCEDURE FOR TRIALS NOT USING ESMS FOR EMERGENCY UNBLINDING SERVICES

5.1 Set Up

- Breaking the treatment code may be conducted by the use of physical code breaks or electronically via an internet or automated telephone based system.
- In case of electronic system a back-up system is required so the code break can be performed manually in the event that electronic system fails.
- Code breaking instructions will be specified clearly in the clinical trial protocol. *Additional instruction detailing steps and contacts for emergency unblinding may need to be filed in*

the Investigator Study File i.e. when emergency unblinding is provided by a local pharmacy and site-specific contact details are required.

- Where appropriate, participants will be issued with emergency cards to be carried at all times. The cards should include the trial identification, emergency contact number and patient's trial identification number as a minimum.
- The KHP-CTO CRA or delegate will test the unblinding system, including contact via the electronic system if applicable, prior to recruitment of the first participant and document the results of the test call in the TMF.

5.2 Process

- Any code break intentional or accidental will be documented and will include as a minimum the date, time, reason for unblinding, name of the person requesting and person breaking the code. Care must be taken when filing documentation and communicating an unblinding event to ensure that the trial team are not unblinded unnecessarily.
- The KHP-CTO will be informed, in writing, of the code break as soon as possible.
- The KHP-CTO CRA or delegate will ensure that the service provider will be informed of any applicable updates to the study documents.

5.3 End of the Trial

- The KHP-CTO CRA will perform reconciliation of physical code breaks at the end of the study. The CRA will verify whether code envelopes are still intact and any code that has been broken or lost during the study has been appropriately documented.
- When using an electronic system confirmation will be obtained from the service provider that the blinding has not been compromised.

6.0 PROCEDURE FOR TRIALS USING ESMS Global Ltd. FOR EMERGENCY UNBLINDING SERVICES

ESMS Global Ltd. provide a 24-hour emergency medical response service for all trials using their services within the scope of this SOP. They operate on-site 24 hours a day, 365 days a year. Information scientists have immediate access to all study documentation, including randomisation information. Under the terms of the master service level agreement in place between the KHP-CTO and ESMS Global Ltd., the procedure below should be followed.

6.1 Set Up

- The KHP-CTO CRA will email ESMS Global Ltd. with notification of a new trial set up once the MHRA CTA application has been submitted and all final documents uploaded onto MATTS.
- This email will include a list of study document titles (according to the MATTS naming conventions), version numbers and issue dates as follows:-

- Investigator's Brochure, Summary of Product Characteristics or relevant medical information, as appropriate.
- An approved protocol summary and any relevant amendments;
- Trial specific patient information leaflets
- Contact details of Trial Physician/ Local site Investigator team.

- A trial-specific work order will be prepared by ESMS Global Ltd. and sent to the KHP-CTO CRA for due diligence checking. Once confirmed as correct, this Work Order will be signed by the KHP-CTO Director or delegate prior to the trial commencing recruitment. A fully executed copy of each trial-specific work order will be sent to the ESMS Global Ltd. Head of Services and one copy filed in the trial Sponsor File.
- The KHP-CTO CRA will ensure that the randomisation data (code-break envelopes, randomisation schedules) are delivered to ESMS Global Ltd. The data will be provided by either physical code break (list, envelopes) or access to an electronic randomisation system and reception of randomisation emails. The CRA will request an email confirmation from ESMS Global Ltd. once physical randomisation data is received. If an electronic system used the CRA will ensure that unblinded access to the randomisation system has been obtained and designated username and password provided to ESMS Global Ltd by the randomisation system provider.
- ESMS Global Ltd. will provide 24hr contact details to be entered on patient cards. These cards will be given to each patient when consent has been obtained.
- Services will only commence when the work order is fully signed and ESMS Global Ltd. has received all necessary trial documentation. ESMS Global Ltd. will set up the trial as defined within their internal SOPs and will confirm setup completion to trial contact. The KHP-CTO CRA will perform the testing of unblinding system prior to recruitment of the first participant. This will be documented in Site Initiation Visit Checklist. A notification of ESMS readiness to provide service will be sent to the KHP-CTO CRA for inclusion in the trial sponsor file.

6.2 The Service

- ESMS Global Ltd. is first on-call to break randomisation codes and provide medical support at all times.
- The KHP-CTO CRA is responsible for informing ESMS Global Ltd. of any updates to study documents.
- ESMS Global Ltd. will conduct all code break activities according to their SOP's.

6.3 End of Trial

The KHP-CTO CRA will provide ESMS Global Ltd. with written notification of the end of the trial, confirmation of receipt by ESMS Global Ltd. will be forwarded to the KHP-CTO.

6.4 Process

- The completed Clinical Trial Enquiry form *(see related templates)* is emailed along with a request for acknowledgement of receipt to the KHP-CTO Pharmacovigilance inbox.
- The KHP-CTO Clinical Trials Administrator (or delegate) will return the acknowledgement of receipt form to ESMS Global Ltd. and inform the KHP-CTO CRA of the request for code break and the outcome.
- The CRA will inform the Chief /Principal Investigator(s) of the code break request.
- All completed Clinical Trial Enquiry forms, Clinical Trial Reports and receipts will be filed in the trial Sponsor file.

7.0 RELATED TEMPLATES

7.1 ESMS Clinical Trial Enquiry Form

7.2 ESMS Clinical Trial Enquiry Report

8.0 APPROVAL AND SIGNATURE

23 November 2021

Jackie Pullen
Director KHP Clinical Trials Office

Date