Neuro-navigated TMS for Chronic SCI patients

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IRAS Reference	--

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CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
CAG	Confidential Advisory Group
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
GAfREC	Governance Arrangement for NHS Research Ethics
HRA	Health Research Authority
HTA	Human Tissue Authority
ICF	Informed Consent Form
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File
nTMS	Neuro-navigated Transcranial magnetic stimulation
SCI	Spinal cord injury
ISNCSCI	International standards for neurological classification of spinal cord injury
EM-SCI	European Multicentre study about Spinal cord injury
PPI	Public patient involvement

STUDY SUMMARY

STUDY OVERVIEW	
Full title	**Validating neuro-navigated TMS stimulation in SCI patients: a feasibility study towards a gene therapy for SCI.**
Objectives	Primary objective: Whether neuro-navigated Transcranial Magnetic Stimulation can be used as an additional outcome measure to EM-SCI assessments in a Spinal Cord Injury trial? Secondary objective: Whether nTMS stimulation combined with MRI Tractography can be used as an adjunct outcome tool with EM-SCI assessments for a planned first in human SCI gene therapy trial.
Type of trial	Single site observational study
Trial design and methods	Recruited patients will undergo nTMS and MRI Tractography in addition to full EM-SCI assessments. Comparisons will be made to assess the sensitivity of TMS as an outcome measure and whether it can be used as an adjunct whilst assessing SCI patients.
Health condition(s) or problem(s) studied	Chronic cervical and thoracic spinal cord injuries (greater than 6 months from injury).
Target sample size	20 patients
Trial duration per participant:	1 month
Main inclusion/exclusion criteria:	Inclusion Criteria: - Single traumatic event at least 6 months prior to recruitment - ISNCSCI grade A, B, C or D - Able to participate in EM-SCI and nTMS assessments and capable of informed consent Exclusion Criteria: - History of Malignancy - History of other Neurological disease - Pregnancy - Other cord lesions or tethering - Cord transaction or penetrating injury
Statistical methodology and analysis:	Analysis will be performed in house using SPSS statistical software (IBM SPSS software version 28).
STUDY TIMELINES	
Study Duration/length	6 months
Expected Start Date	February 2023
End of Study definition and anticipated date	31 August 2023

1 INTRODUCTION

This is an exciting time for translating experimental Advanced Therapies into treatments for spinal cord injury (SCI). There are currently no regenerative therapies available that target the underlying biology. Over the last 5 years we have developed a viable gene therapy approach for treating SCI in pre-clinical models. We are on the cusp of translating this therapy to first-in-human studies. We are leading a programme to establish a world-first regenerative gene therapy for traumatic SCI affecting upper limb mobility (since recovery of arm/hand function is one of the highest patient priorities). Our team will develop an innovative trial design involving neurosurgical delivery of the gene therapy into the spinal cord, followed by specialist neuro-rehabilitation.

For a clinical trial to have the best chance of success, we need to address key steps which include validation of new assessment methods for the clinical trial. Our aim is to determine whether neuro-navigated Transcranial Magnetic Stimulation (nTMS) can be used as an adjunct to standard assessments of function in SCI patients. Following two patient and public involvement events (patient focus group and feedback for project design with our rehabilitation partners), we will recruit chronic SCI subjects to carry out European Multicenter Study about SCI (EM-SCI) assessments. EM-SCI assessments are well established assessment tools for SCI patients and include the EM-SCI 'core' assessments (ISNCSCI, WISCI-III, Walk Test, SCIM 3) and EM-SCI 'additional' assessments (GRASSP, Pain score, neurophysiology). We will compare and validate nTMS with EM-SCI assessments in stable chronic SCI patients with both cervical and thoracic injuries. nTMS with combined Tractography MRI of the cortico-spinal tract (the main motor pathway of the spinal cord) will allow functional characterisation and density measurements of this tract in SCI patients.

2 BACKGROUND AND RATIONALE

Worldwide, more than 20 million people live with the devastating consequences of a traumatic SCI, with >250,000 new injuries suffered each year[1,2]. Along with loss of sensory and motor function and paralysis, many patients suffer incontinence, chronic pain and depression. SCI therefore imposes severe limitations on mobility, independence, full participation in society and quality of life. SCI also has a high financial burden, with healthcare costs among the highest of any medical condition (estimated at £1.4 billion per annum in the U.K.)[2]. Current treatments rely on early surgical intervention for mechanical decompression, symptomatic relief, supportive care and rehabilitation. There are currently no adequate therapies available. SCI therefore represents a clear unmet need for which new treatment options are vital.

Most spinal cord injures occur in the neck (cervical) region, causing upper limb paralysis. Regaining use of the hands (the ability to reach, grip, hold and pick up objects) would enable independent living, is the highest rated patient priority, and would have immense impact for reducing healthcare burden and improving quality of life. King's College Hospital has one of the

largest neurosurgical units in the United Kingdom. It provides specialist acute input for all SCI covering a catchment of over 4 million people. Over the last 5 years it has admitted and treated an average of 65 SCI patients per year, with around half of these patients with a traumatic SCI. KCH's rehabilitation partner is the world-renowned National Spinal Injuries Centre (NSCIC) at Stoke Mandeville, and KCH is NSIC's largest referring centre. There is an urgent need to find novel interventions to improve outcome in SCI patients both within our large patient population at King's and also the wider SCI community.

We have pioneered the use of Chondroitinase ABC (ChABC) for treating SCI, since the first *in vivo* demonstration that local intrathecal ChABC injections could restore sensorimotor hindlimb function to paralysed rats, to the recent development of an advanced gene therapy approach for restoring upper limb function (Figure 1)[3,4]. ChABC has the largest body of pre-clinical evidence supporting efficacy than any other experimental treatment for SCI and is considered a leading candidate for clinical translation, with efficacy demonstrated by many labs worldwide and in numerous species, including mice, rats, dogs and primates. We developed a vector-based gene therapy strategy for ChABC and demonstrated improved function in pre-clinical SCI contusion models. With this approach we are addressing the ambitious challenge of developing regenerative therapies that enable functional reconnection of damage nerve fibres and engage paralysed muscles. GMP grade vectors are being produced and regulatory approvals are being sought for a first-in-human clinical trial.

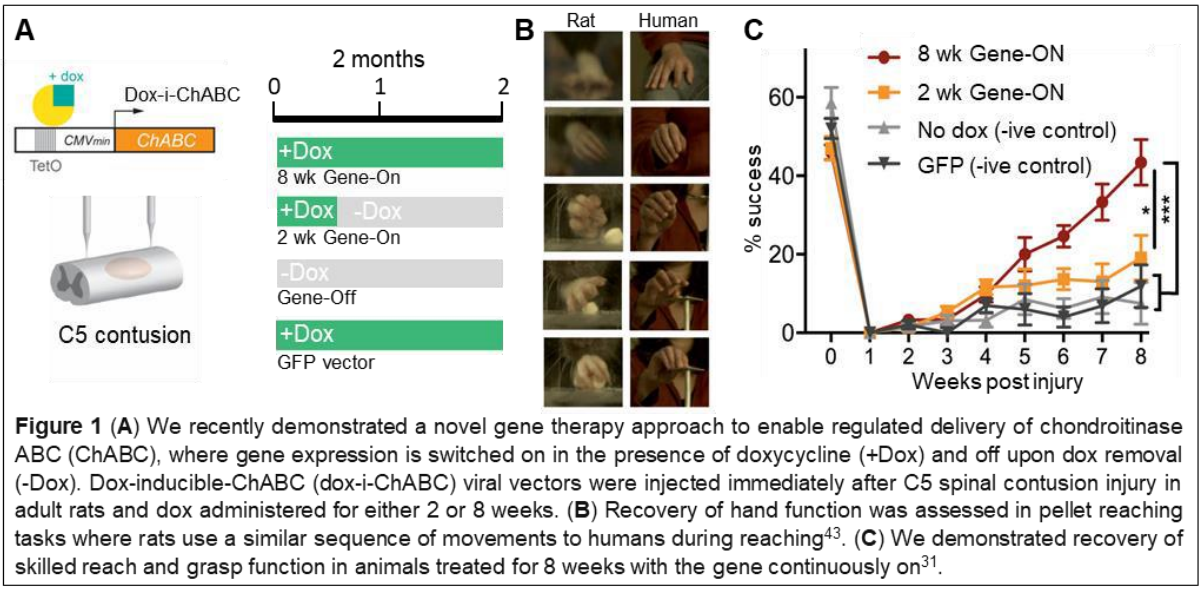


Figure 1 (**A**) We recently demonstrated a novel gene therapy approach to enable regulated delivery of chondroitinase ABC (ChABC), where gene expression is switched on in the presence of doxycycline (+Dox) and off upon dox removal (-Dox). Dox-inducible-ChABC (dox-i-ChABC) viral vectors were injected immediately after C5 spinal contusion injury in adult rats and dox administered for either 2 or 8 weeks. (**B**) Recovery of hand function was assessed in pellet reaching tasks where rats use a similar sequence of movements to humans during reaching[43]. (**C**) We demonstrated recovery of skilled reach and grasp function in animals treated for 8 weeks with the gene continuously on[31].

Key to the success of the trial is the ability to assess the functional changes in SCI patients. The EM-SCI 'core' (ISNCSCI, WISCI-III, Walk Test, SCIM) and EM-SCI 'additional' assessments (GRASSP, Pain score, neurophysiology) are validated assessment tools utilized widely used in SCI trials[5]. While the state of art in the field is at the cusp of a breakthrough trial, we believe an additional assessment with neuro-navigated Transcranial Magnetic Stimulation (nTMS) will improve the chance of trial success since it will have greater sensitivity to pick up subtle changes. Moreover, we can select participants with residual CST function more likely to respond to a neuroplasticity- promoting treatment. nTMS is a non-invasive method using a magnetic field to stimulate the underlying cerebral cortex. In SCI, non-navigated TMS has been used to both assess function and as an adjunct to rehabilitation to promote recovery[6,7].

nTMS allows for an individual location of the magnetic stimulation within an acceptable margin of error derived from the registration process. When compared with non-navigated TMS, the navigated TMS allows for more spatially discrete cortical stimulation and more stable motor evoked potentials with significantly higher amplitudes and shorter latencies[8]. Also, when different navigation methods are compared, 'E-field' navigation proved to be superior to line-navigation method[9]. At King's, we use an E-Field nTMS. We combine nTMS with MRI tractography, a 3D modelling technique used to visually represent nerve tracts using data collected by diffusion MRI. This accurately delineates the location of the motor cortex. The advantage for this is pairing a positive TMS cortical response with a defined_subcortical tract that carries that same motor information, thus confirming a true positive response.

3 OBJECTIVES

3.1 Primary Objective

Can neuro-navigated Transcranial Magnetic Stimulation be used as an additional outcome measure to EM-SCI assessments in a Spinal cord injury trial?

– Compare EM-SCI assessment with nTMS in ten chronic thoracic SCI patients

– Compare EM-SCI assessment with nTMS in ten chronic cervical SCI patients

3.2 Secondary Objectives

nTMS stimulation combined with MRI Tractography can be used as an adjunct outcome tool with EM-SCI assessments for a planned first in human SCI gene therapy trial.

Specifically, nTMS will demonstrate sensitivity for cortico-spinal tract function, giving a novel tool for stratifying and selecting patients for SCI trials.

4 STUDY DESIGN

This is a pilot study in the assessment of nTMS as an adjunct tool in measuring outcome within chronic spinal cord injury patients. Initial PPI events will be performed where patients will be engaged in obtaining feedback on study design and protocol for both the pilot nTMS study and the potential subsequent Gene therapy trial. Following these events, suitable patients who meet the inclusion criteria and have displayed interest in participation will be consented for the study. Patients will then attend for a single day of assessments as follows:

1 – The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) assessment protocol consists of two sensory examinations, a motor examination, and a classification framework (the impairment scale) to quantify the severity of the spinal cord injury. The grading is from A to E, with A being a complete injury with no motor or sensory function and E being normal sensory function. Patients recruited will vary between A and D to give an indication of variability in the motor response to allow comparisons between injury severity.

2 – Neurophysiology. Three standard neurophysiological measures will be registered: MEP (motor evoked potentials), SSEP (somatosensory evoked potentials) and NCV (nerve conduction velocity). MEPs and SSEPs of the tibialis and ulnar nerves quantify the status of the efferent and afferent pathways in the spinal cord. The NCV will be used to exclude peripheral nerve lesions.

3 – Functional Tests. Assessment of the walking ability of patients with movement disorders is an important outcome measure in rehabilitation. The Walking Index for Spinal Cord Injury II (WISCI II) has been validated in SCI patients, The WISCI II has an original scale that quantifies a patient's walking ability; a score of 0 indicates that a patient cannot stand and walk and the highest score of 20 is assigned if a patient can walk more than 10m without walking aids of assistance. In addition, the following two time tests will be performed: Timed Up & Go (TUG) test and 10-metre walking test (10MWT).

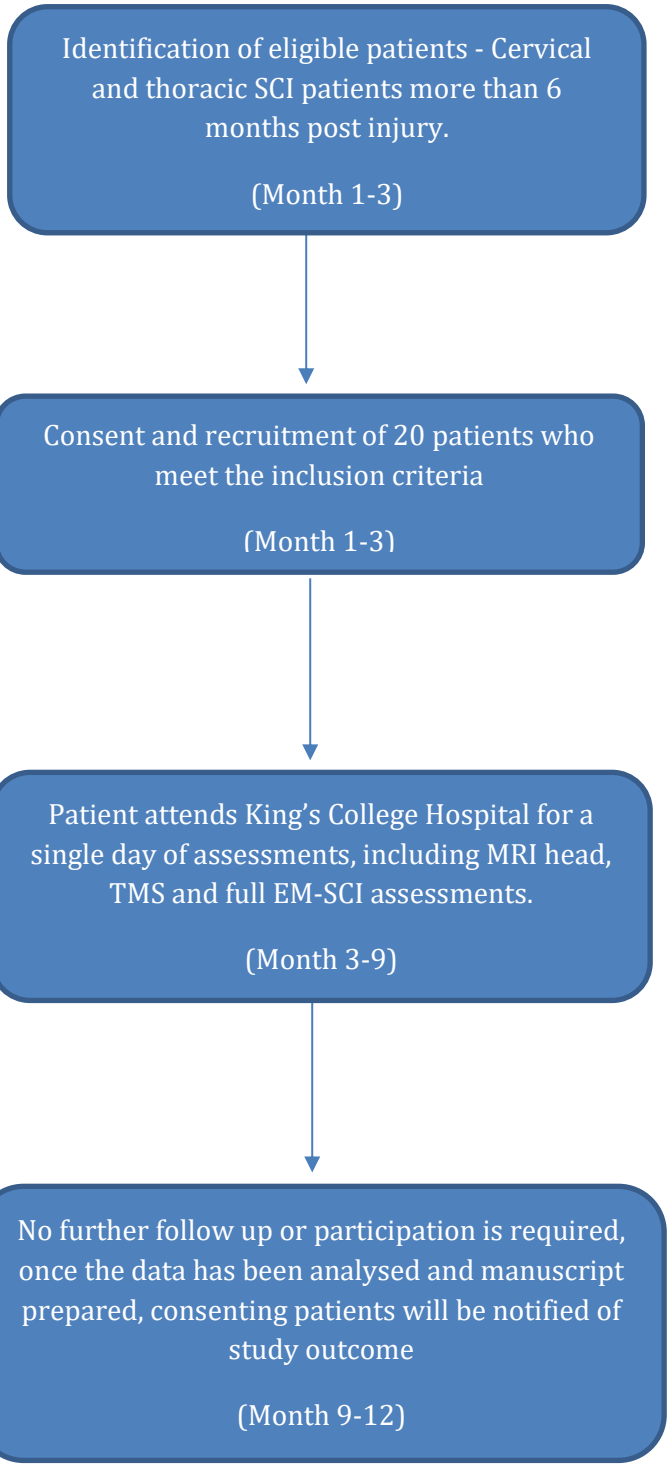
4 - Spinal Cord Independence Measure 3 (SCIM 3). The Spinal Cord Independence Measure (SCIM) is a disability scale developed specifically for patients with spinal cord lesions. It focuses on the requirement of personal assistance and/or technical aids with domains in self-care, respiration and sphincter management and mobility. The score is between 0 and 100.

5 - Graded and Redefined Assessment of Strength, Sensibility and Prehension version 1 (GRASSP v1)10. The GRASSP is an outcome measure to assess hand function in patients with a cervical spinal cord injury. It consists of three domains: 1. Strength, 2. Sensation and 3. Prehension: including relevant finger positioning performance with 6 Activities of Daily Living. The score is between 0 and 116.

6 - MRI Tractography followed by neuro-navigated Transcranial Magnetic Stimulation will be undertaken. The rationale is that nTMS will provide a more sensitive characterisation of a functional CST in SCI patients11. Moreover, nTMS provides spatial resolution of the tracts which standard neurophysiology cannot determine. The addition of MRI tractography allows accurate neuro-navigated localisation of the CST and quantification of the fibre density of the CST.

After acquisition of the MRI scans, nTMS-seeded tractography will be performed. nTMS positive motor responses will be used as regions of interest and another region of interest will be placed in the brainstem at the level of the superior cerebellar peduncle. This technique will provide somatotopic tractography. DTI-derived metrics (Fractional Anisotropy (FA), Axial Diffusivity (AD), Radial Diffusivity (RD), Mean Diffusivity (MD) and Hindrance Modulated Orientation Anisotropy (HMOA)), number of fibres and volume will be calculated for both CSTs. Our hypothesis is that an abnormal cortical excitability will correlate with abnormal CST metrics supporting microstructure impairment. This may be particularly true with the tract specific metric, HMOA.

Comparisons between EM-SCI and nTMS/tractography assessments will be made to determine if nTMS can be used as an adjunct which is more sensitive in the assessment of SCI patients. For instance, nTMS can induce motor evoked potentials in patients with no active movement detected in neurological examination and this can have an impact in terms of prognostication of motor recovery, which is especially important for SCI trials.


Identification of eligible patients - Cervical and thoracic SCI patients more than 6 months post injury.
(Month 1-3)
Consent and recruitment of 20 patients who meet the inclusion criteria
(Month 1-3)
Patient attends King's College Hospital for a single day of assessments, including MRI head, TMS and full EM-SCI assessments.
(Month 3-9)
No further follow up or participation is required, once the data has been analysed and manuscript prepared, consenting patients will be notified of study outcome
(Month 9-12)

5 CONSENT

The Informed Consent form must be approved by the REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator or designee must ensure that each trial participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with their participation. Participants reserve the right to withdraw consent at any point without reason.

Alternatively, recognising many centres have transitioned to virtual outpatient appointments and may not see a participant in person until the day of surgery, verbal informed consent can be obtained by telephone. This must be countersigned by a second investigator, to confirm that the individual received a verbal description of the study, had received the PIS, and had had sufficient time to consider the information and an opportunity to ask questions, and voluntarily agreed to participate in this study.

ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

- Single traumatic event at least 6 months prior to recruitment

- ISNCSCI grade A, B, C or D

- Able to participate in EM-SCI and nTMS assessments and capable of informed consent

5.2 Exclusion Criteria

- History of Malignancy

- History of other Neurological disease

- Pregnancy

- Other cord lesions or tethering

- Cord transaction or penetrating injury

RECRUITMENT

Participants will be identified and recruited from spinal cord injury follow up clinics at King's College Hospital, where eligible patients will be approached. Patients will also be approached via Participant identification centres, with Stoke Mandeville Hospital (National spinal injuries unit) the agreed site for patient referrals.

6 PATIENT AND PUBLIC INVOLVEMENT (PPI)

Two Public Patient Involvement (PPI) events have taken place in the planning and preparation of this study. The first event took place in the National Spinal Injuries Centre at Stoke Mandeville (NSIC), England in November 2022. This was followed by an event in the National spinal injuries unit in Glasgow (February 2023).

Both involved presentations on Gene therapy as a novel treatment option for spinal cord injury and neuro navigated TMS as an assessment tool in chronic SCI. Participants were also consulted on the study design including the proposed full day of assessments planned.

Feedback from the PPI event's was overwhelmingly positive, with participants supportive of new studies that may further the management of SCI patients. Moreover no concerns were raised against the study design, and participants felt the full day of assessments was definitely feasible. All participants if eligible felt they would be interested in partaking within the neuro TMS trial despite any potential risks.

7 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the KCH R&I Office, and deemed sufficient to cover the requirements of the study.

The research costs for the study have been supported by AO Spine.

8 DATA HANDLING AND MANAGEMENT

Personal data will be obtained with full consent and transparency of its use. Confidentiality will be maintained through de-identification of participants.

Data will be made de-identifiable and stored in a secure university/hospital computer at King's College Hospital and King's College London, and only shared between accredited members of the direct care team via encrypted email. Personal data once no longer required will be erased in accordance with GDPR guidance, any remaining data/information will remain non-identifiable.

9 PEER AND REGULATORY REVIEW

The study will undergo initial peer review within the research team.
The study was deemed to require regulatory approval from the following bodies - HRA and REC. Each approval will be obtained before the study commences.

10 ADVERSE EVENTS AND INCIDENT REPORTING

10.1 Definitions of Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the intervention/treatment/procedure involved.
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

10.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

Severity

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

Expectedness

Category	Definition
Expected	An adverse event which is consistent with the available information about the intervention/treatment/procedure in use in this study.
Unexpected	An adverse event which is not consistent with the available information about the intervention/treatment/procedure in use in this study*

* this includes listed events that are more frequently reported or more severe than previously reported

10.3 Procedures for recording adverse events

- All adverse events will be recorded in the medical records in the first instance.
- All Adverse events will be recorded in the CRF following consent.
- All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.
-

10.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the medical records and the CRF.

All SAEs (except those specified in section 16.2 as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete an SAE form and the form will be emailed to the R&I Office (kch-tr.researchqualityassurance@nhs.net) within 1 working day of becoming aware of the event.

Where the event is unexpected and thought to be related to the intervention/treatment/procedure this must be reported by the Investigator to the REC and Health Research Authority, using the SAE Report form for non-CTIMPs (available from the HRA website) within 15 days.

10.5 Serious Adverse Events that do not require reporting

You may choose not to report some particular SAEs to the CI/R&I Office, for example if they are expected to occur on a regular basis and offer no further new information to your safety profile or are related to the disease area of the participants. It should be specified that where the frequency or severity of these events is unusual they must be reported. These events must continue to be recorded in the medical records, CRF however you may state that you will not complete an SAE form and forward it to the CI/R&I Office. Provide the rationale for doing so.

10.6 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC, Health Research Authority and R&I office of the measures taken and the circumstances giving rise to those measures.

10.7 Protocol deviations and notification of protocol violations

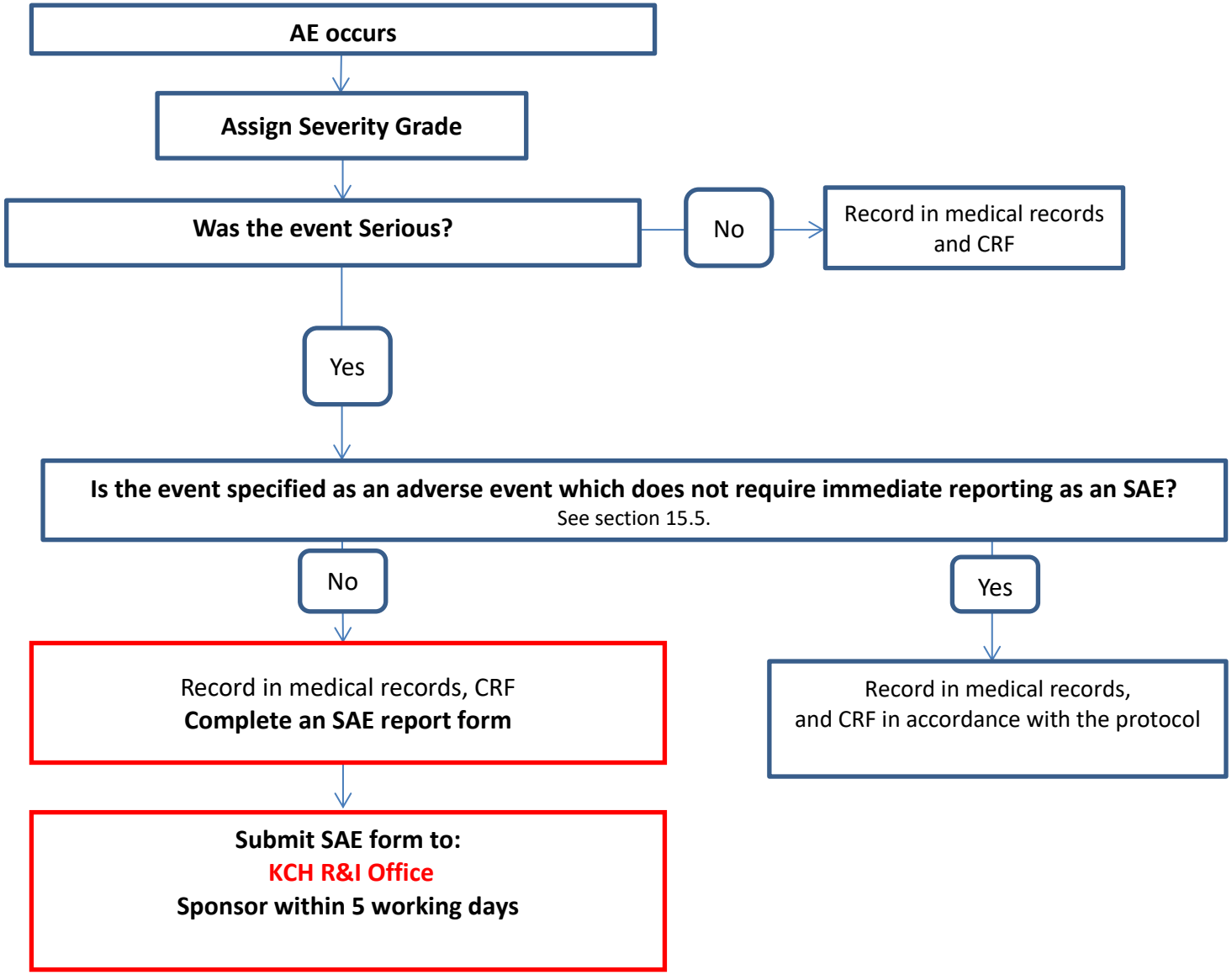
A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or
(b) the scientific value of the study.

The CI and R&I Office should be notified immediately of any case where the above definition applies during the study conduct phase.

Flow Chart for SAE reporting



10.8 Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.
b. It is contrary to specified or expected standard of patient care or service.
c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d. It puts the Trust in an adverse position with potential loss of reputation.
e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.
A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

11 MONITORING AND AUDITING

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

12 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files

13 INDEMNITY ARRANGEMENTS

KCH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered and Trust approved. Potential claims should be reported immediately to the R&I Office

King's College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that KCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. King's College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

14 ARCHIVING

Research data generated will be stored for up to 5 years following the end of the study. Physical consent forms and some physical personal will also be retained and stored for this time period.

15 REFERENCES

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