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WHEAT International Trial

Safety Reporting Manual (for sites)

Version 2.0 effective 20 October 2022

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Associated Documents

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WHEAT Protocol	1.1 04 October 2022
WHEAT SAE Report Form	1.0 13 September 2022
WHEAT PD/PV Report Form	1.0 04 August 2022
WHEAT Trial Procedures Guide	2.0 20 October 2022
WHEAT Trial Procedures Guide – Continuing Care	1.0 20 October 2022

1. Introduction

The purpose of this document is to describe the procedures involved in detecting and recording expected Adverse Events (AEs) and Serious Adverse Events (SAEs), as well as reporting unexpected Serious Adverse Events (SAEs) requiring notification to Sponsor.

2. Scope

This procedure manual is applicable to all delegated personnel working on the WHEAT Trial at all participating sites.

It is not the intention that this manual be read as a standalone document and the current version of the protocol should also be read in conjunction.

3. Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
DSUR	Developmental Safety Update Report
eCRF	Electronic Case Report Form
ICTU	Imperial Clinical Trials Unit
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare Products Regulatory Agency
PI	Principal Investigator
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction

4. Responsibilities

Chief Investigator (CI)	• Review the SAE report form from site • Determine whether SAE is related to the trial/trial-related activities • Responsible for sign-off of SAE • Provide advice and guidance to participating sites where required
Principal Investigator (PI)	• Responsible for immediately reporting all unexpected/trial-related SAEs • Reviewing unexpected/trial-related SAEs for causality and severity, unless this is delegated to another study doctor on the study delegation log • Signing off documentation i.e. SAE Report forms, unless this is delegated to another study doctor on the study delegation log
Study Physician/Sub-Investigator	• Safety-recording and reporting duties delegated by the PI • Responsible for immediately reporting all unexpected/trial-related SAEs • Reviewing SAEs for causality and severity • Ensuring the relevant documentation is obtained to ensure a correct judgement regarding an event • Signing off documentation i.e. SAE Report forms
Study Nurse/Coordinator	• Duties delegated by the PI. • Responsible for immediately reporting all unexpected/trial-related SAE report forms via email to the Sponsor • Identify at each evaluation if any expected and unexpected/trial-related SAEs have occurred • Ensure the safety events (expected and unexpected) are recorded in the patient's medical records • Ensure any follow up information on AE/SAE are reported in the form
Study Manager/ Monitor	• Review all SAE Report forms to ensure all available information has been entered into BadgerNet • Ensure unexpected/trial-related SAEs are reported to the Trial Joint TSC/DMC • Report all unexpected/related SAEs to the approving Research Ethics Committee (REC) •

5. References

- WHEAT Protocol V1.1 dated 04 Oct 2022

6. Definitions

6.1 Definition of a Serious Adverse Event (SAE)

While this is not a Clinical Trial of an Investigational Medicinal Product/Device, the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK), provides a definition of a Serious Adverse Event which is applied to the WHEAT Trial:

Serious Adverse Event (SAE):

Any adverse event that:

- results in death;
- is life-threatening;
- requires prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect (not applicable to WHEAT).

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient 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.

6.2 Definition of Severity

The assignment of severity should be made by the investigator responsible for the care of the patient using the definitions listed in Table 1 below.

If any doubt about the seriousness/severity exists the local investigator should notify ICTU who will notify the Chief Investigator.

Table 1. Definitions for assessment of severity

MILD	Aymptomatic or mild symptoms; clinical or diagnostic observations only; no change in baseline age-appropriate behaviour*; no change in baseline care or monitoring indicated
MODERATE	Resulting in minor changes of baseline age-appropriate behaviour*; requiring minor changes in baseline care or monitoring***
SEVERE	Resulting in major changes of baseline age-appropriate behaviour* or non-life threatening changes in basal physiological processes**; requiring major change in baseline care of monitoring***
LIFE THREATENING/DISABLING	Resulting in life-threating changes in basal physiological processes**; requiring urgent major change in baseline care
FATAL	Death related to Adverse Event (AE)

*Age-appropriate behaviour refers to oral feeding behaviour, voluntary movements and activity, crying pattern, social interactions and perception of pain

**Basal physiological processes refer to oxygenation, ventilation, tissue perfusion, metabolic stability and organ functioning

***Minor care changes constitute: brief, local, non-invasive or symptomatic treatments

***Major care changes constitute: surgery, addition of long-term treatment, upscaling care level

Ref: Fig. 1: Tables from the Neonatal Adverse Event Severity Scale. | Journal of Perinatology (nature.com)

6.3 Assignment of Causality

The assignment of causality should be made by the investigator responsible for the care of the patient using the definitions listed in Table 2 below. If any doubt about the causality exists, the local investigator should notify ICTU who will notify the Chief Investigator. In the case of

discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the approving NHS Research Ethics Committee (REC) will be informed of both points of view.

Table 2. Definitions for assessment of causality

UNRELATED	The AE is definitely not associated with the trial intervention.
UNLIKELY	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after a trial-related procedure). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
POSSIBLE	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after a trial-related procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely. For example, the event starts a reasonable time after the trial-related procedure, stops/improves when the trial-related procedure has been stopped; cannot be reasonably explained by known characteristics of the patient's clinical state.
DEFINITE	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. For example, starts a reasonable time after the trial-related procedure; stops/improves when the trial-related procedure has been stopped; can reasonably be explained by known characteristics of the trial-related procedure.

7. Safety Reporting Procedure for Participating Sites

7.1 Expected Serious Adverse Events (SAEs)

The following are serious adverse events that could be reasonably anticipated to occur in this population of infants during the course of the trial or form part of the outcome data.

Expected SAEs do not require reporting by the trial sites as SAEs <u>if they are not thought to be related to the allocated trial intervention</u> but do require relevant data to be captured in the summary EPR systems (BadgerNET Summaryor BadgerNET EPR) as part of routine clinical care:

- Death (unless cause not anticipated in this population)
- Necrotising enterocolitis or gastrointestinal perforation
- Bronchopulmonary dysplasia (or chronic lung disease)

- Intracranial abnormality (haemorrhage or focal white matter damage) on cranial ultrasound scan or other imaging
- Pulmonary haemorrhage
- Pneumothorax
- Anaemia requiring blood transfusion
- Hyperbilirubinaemia
- Hyperglycaemia
- Hypoglycaemia
- Coagulopathy requiring treatment
- Hypotension
- Hypertension
- Impaired renal function
- Patent ductus arteriosus (PDA)
- Retinopathy of prematurity
- Sepsis
- Fractures
- Clinically significant liver failure
- Clinically significant extravasation injury
- Clinically significant left ventricular hypertrophy on echocardiography
- Hydrocephalus
- Surgery for a condition not anticipated in this population

These events should be recorded in the patient's medical records from the time of consent to final trial assessment.

Only if these events are thought to be causally related to the allocated pathway of care would they require urgent reporting to the trial centre as outlined below (7.2 Unexpected/Trial-Related SAEs).

7.2 Unexpected/Trial-Related SAEs

Unforeseen SAEs and those related to the intervention allocated at randomisation must be reported to ICTU by a member of site staff within 24hours of becoming aware of the event. Site staff may email a completed SAE form to ICTU (WHEAT@imperial.ac.uk). Paper forms, with instructions, will be made available with the trial documentation to enable anyone to report an SAE. If following the reporting of an SAE additional information

becomes available, a new SAE form should be completed. The PI at the site will assess whether the SAE was as a result of trial related activities (related).

ICTU will forward a copy of the SAE form to the Chief Investigator (CI) as soon as possible on receipt. The CI will review whether the SAE was as a result of trial related activities (related). If the assessments of the PI and CI do not agree further discussion can take place and/or if either assesses the SAE to be related and unexpected it will be further reported as below.

All unexpected and trial intervention related SAEs will be submitted to the Research Ethics Committee (REC) that gave a favourable opinion of the trial within 15 working days of the CI becoming aware of the event, using the HRA report of serious adverse event form (see HRA website). In addition, all related and unexpected SAEs will be reported to the sponsor and the Canadian trial team (IWK) and be reported to the DMC and relevant R&D offices including IWK.

Related and unexpected SAEs are defined as:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

To report an unexpected/trial-related SAE:

Complete an SAE form & submit to the Study Coordination Centre (ICTU) as soon as possible (within 24 hrs). SAE forms have been included in your *Local Information Pack*.

ICTU Contact: WHEAT Trial Manager
wheat@imperial.ac.uk

7.3 Guidance on reporting unexpected/trial-related SAEs

- Each completed SAE report form should systematically be reviewed and validated by the site Principal Investigator (PI) to ensure that

relationship and causality are assessed and documented in the source notes.

- If any further information becomes known regarding an existing SAE, the investigator must report it by amending the original SAE report form.
- At each contact with the subject during the treatment period, the Investigator must seek information on adverse events by examination.
- All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the patient medical records
- The clinical course of each event should be followed until resolution or stabilisation.
- The completed SAE form will be signed off by the PI.
- The Chief Investigator or designated deputy will review the SAE report form as soon as possible. In the event of missing information the Chief Investigator or designated deputy will contact the ICTU Trial manager or the site staff if it falls in a weekend/bank holiday to inform of any queries.
- The ICTU Trial Manager will contact the site to obtain further information about the SAE, as soon as possible following the event being reported and during the follow-up phase of the event, to obtain any missing or other relevant information.
- Any follow-up information regarding a SAE must also be recorded in the patient medical notes and reported within the same SAE form previously reported.
- All SAEs should be recorded & reported (unexpected/trial-related SAEs only) from the time of consent to final patient study visit.
- An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.
- All unresolved SAEs should be followed by the Investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At neonatal discharge, the Investigator should document any ongoing SAEs, and these should be managed as per local practice

8. Revision History

Version	Date Effective	Reason for update (page and section of change)
2.0	20 Oct 2022	Clarification that trial-related as well as unexpected SAEs are to be reported to Sponsor.