SAFETY REPORTING MANUAL FOR INVESTIGATOR SITES

Protocol No: 22SM8039

Sepsis Trials in Critical Care

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1. Introduction

The purpose of this document is to describe the procedures for appropriately recording and reporting adverse events which occur during participants' involvement in the SepTiC study.

2. Scope

This manual is applicable to the SepTiC study and outlines the safety reporting procedures for participating investigator sites. This manual is to be used alongside the study protocol and Investigator Brochure/SmPC.

3. Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
IB	Investigator Brochure
ICTU	Imperial Clinical Trials Unit
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Authority
PI	Principal Investigator
SmPC	Summary of Product Characteristics
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SSAE	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
SSPM	Study Specific Procedure Manual

4. Responsibilities

Chief Investigator	• Decide with Sponsor which SAEs do not need expedited reporting • Review any SAEs within required timeframes • Clarify any uncertainty about AE classification • Meet reporting requirements to REC/s and MHRA • Perform an evaluation of all events with respect to causality and expectedness • Ongoing safety evaluation, e.g. in conjunction with the pharmaceutical company, and with support from the Study Manager and/or Monitor/s as required, including trend analysis and signal detection, of any IMP(s) and any findings that may affect the health of subjects • Reviews and approves the Development Safety Update Report (DSUR) • Reviews and signs Annual Progress Report
Principal Investigator	• Assess each serious adverse event reported at the investigator site for: severity, seriousness, causality. • Responsibilities
Site Staff	• Complete SAE form as required • Responsibilities
Study Manager/Monitor	• Track reported SAEs via OpenClinica Reporting • Oversee reporting procedures including follow-up information from sites • Follow up on queries raised by Data Managers, Monitoring and pharmacovigilance personnel

5. References

- Reference any applicable regulations or associated policies/procedures
- General Data Protection Regulation (GDPR) (EU) 2016/679
- Medicines for Human Use (Clinical Trials) Regulations 2004

6. Procedures

Contact Details

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6.1. Definitions

Reference Safety Information (RSI)	The information used for assessing whether an adverse reaction is expected. For this study it is contained in the Investigator's Brochure (IB).
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. *Note: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the trial medication, whether or not considered related to the investigational medicinal product (IMP).*
Adverse Reaction (AR)	All untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions (ARs). The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event (SAE)	An SAE is defined as any event that: • results in death***** • is life-threatening****** • requires hospitalization*******, or prolongation of existing inpatient's hospitalisation. • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect *****For this study, death or any events that are captured as an outcome in the eCRF do not require reporting as an SAE unless, in the opinion of the local PI, the death was attributable to a study intervention/IMP or the trial protocol. ** Life-threatening, in the definition of an SAE or SAR, refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event

	which hypothetically might have caused death if it were more severe. *** Hospitalisation means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission). Pregnancy is not considered an SAE but should be recorded and followed up to ensure a congenital abnormality does not occur.
Serious Adverse Reaction (SAR)	A SAR is defined as a SAE that is judged to be related to any dose of study drug administered to the subject.
Suspected Serious Adverse Reaction (SSAR)	Any AR that is classified as serious and which is consistent with the safety information of the IMP as listed in the Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC)
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any SAR that is NOT consistent with the applicable product information as set out in the RSI as follows: • within the Summary of Product Characteristics (SmPC) for that product (in the case of a product with a marketing authorisation) • within the Investigator's Brochure (IB) for that product (in the case of any other IMP)

Definitions, procedures, and responsibilities for recording and reporting AEs/ /SAEs are also detailed in the trial protocol.

6.2. Defining Adverse Events

For clinical trials of an Investigational Medicinal Product (CTIMP) an adverse event (AE) is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

It is essential that all AEs that occur during the course of the study are appropriately reported in order to ensure the participants' continuing safety.

AEs that are **not** considered serious should be included in the subject notes. The definition of seriousness is found in section 6.1.

6.2.1 Causality

The assignment of causality for adverse events should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists, the local investigator should inform the study coordination centre who will notify the Chief Investigator. The pharmaceutical companies and/or other clinicians may be asked to advise in

some cases. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. If no agreement is made, the MHRA will be informed of both points of view.

Unrelated	No evidence of any causal relationship
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 trial medication). 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 administration of the trial medication). 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.
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

6.3. Reporting Procedure

As with all recording and reporting, subject confidentiality and adherence to the General Data Protection Regulation (GDPR) (EU) 2016/679 must be maintained on all reports.

As this is a trial is conducted in critically ill patients with life-threatening sepsis then adverse events are expected to occur regularly in most, if not all, patients. Therefore, unless an adverse event is assessed to meet Serious Adverse Event criteria, these adverse events will not be reported in the case report form and simply noted in the patient's local medical record.

For this study, the Reference Safety Information (RSI) is detailed in the Sargramostim Investigators Brochure (IB). Sites should ensure they are using the most up-to-date version of this document. The IB includes a list of adverse events and known side-effects considered to be expected for the study drug.

6.3.1. If the AE is assessed as serious, the PI or staff member must enter on eCRF **immediately of becoming aware or within 24**

hours occurring during the patient's ICU stay up to a maximum of 28 days.

(i) As per protocol death does not require reporting as an SAE unless attributable to the intervention/IMP.

(ii) The following events do not require reporting as these are captured via secondary outcomes: - organ failure and support, or a new infection including Clostridium Difficile infection.

Active monitoring of patients after discharge from ICU or after 28 days is not required, but if the PI becomes aware of safety information that appears to be drug or trial related, involved a participant who participated in the study, even after study completion, this should be reported via the eCRF.

6.3.2. The SepTiC SAE reporting form is available via the OpenClinica study database. There are three different SAE report types:

- **Initial –** To be completed if the SAE is not resolved at the time of reporting.
- **Interim –** To be completed after an initial SAE report if there is a follow-up but the SAE is not resolved.
- **Final –** To be completed only when the SAE is resolved. If the SAE is resolved at time of reporting, the first report can be the final report.

6.3.3. Local requirements at each site, e.g., NHS Trust clinical governance procedures, should also be followed.

6.3.4. After completing and submitting the SAE form, the sponsor team may request further information from the site. All requests for further information should be responded to as soon as possible.

6.3.5. All SAE's and follow-up information should be recorded in the patients' medical records.

6.3.6. All SAE's must be followed up until resolution or end of trial if this is sooner.

6.4. Review procedure

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/eCRF)

6.5. SUSAR reporting procedure

If an SAE is determined to be **related and unexpected** (not previously described in the RSI, or the nature or severity is not consistent with the RSI) to the study medication then it is considered a SUSAR.

6.5.1. The SepTiC SAE form should be completed on OpenClinica following the steps listed in section 6.3

6.5.2. The patient should be unblinded. Refer to the SepTiC IMP Management Plan for the unblinding procedure.

7. Revision History

SSPM Ref.	Date Effective	Reason for update (page and section of change)
v1.0	07 Nov 2023	First version