Protocol no. 22SM8039

IMP MANAGEMENT PLAN

Effective Date: 13 Mar 2024

Prepared by: **Name:**	**Title:**	**Signature:**	**Date:**
Janis Best-Lane	Clinical Trial Manager	Digitally signed by Janis Best-Lane Date: 2024.03.13 17:35:39 Z	
Approved by: **Name:**	**Title:**	**Signature:**	**Date:**
Mary Cross	Operations Manager	Mary Cross Digitally signed by Mary Cross Date: 2024.03.18 13:55:20 Z	

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1. Introduction

The purpose of this document is to describe the procedures involved in the management of all aspects of IMP order, delivery, use and destruction during the course of the trial.

2. Scope

This procedure is applicable for the Sponsor Trial Team and site teams (usually pharmacy) working on the SepTiC trial who will be involved in ordering, delivery receipt and destruction of the SepTiC IMP.

3. Abbreviations

GCP	Good Clinical Practice
ICTU	Imperial Clinical Trials Unit
IMP	Investigational Medicinal Product
ISF	Investigator Site File
QP	Qualified Person
SSPM	Study Specific Procedure Manual

4. Responsibilities

Chief Investigator	• All roles delegated to the Study Manager / Monitor, as described below and in the text, can be performed by the CI. • To oversee the management of IMP as per GCP and relevant clinical trial regulations.

Trial Manager/Monitor (Blinded)	• To ensure that IMP is not supplied to a participating site until all required documentation has been obtained. • To review and approve completed IMP release forms (SOP_FRM_CR004) for activation of participating sites. • Order IMP stock from the manufacturer (Partner Therapeutics) to the distributer (Victoria Pharmaceuticals). • Order IMP stock from the distributer to site (Victoria Pharmaceuticals) to the sites. • To monitor on-going IMP management and accountability at participating sites according to the study Monitoring Plan. • Request sealed envelope access for unblinded pharmacist from CDS team.
Imperial CTU Clinical Database Team (CDS)	• Maintain unblinded kit code master list • Allocate IMP kits to study sites on Sealed Envelope system when IMP receipt is confirmed by unblinded pharmacist. • Activate equal number of IMP and placebo kits to be dispensed by pharmacy to ICU • Replenish kits via sealed envelope like for like (IMP and placebo).
IMP Distributer (Victoria Pharmaceuticals)	• Take receipt of stock from the manufacturer (Partner Therapeutics) and complete packaging and labelling of product in preparation for delivery to sites. • Fulfil IMP orders and arrange delivery to participating sites. • Maintain oversight of IMP stock levels

Unblinded Pharmacist	• Complete Unblinded Pharmacist training and request access to Sealed Envelope Database • Confirm delivery of IMP kits to CDS Team • Check the unblinded activated kits on sealed envelope that should be dispensed to ICU are equal IMP and placebo. • Dispense correct kits to ICU • Contact the CDS team to arrange kit replenishment at site when the ICU has 2 kits left. • Contact study team to arrange redelivery when pharmacy has 2 kits left.

5. References

- Guideline for Good Clinical Practice E6 (R2) (EMA/CHMP/ICH/135/1995) December 2016
- Pharmacy/ICU/Ward Accountability log
- IMP Destruction Log
- IMP Release Form
- IMP Temperature Deviation Form
- The Medicines for Human Use (Clinical Trials) Regulations 2004
- SepTiC IMP Handling Manual
- SepTiC IMP Order Tracker
- SepTiC IMP Temperature Log

6. Procedures

6.1. IMP Order

6.1.1. IMP order procedures – From Manufacturer to Site

- The IMP will be ordered by the study manager from the manufacturer (Partner Therapeutics). The order will be based on projected site activation and site recruitment. The IMP will be ordered once the amount is confirmed with the distributer (Victoria Pharmaceuticals) to ensure the stock amount can be stored.
- Once Victoria Pharmaceuticals receives the stock from the manufacturer the kit codes will be provided to the study team. These kit codes will then be updated on the **SepTiC IMP Order Tracker**.
- The unblinded pharmacist will be nominated by the site prior to any order of IMP. There may be more than one unblinded pharmacist at

site. The unblinded pharmacist will receive training and access to the unblinded database sealed envelope. See section 6.2.1 for more instructions.

- An IMP release form will be completed for each site before any IMP is delivered to site. This form includes the essential documents required to be in place at site before the initial shipment of IMP is sent to sites.

Imperial Clinical Trials Unit	Investigational Medicinal Product (IMP) Release Form	SOP_FRM_CR004

Investigational Medicinal Product (IMP) Release Form

Sponsor: Imperial College London			**ICTU Project No:**		**Protocol No:** 22SM8039
Study Title: SepTiC			**Chief Investigator:** Prof Anthony Gordon		
Principal Investigator:			**Site name/ number:**		
	YES	**N/A◊**	**Comments / Version date of document approved***	**Location**	
				TMF	**ISF**
Regulatory approval/notification i.e. MHRA					
Regulatory approval of amendment					
IMP Import Licence (if applicable)					
Approval of protocol by relevant Research Ethics Committee (REC) or Institutional Review Board (IRB) (add version and date of					

- An **IMP order form** will be completed by the study team via the order form provided by Victoria Pharmaceuticals. The IMP kit list is arranged in blocks of 4 and so 4 kits will be ordered at a time. The first order will be for 8 kits for all sites. The **SepTiC IMP Order Tracker** will be used to determine which 8 kits should be ordered for each site. These kit codes are included on the order form.
- Once complete, the order form will be sent by the Sponsor Trial Team to the IMP distributer Victoria Pharmaceuticals.
- Victoria Pharmaceuticals will arrange the fulfilment of the order.

6.1.2. Receiving delivery of the IMP

- The IMP will be delivered temperature controlled by an approved courier. Once delivered, the courier will provide an update of the temperature logs of the IMP in transit. If there are any deviations, the courier will inform the site team who will complete the information on the delivery docket and send this to Victoria Pharmaceuticals and the study team. Victoria Pharmaceuticals will contact the QP immediately and confirm if fit for use. If the QP is not immediately available, then the trial team will inform the site to quarantine the stock until deemed fit for use by the QP.
- Along with the IMP the delivery, the package will contain the following information: - QP certificate, and delivery docket/confirmation of receipt, which will be filed in the pharmacy

ISF. A copy of the delivery docket will also be emailed to the study team and filed in the TMF.

- The initial delivery will include 8 kits in total of sargramostim/placebo, each kit will contain 16 vials, the pharmacist will enter the received kits on the accountability log.
- The unblinded pharmacist will then email the CDS team (cds_support@imperial.ac.uk) using the **SepTiC Initial Allocation kit email template** to inform them that they have received the kits with the kit numbers. The email will include the following information:-
  - a) kit codes
  - b) expiry date
  - c) status - fit for use, lost or damaged
- Only kits that are deemed 'fit for use' will be activated for randomisation by the CDS team.
- The CDS team will then allocate the 8 kits that were received to the site so that when the unblinded pharmacist logs in to sealed envelope the received kits will be listed.
- The CDS team will activate 4 of the 8 kits via Sealed Envelope (ensuring an even allocation of IMP and placebo)
- The unblinded pharmacist logs in to Sealed Envelope to check the kits are listed at the site, which 4 have been activated and should be dispensed to ICU.
- The pharmacist will document the kit codes on the Pharmacy Accountability log upon delivery and when dispensed to ICU. This log will be checked at each monitoring visit.
- The ICU team (are blinded) upon receiving the stock from pharmacy will enter the 4 kit codes on an ICU accountability log. This log will be checked at each monitoring visit.
- The IMP must be stored in a fridge 2-8°C, and temperature maintained, via a local temperature log or a provided **SepTiC IMP Temperature Log**
- When a patient is randomised the ICU team update the ICU Accountability Log.
- When the ICU has 2 kits remaining more stock should be ordered from Pharmacy. The unblinded pharmacist emails the CDS team to request the activation of 2 kits. The CDS team activates these kits, the pharmacist logs in to the unblinded list (via sealed envelope) and arranges for these kits to be dispensed, ensuring they are replaced like for like (IMP/Placebo).

- When the pharmacy has 2 kits remaining, the pharmacist should inform the study team and a new order will be placed with Victoria Pharmaceuticals.
- The replenishment of kits will be determined depending on site recruitment. A further 8 or 4 kits will be ordered, the orders are always placed in blocks of 4.

6.1.3 Inventory, Order, Accountability and Returns Management

- The tracking of the IMP from order, delivery and to site will be maintained via the Pharmacy and ICU accountability logs.
- The Pharmacy Accountability log will be completed when the IMP is received and dispensed to ICU.
- The ICU Accountability log will be completed when the IMP is collected from pharmacy and dispensed to ICU.
- Any unused, damaged and empty vials should be thrown away. This includes vials that still have liquid or powder in them and that are older than the use by date and/or expiration date. For any unused or damaged kits the pharmacist should inform the study team prior to any destruction.
- An **IMP destruction log** will be completed if stock remains in pharmacy and not used, such as if the stock has expired or at the end of the study. Prior to destruction the pharmacist will first confirm with the study team that the stock can be destroyed and will then inform the CDS team, to ensure this stock is not activated for randomisation on sealed envelope.

6.2. Maintaining IMP blinding

Please note that the SepTiC Trial Management Team (septic@imperial.ac.uk) are blinded to the study allocation. Do not email or copy this email into any correspondence that contains unblinded study information.

6.2.1. Unblinded Pharmacist

- Each site will provide the trial team with a nominated unblinded pharmacist (or more than one). The unblinded pharmacist will have access to the unblinded kits on the database (sealed envelope). This will be provided by the CDS team once the unblinded pharmacist has completed the required training and the site is activated on OpenClinica and Sealed Envelope
- The unblinded pharmacist is responsible to check the suitability of the kits, liaise with the CDS team when the kits have been delivered, and for replenishment.

- Upon each IMP delivery the unblinded pharmacist will ensure the delivered kit codes are entered on the pharmacy accountability log and will keep this log up to date.
- For all emails from the unblinded pharmacist to the CDS team the following email address should be used:- **cds_support@imperial.ac.uk**
  - Email templates including the subject heading should be used:-

    SepTiC, Initial Allocation Kit - Site Name [Site Number], IMP Kit Allocation needed – High Importance

    SepTiC, Site Name [Site Number], IMP Kit Re-stock needed – High Importance
- This process will be repeated each time the ICU complete an order and the unblinded pharmacist will activate the kits via the CDS team and sealed envelope.
- The unblinded pharmacist must ensure that each activation includes an even number of IMP and placebo. When the pharmacy has 2 kits remaining, a new order should be submitted to the Sponsor trial team for more kits.

6.2.2. Sealed Envelope

- The unblinded pharmacist will receive access to view the unblinded kit codes on sealed envelope.
- The access via sealed envelope will be read only, the pharmacist will not be required to amend any information, this will be updated by the CDS team.
- The unblinded pharmacist will be able to view the kits that have been allocated to the site, the pharmacist will check this information is correct with the kits that were delivered.
- The pharmacist will check and dispense the kits to ICU that have been activated
- In the event of emergency unblinding the pharmacist will unblind the patient via the randomisation tab

6.3. IMP Destruction

6.3.1. Disposal of used/unused IMPs

- Used vials can be disposed of by the site team, there is no need to complete a returns form nor a destruction log for these.

6.3.2. Disposal of defective/recalled IMP

- If IMP is defective the site team must inform the study team as soon as possible, see section 5.11 of the IMP Handling Manual.

- If the IMP is recalled sites will be informed to quarantine the IMP and whether the IMP should be returned to the manufacturer or destroyed at site. See section 5.11 of the IMP Handling Manual.

6.4. Unblinding

- The sponsor Trial Manager and Trial Monitors will be blinded to the study allocation.
- In the case of emergency unblinding, the site staff should immediately notify the Study Manager and Sponsor which participant needs to be unblinded.
- See section 5.9 of the IMP Handling Manual for more information.

7. Revision History

SSPM Ref.	Date Effective	Reason for update (page and section of change)
XX000.00	DD MMM YYYY	

ATTACHMENT A: IMP ORDER FORM

Belfast Health and Social Care Trust caring supporting improving together	Victoria Pharmaceuticals	Document Type and Number FORM CT1.4F1
Clinical Trials Technical Agreement Template		Revision: D

APPENDIX B: Order Form IMPB:

Request for Dispatch of an Investigational Medicinal Product (IMP)

Victoria Pharmaceuticals
Plenum Building
The Royal Hospitals
Grosvenor Road
Belfast BT12 6BA
Tel: 02896150034

Trial Title:	**SepTiC**	**Eudract Number:**	**N/A**
Protocol Number:	**22SM8039**	**Version/Date:**	**V1.1 22-Aug-2023**
Product Specification File Version and Date:	**IMP2023/01, Version A**		
Sponsor Name:		**Chief Investigator Name:**	
Imperial College London		Professor Anthony Gordon	
		Contact Telephone Number:	
		0203 3126328	
Description of IMPs:		**Quantity/Patient Numbers Required:**	
GM-CSF Sargramostim (Trade name Leukine) / Placebo			
Delivery Details:			
Contact Name:			
Site Address:			
Contact Telephone Number:			
Date Medication Required at Site:			
Order Given By:			
Name:			
Job Title:			
Signature:			
Date:			
Contact Telephone Number:			
Please Quote Relevant Purchase Order Number:			