Investigational Medicinal Product (IMP) Handling Manual

Version 2.0

Date: 22.04.2024

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TABLE OF CONTENTS

TABLE OF CONTENTS 2
1. INTRODUCTION 4
2. SCOPE 4
3. ABBREVIATIONS 4
4. RESPONSIBILITES 4
5. PROCEDURES 5
5.1 Description of IMP 5
5.2 IMP Packaging and Labelling 6
5.2.1 IMP Packaging 6
5.2.2 IMP Labelling 6
5.3 IMP Shipment and Storage 7
5.3.1 IMP Site Supply and Stock 7
5.3.2 IMP Storage in Pharmacy and ICU 9
5.4 IMP Randomisation/Allocation 9
5.5 IMP Prescription/Dispensing 10
5.6 IMP Preparation/Administration 10
5.7 Stopping IMP 17
5.8 IMP Returns and Destruction 17
5.9 Emergency unblinding 17
5.10 IMP Quarantine and Reclaim 18
5.11 IMP Recall 18
5.11.1 Identifying defective IMP 18
5.11.2 Reporting procedures 19
5.11.3 Alerting participants 21
5.11.4 Replacing defective IMP stock 21
6. Version History 21

ASSOCIATED DOCUMENTS AND FORMS

1.	IMP release form
2.	SmPC / IB for Sargramostim
3.	IMP carton label for Sargramostim/placebo
4.	IMP vial label for Sargramostim/placebo
5.	SepTiC Temperature deviation form
6.	IMP order form
7.	IMP Pharmacy accountability log
8.	IMP ICU accountability log
9.	IMP Ward accountability log
10.	Sealed Envelope (unblinded Pharmacist) Training
11.	IMP authorisation for destruction form
12.	IMP temperature excursion form

1. INTRODUCTION

The purpose of this document is to describe the procedures involved in all aspects of Investigational Medicinal Product (IMP) management by the staff at the investigational site. This includes the receipt, storage, documentation, dispensing, replacement, destruction and unblinding, where applicable, of the IMP at the site.

2. SCOPE

This procedure covers all aspects of IMP handling from Sponsor authorisation of the site to the archiving of documentation at the site.

3. ABBREVIATIONS

CI	Chief Investigator
DMRC	Defective Medicines Reporting Centre
eCRF	electronic Case Report Form
EDC	Electronic data capture
IB	Investigator Brochure
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MDR	Medicines Defect Report
MHRA	Medicines and Healthcare products Regulatory Agency
PF	Pharmacy File
PI	Principal Investigator
QP	Quality Person
SmPC	Summary of Product Characteristics

4. RESPONSIBILITES

Chief Investigator (CI)	❖ All roles delegated to the Study Manager / Monitor, as described below and in the text, can be performed by the CI. ❖ Oversight of compliant IMP management
Principal Investigator (PI)	❖ Take overall responsibility for the trial at the site. ❖ Ensure facilities, staff resources and education are appropriate to carry out the trial. ❖ Delegate tasks responsibly and ensure they are documented on the Site Staff Signature and Delegation of Duties Log.

	❖ Be available to give advice, support and to sign off documents as required. ❖ Responsible for the accountability of all IMP at the site. ❖ Responsible for following the unblinding process in emergency situations.
Pharmacy staff	❖ Meet all regulatory and trial-specific requirements for IMP accountability including ordering, receipt, storage, temperature monitoring, destruction, and documentation. ❖ Unblinded pharmacist ensures equal number of IMP and placebo is dispensed to ICU via Sealed Envelope unblinded access, and follows all required processes as defined in the Sealed Envelope (unblinded Pharmacist) Training.
Local Research Nurse / Local Research Coordinator (or equivalent)	❖ Perform duties delegated by the PI (documented on the Delegation of Duties Log). ❖ Assist in collecting, collating, and processing documentation. ❖ Responsible for receipt, storage, dispensing, and documentation in the ICU and the ward (where possible).
Study Manager/ Monitor	❖ Authorise participating sites and release of IMP. ❖ Oversee site ordering and supply procedure. ❖ Review security and conditions of IMP storage.

5. PROCEDURES

5.1 Description of IMP

The IMP involved in this trial is Sargramostim (Leukine®) a recombinant human granulocyte-macrophage colony-stimulating factor as shown in Table 1. In the following document the Leukine (Sargramostim) will be referred to as the IMP.

Table 1: IMPs

Name	Active component
Leukine®	Sargramostim

5.2 IMP Packaging and Labelling

5.2.1 IMP Packaging

Each hospital will be supplied with 8 kits from the manufacturer initially: 4 IMP, 4 placebo.

Each kit contains 16 vials which is equal to one patient worth of IMP/placebo. The kit consists of 2 x 8 vial boxes which will be packaged together to create the 16-vial total kit. The dimensions of each 8 vial box are as follows:

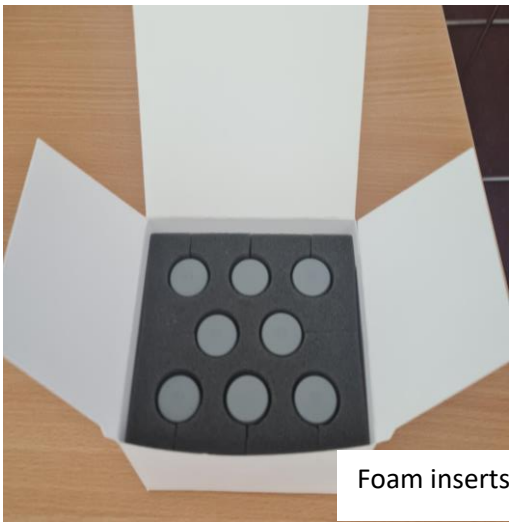
L104mm
W95mm
H68mm

Each vial contains 250µg of the IMP or placebo.

The vial dimensions are:

44mm height
69mm circumference
22mm diameter

A paper board box containing a foam set inner will be used.

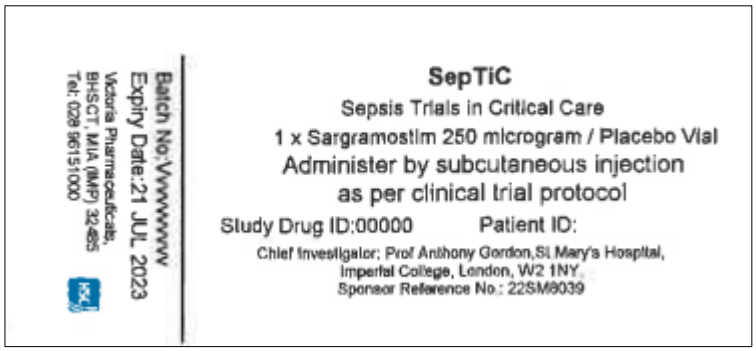


5.2.2 IMP Labelling

The IMP will have outer study-specific labelling as approved by the regulatory authority. Both the outer box and each vial will have individual labels as seen below. This includes:

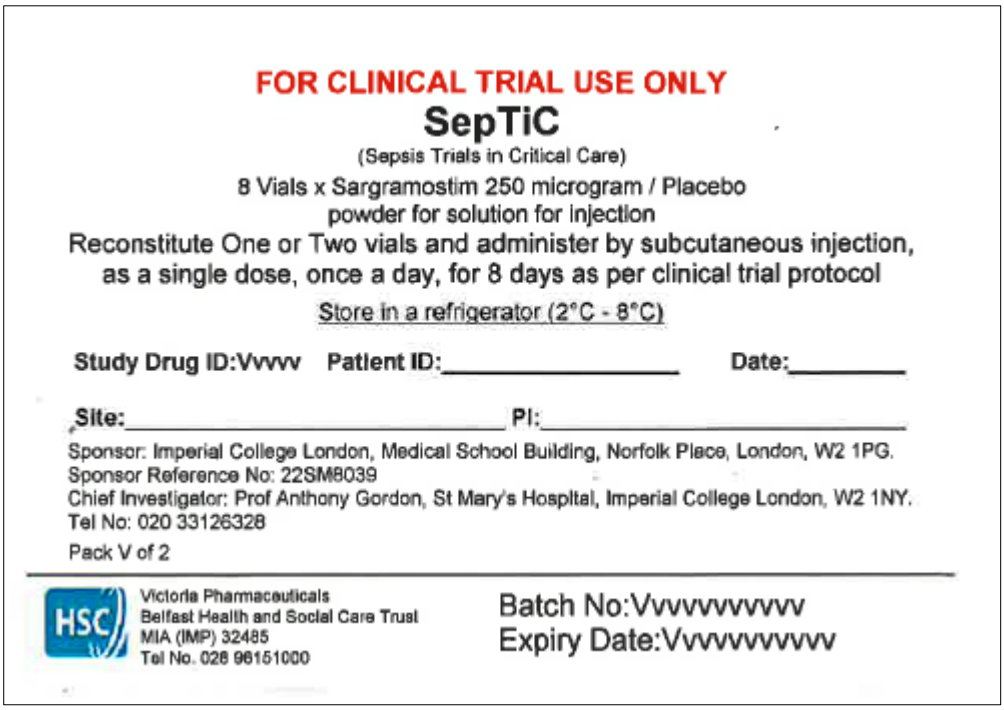
- Trial name
- IMP name
- Study drug ID

- Patient ID
- CI address
- Sponsor reference number
- Batch number
- Expiry date
- Distributer address and contact information



Vial label *left*

Box label *below*



5.3 IMP Shipment and Storage

5.3.1 IMP Site Supply and Stock

- The initial IMP for each site will be ordered, following formal site authorisation and completion of an **IMP Release Form** by the Study Manager/Monitor.
- Site authorisation will be confirmed in writing after essential documents including local research approval and signed Clinical Trial/Pharmacy agreements have been provided to the Study Manager, as applicable.
- IMP stock will be delivered to site via a temperature-controlled courier. The receiving site will confirm receipt of stock and will receive the following:-

  - a delivery docket/confirmation of receipt
  - QP certificates
  - Certificate of analysis (CoAs).
- If there has been a temperature deviation on route the courier will inform the distributer who will inform the Sponsor study team. The site will be informed if stock should be quarantined until confirmation from the manufacturer/study team that the stock can be released and is fit for use.
- A temperature logger will not be included in the delivery.
- The delivery docket should always be emailed to the distributer and the study team:- **VictoriaPharmVISA@belfasttrust.hscni.net** and **septic@imperial.ac.uk**. once stock is received and deemed fit for use.
- The pharmacy will receive an initial shipment of 8 kits from the manufacturer: 4 IMP and 4 Placebo once the site is activated.
- The unblinded pharmacist will have online access to the unblinded list of which kits contain the active drug and the placebo, allowing them to keep track of what is available on site. This will be done via secure access to the sealed envelope database.
- Upon delivery the pharmacist will first check that the kits are fit for use (undamaged and in good order). The pharmacist will then document the kit codes of the delivered IMP on the **Pharmacy Accountability Log**
- The pharmacist will then contact the Clinical Data Systems team (CDS team) **cds_support@imperial.ac.uk** using the SepTiC Initial Allocation email template and inform them which kits were received. If any kits are damaged the pharmacist will include this information in the email to the CDS team, who will ensure these are not included in the allocated site list.
- The CDS team will then allocate the 8 kits to the site, and activate 4 kits that should be dispensed to ICU. The 4 kits will be equal 2 IMP and 2 placebo.
- The unblinded pharmacist logs in to Sealed Envelope to confirm which kits should be dispensed to ICU. The **Pharmacy Accountability Log** is completed and the kits are dispensed.
- The ICU team completes an **IMP Order form** and provides this to pharmacy. Pharmacy fulfil the order and countersigns the form.
- The ICU team enters the IMP kits on their **ICU Accountability Log**. The IMP kits will be stored in the ICU fridge and kept at 2-8°C.
- The site should monitor the temperature of the fridge using their own monitoring system, if this is unavailable the study team can provide the site team with an IMP Temperature Log.
- When a patient is randomised, the ICU will complete the **ICU Accountability Log**. Once the ICU uses up two kits (two patients), they will request more stock from pharmacy.
- The pharmacist will contact the CDS team who will activate two kits, ensuring these are matched like for like for the kits that have been used. The pharmacist will dispense the kits to ICU and both accountability logs should be updated. ICU stocks should be replenished to 4 boxes prior to weekends or holiday periods if pharmacy dispensing will not be available.

- The unblinded pharmacist will be aware which boxes have to be replenished: IMP or placebo, as they have access to the list of unblinded kits on Sealed Envelope and can see which unblinded kits have been randomised to patients.
- Stock levels are controlled via the **Pharmacy Accountability Log**. When there are two kits left in pharmacy storage, the pharmacy should inform the study team to send further shipment. Note, if a site is recruiting quickly and it is felt that resupply should happen earlier this should be discussed with the trial manager / monitor and may be facilitated. Orders of kits will always be sent in multiples of 4.
- The study team will liaise with the manufacturer for further shipment.

5.3.2 IMP Storage in Pharmacy and ICU

- IMP will be stored in pharmacy and ICU refrigerated at 2-8°C. Vials should be stored in the original carton until ready for use and protected from direct light exposure during storage. The IMP must not be frozen or shaken. It must not be used beyond the expiration date printed on the vial.
- IMP must only be accessible to/by appropriate staff on the delegation log or the clinical personnel who will be administering the IMP.
- Storage conditions should be monitored by local staff and any temperature excursions noted on the study **Temperature Deviation form** and via email to the study team.
- Short-term excursions outside of label storage conditions have been studied, the results are as follows:
  - Vials stored at 2-8°C were stable for up to 60 months.
  - Vials stored at 15°C were stable for up to 12 months.
  - Vials stored at 25°C were stable for up to 3 months.
  - Vials stored at 40°C were stable for up to 1 month.
- All temperature excursions must be noted/documented via the temperature log, **the study team must be notified if the temperature exceeds 15°C**, and a **Temperature Deviation Form completed**. The IMP should be placed in quarantine until the Trial Team confirm that this can be removed from quarantine and used as stock.

5.4 IMP Randomisation/Allocation

Randomisation will be performed using the electronic data capture (EDC) in this case OpenClinica via sealed envelope. Once the shipment of IMP arrives, the unblinded pharmacist will email the CDS team (**cds_support@imperial.ac.uk)** to inform them which kits have been delivered. The CDS team then upload these kits to Sealed Envelope and allocate 4 kits (2 IMP and 2 Placebo) to be dispensed to ICU. The unblinded pharmacist will log in to Sealed Envelope and confirm the kit codes are correct and check the kits required to be dispensed to ICU, these are then dispensed. When more stock is required on ICU the unblinded pharmacist will email the CDS team (**cds_support@imperial.ac.uk**) and the steps above are repeated:-

1. The unblinded pharmacist informs the CDS team which kits have been delivered to the site and whether they are fit for us.
2. The CDS team activate 4 kits (2 IMP and 2 placebo) for dispensing to ICU
3. The unblinded pharmacist logs in to check which kits and dispenses to ICU

When the patient is ready for randomisation the site staff will use OpenClinica to randomise the patient to a specific kit number.

The dose will be 500µg (two vials) for patients ≥50kg, and 250µg (one vial) for patients <50kg, once a day for 8 days. Therefore, one kit of 16 vials will last one patient a full length of treatment if the patient is ≥50kg. The treatment allocation will be for 8 days, the patient must receive the treatment during this time while in ICU, if the patient does not, this will be a protocol deviation. If the patient is discharged from ICU within the 8 days site staff are encouraged to continue the treatment on the ward up until day 8, however if a dose is missed on the ward this is not a protocol deviation.

The patient ID should be written on each individual vial and kit.

Kit numbers should be recorded on the **SepTiC Follow-Up Calculator**

5.5 IMP Prescription/Dispensing

- The study does not mandate a study drug prescription template; however the following information is expected to be populated on the site prescription information in the patient medical records (whether paper or electronic): -
    - SepTiC Study Drug/Placebo" Dose / Once per day / Route = SC for maximum of 8 days
- The ICU should keep the ICU accountability log up to date which keeps track of which IMP kits are available in the ICU. When two have been used the ICU team should contact the pharmacy to request a further two kits. The ICU accountability log will have record of which kits have been used.
- The ICU accountability log should be filled out to confirm when the IMP was sent to the ICU.
- **The ICU should have at least two kits available in ICU at all times (ideally one kit of IMP and one placebo) therefore during out of hours/ weekend when the pharmacy is unavailable the ICU should be restocked from the pharmacy supply ahead of the weekend / holiday period.**

5.6 IMP Preparation/Administration

When the patient is randomised, nursing staff will collect the allocated IMP kit from the ICU fridge. The patient study ID should be written on each individual vial and outer box and stored by the patient's bedside for the duration of treatment with accordance to stability data:

- Vials stored at 15°C were stable for up to 12 months.
- Vials stored at 25°C were stable for up to 3 months.

Once the IMP has been reconstituted with sterile or bacteriostatic water for injection, it should be used immediately. The following table shows stability data of reconstituted IMP:

Table 2: Leukine Chemical and Microbial Stability Data with Aseptic Reconstitution

Product Description	Storage Temperatures	Chemical and Microbial Stability Time
Unopened Lyophilized Vials	2-8°C	Until labeled expiration date
Reconstituted Leukine with Sterile Water for Injection	2-8°C	24 hours[1]
	25°C	24 hours[5]
Reconstituted Leukine with Bacteriostatic Water for Injection	2-8°C	20 days[1]

Prefilling syringes with reconstituted lyophilized IMP is not recommended.

A study evaluated the stability of lyophilized IMP reconstituted with Bacteriostatic Water for Injection and stored in syringes demonstrated no microbial stability at any time and is therefore not recommended.

Silicone oil (which is sometimes used in disposable syringes) has been shown in the literature to cause protein aggregation and is therefore not advised.

Reconstitution of the IMP using **aseptic non touch technique**.

Preparing to Inject IMP

- It is important that you do not try to give the injection unless you have appropriate training.
- Do not use IMP beyond the expiration date printed on the vial label.
- Take the IMP vial out of the refrigerator before use and allow it to reach **room temperature** before preparing an injection.
- The IMP is a powder that requires the addition of Sterile Water for Injection or Bacteriostatic Water for Injection to make a clear, colourless single-dose solution

Step 1: Prepare

A. Remove IMP vial from the refrigerator.

On a clean, well-lit surface, place the vial at room temperature and allow it to reach room temperature before preparing an injection.

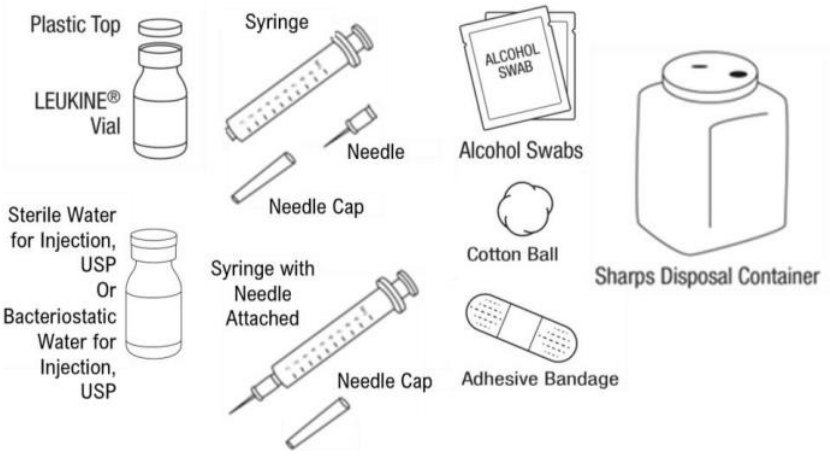
- Do not try to warm the vial by using a heat source such as hot water or microwave.
- Do not leave the vial in direct sunlight.
- Do not shake the vial.

B. Gather supplies needed for your injection.

Wash your hands thoroughly with soap and water. Dry them with a clean towel.

On a clean, well-lit surface, place the:

- IMP vial
- Vial of liquid to add to the powdered IMP vial (Sterile Water for Injection or Bacteriostatic Water for Injection)
- Syringe and needle (leave cap on) to add the liquid to the IMP vial (Note: sometimes the needle may already be attached to the syringe)
- Syringe and needle (leave cap on) to inject the IMP dose (Note: sometimes the needle may already be attached to the syringe)
- Alcohol swabs
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container



C. Check your supplies.

- Make sure the names on the vials match the names on the prescription labels.
- Make sure expiration dates printed on the vials have not passed.
- Only use the disposable syringes and needles
- If any of the needle or syringe packaging are opened or damaged, do not use them.
- Only use the syringes and needles one time. Throw away (discard) any used syringes and needles in a sharp's disposal container.

D. Prepare your supplies.

- Open the packages with the needles and syringes, but do not remove them from the package until you are ready to use them.
- Flip the plastic tops up and off the vials of IMP and liquid. Do not remove the grey rubber stopper. (See Figure A)
- Clean the rubber stoppers with a new alcohol pad for each vial. Let them air dry by themselves (do not blow on them). (See Figure B)
- Locate the needle and syringe to add the liquid to the powdered IMP vial.
- Take the syringe out of the package and twist the needle (with needle cap still on) onto the syringe, if the needle is not already attached.


Figure A


Figure B

E. To fill the syringe with liquid to add to the powdered IMP vial:

- Hold the syringe that you will use to add the liquid to the IMP vial in one hand. With the needle cap still on, pull back on the plunger of the syringe to add 1 mL of air (see Figure C).
- Hold the syringe by the barrel with the needle cap pointing up. Carefully pull the needle cap straight off and away from your body (see Figure D).
- Do not put down the syringe or allow the needle to touch anything. If the needle touches any surface, including your hands, throw away the needle and syringe and start over with a new syringe and needle.
- Locate the vial of liquid to add to the powdered IMP vial (Sterile Water for Injection or Bacteriostatic Water for Injection) and place it on a flat surface.
- Insert the needle straight down through the centre of the rubber stopper.
- Draw up 1ml of Water For Injection in a disposable syringe using an aseptic non-touch technique. (see Figure E)
- Keep the needle in the vial and turn the vial upside down (see Figure F). Make sure the liquid is covering the needle tip.
- Keep the vial upside down and slowly pull back on the syringe plunger until 1 mL of liquid is in the syringe barrel (see Figure F). Keep the needle tip in the liquid.
- Keep the needle in the vial and check for air bubbles in the syringe. Air bubbles will not hurt you, but you may not have gotten enough liquid in the syringe.
- If there are air bubbles, gently tap the syringe barrel with your finger until the air bubbles rise to the top of the syringe (see Figure G). Gently push the plunger up to push the air bubbles out of the syringe.
- Keep the needle tip in the liquid and again pull the plunger back until 1 mL of liquid is in the syringe. Repeat these steps as needed until 1 mL of liquid without air bubbles is in the syringe.
- Pull the syringe and needle completely out of the vial when you have 1 mL of liquid.


Figure C

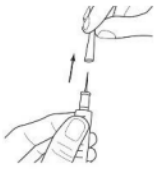


Figure D


Figure E

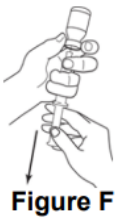


Figure F


Figure G

F. To add liquid to the IMP vial to dissolve the powder:

Figure H

- Locate the vial of IMP and place it on a flat surface.
- Insert the needle of the syringe containing the liquid through the centre of the rubber stopper of the IMP vial.
- Slowly push the syringe plunger down until all the liquid from the syringe is in the IMP vial (see Figure H).
- Pull the syringe and needle completely out of the IMP vial. Do not put the cap back on the needle. Discard the used syringe with needle attached in a sharp's disposal container.
- Gently roll the IMP vial between your palms until the powder is completely dissolved and the solution is clear and colourless (see Figure I). Do not shake the vial.

Figure I

- Use the vial immediately and only one time. Do not save partially used IMP vials for later use.
- If you do not use the liquid vial immediately, write the day and time on the vial so you know when it must be thrown away. You may store the unused liquid IMP vial in the refrigerator (2°C to 8°C). You must use the liquid IMP within 24 hours if mixed with Sterile Water for Injection or within 20 days if mixed with Bacteriostatic Water for Injection. Discard unused or partially used liquid IMP.

G. Prepare the IMP dose to be given.

Figure J

- Locate the vial of liquid IMP and place it on a flat surface.
- If IMP vial is cold from the refrigerator, allow to warm to room temperature.
- Clean the IMP vial rubber stopper with a new alcohol pad. Let air dry. (See Figure J)
- Locate the needle and syringe to inject the IMP dose.
- Take the syringe out of the package and twist the needle (with cap still on) onto the syringe, if the needle is not already attached.
- Hold the syringe you will use to give your dose in one hand. With the needle cap still on, pull back on the plunger of the syringe and draw air into the syringe. (See Figure K)

Figure K

- Hold the syringe by the barrel with the needle cap pointing up. Carefully pull the needle cap straight off and away from your body (see Figure L).
- Do not put down the syringe or allow the needle to touch anything. If the needle touches any surface, including your hands, throw away the needle and syringe and start over with a new syringe and needle. (See Step 4: Proper disposal)

Figure L

- Keep the liquid IMP vial on the flat working surface and insert the needle straight down through the centre of the rubber stopper.

- Push the syringe plunger down and inject all the air from the syringe into the vial. Keep your finger on the plunger so air does not come back into the syringe. (See Figure M)
- Keep the needle in the vial and turn the vial upside down (see Figure N). Make sure the liquid is covering the needle tip.
- Keep the vial upside down and slowly pull back on the syringe plunger to fill the syringe barrel with the IMP (see Figure N). Keep the tip of the needle in the liquid.
- Keep the needle in the vial and check for air bubbles in the syringe. Air bubbles will not hurt you, but too large an air bubble can reduce your dose of IMP.
- If there are air bubbles, gently tap the syringe barrel with your finger until the air bubbles rise to the top of the syringe (see Figure O). Gently push the plunger up to push the air bubbles out of the syringe.
- Keep the needle tip in the liquid and again pull the plunger back to the number on the syringe barrel that matches your dose (mL). Repeat these steps as needed if there are still air bubbles in the syringe.
- DO NOT remove the needle from the vial yet.
- Lie the vial down on its side with the needle still in the vial (see Figure P).

Figure M

Figure N

Figure O

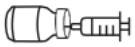


Figure P

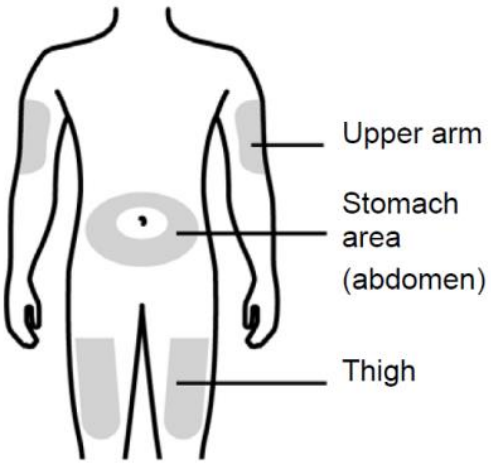
Step 2: Select and Prepare the Injection Site

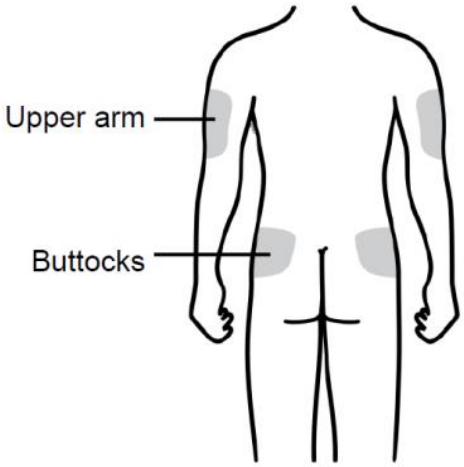
H. Prepare and clean your injection site.
You can use:

- Thigh
- Stomach area (abdomen), except for a 2-inch area right around your navel (bellybutton)
- Upper outer area of your buttocks (only if someone else is giving you the injection)
- Outer area of upper arm

- Clean your injection site with an alcohol swab.
- Let your skin dry.
- Do not touch this area again before injecting.
- If you want to use the same injection site, make sure it is not the same spot on the injection site area you used for the previous injection.

- Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.





Injecting LEUKINE

Step 3: Subcutaneous (under the skin) injection

I. Remove the syringe and needle that contains the IMP dose from the IMP vial.

J. Pinch your injection site between your thumb and first finger. Be careful not to touch the injection site itself. Keep skin pinched while injecting.

K. Hold the syringe between the thumb and first finger of the other hand. Insert the needle all the way into the skin quickly at a 45-to-90-degree angle.

L. Using slow and constant pressure, push the syringe plunger until it reaches the bottom to inject all of the IMP.

M. When done gently pull the needle out of your skin.

- Cover the site with cotton ball or gauze if there is blood. Apply an adhesive bandage strip, if needed.
- Do not rub the injection site.

Step 4: Proper disposal

N. Appropriately discard all supplies used.

- After one use, the IMP vial must be discarded even if it still contains liquid. Vials are for one-time use only.
- Throw away all used vials of IMP and other liquids. This includes vials that still have

liquid or powder in them and that are older than the use by date and/or expiration date.
- Do not recap needles. Discard needles and syringes in a sharp's disposal container.

5.7 Stopping IMP

Discontinuation of IMP may occur for the following reasons:

- At the request of the participant or their personal/professional legal representative
- Adverse Event/ Serious Adverse Event
- Allergic reaction to IMP
- If the investigator considers that a participant's health will be compromised due to adverse events or concomitant illness that develop after entering the study.

5.8 IMP Returns and Destruction

At the completion of the trial, the study staff via the monitor, will ensure the destruction of all unused IMPs (after close-out and before archiving). An IMP Management Plan will be generated to manage all aspects of IMP order, delivery, use and destruction during the course of the trial.

5.9 Emergency unblinding

- Each participant will be assigned a unique trial ID which is linked to the treatment allocation.
- The treatment code must not be broken except in medical emergencies when the appropriate management of the participant necessitates knowledge of the treatment, or in the event that expedited reporting to the Research Ethics Committee (REC) and MHRA of a Suspected Unexpected Serious Adverse Reaction (SUSAR) is required.
- The trial EDC system (Sealed Envelope) will include an automated unblinding facility, in case unblinding is required.
- In the event that emergency unblinding of an individual participant is required, Investigators are encouraged to discuss the need for emergency unblinding with the Sponsor / Chief Investigator (or designee) / ICTU, if the circumstances permit such a discussion. If discussion prior to emergency unblinding cannot take place, the coordination centre (ICTU) should be informed afterwards.
- The unblinded pharmacist has access to unblinded information at site level. For audit purposes to unblind the treatment of one patient the unblinded pharmacist should log in to sealed envelope click the randomisation tab, then select the patient, then 'unblind' and enter the reason and that this was discussed with the PI and the Sponsor study team.
- If the unblinded pharmacist is not available the study manager also has the ability to unblind via sealed envelope and so is able to do so if required.

- It is noted that in this study there is little added value of unblinding the GM-CSF as there is no treatment available for any untoward reaction. Clinicians are advised to stop the treatment immediately and continue to monitor the patient until resolution.

5.10 IMP Quarantine and Reclaim

IMP should be quarantined under the following circumstances by the Pharmacy department (or equivalent) at participating sites:

- Temperature excursion during shipment transit
- Temperature excursion during storage at Pharmacy or equivalent
- Violation of other required conditions i.e., protection from light, either during shipment transit or during storage at Pharmacy or equivalent
- Damage of IMP packaging that may affect the IMP i.e., mould, breakage of vials.
- Inadequate labelling or incorrectly labelled IMP packaging
- IMP has reached expiry date.
- The Trial Manager, Sponsor or manufacturer/supplier has instructed to do so.
- The study has finished.

All shipment of IMP must be noted on the Pharmacy Accountability Log. If a shipment arrives faulty or cannot be dispensed due to the reason above the study team should be notified as soon as possible. The study team will organise a replacement shipment.

When IMP stock has expired or the trial is completed, IMP must be quarantined immediately to avoid possibility of dispensing the expired IMP/remaining IMP in error.

5.11 IMP Recall

For some studies, there may be an IMP defect, whereby the IMP at participating sites must be quarantined and will be collected or required to be sent back to the manufacturer/supplier for investigation/destruction.

5.11.1 Identifying defective IMP

A defective IMP may be identified by:

- A healthcare professional at a participating site, observing clinical symptoms/events that may indicate a defective product has been used (Note: this can be an adverse drug reaction or lack of efficacy)
- A healthcare professional, pharmacist or member of the research team recognising that the product is defective, prior to use i.e., incorrect packaging, unusual colour of product etc.
- The IMP manufacturer and/or packager, before or after production/packaging or shipping to participating sites
- The MHRA, upon inspection, or R&D/other auditing bodies

The following should also be considered when assessing a potential IMP defect:

- Was the product stored correctly? (To exclude incorrect storage as the cause of the suspected defect)
- If the defect is visible, was the defect identified in a new previously unopened container or had the container previously been used? (To exclude user errors such as product mix-ups)
- Are there other unopened containers of the same batch available, which could be checked?
- If the product requires preparation, such as addition of a diluent, was the correct procedure followed and/or correct diluent used?
- If the product is used with a medical device, could the device be the cause of the incident?

The following actions should be taken at all participating sites following identification of a potential defective IMP:

- Prevent use if possible
- Retain/preserve evidence if possible
- Prevent interference with the product if possible
- Note as much information as possible regarding any clinical incidents, where the health of a participant has been affected either due to an adverse drug reaction of lack of efficacy

Notification of a defect in an IMP can be issued from:

- The manufacturer
- The MHRA
- The Trial Sponsor or delegate (i.e., Trial coordinating team)

5.11.2 Reporting procedures

Participating sites must notify the Study Manager/Monitor at the trial coordinating center immediately after identifying an IMP defect, by telephone or email.

The MHRA will be notified immediately by the IMP manufacturer/supplier and/or the trial Sponsor/delegate (whoever is leading), if not identified by the MHRA themselves.

This would be reported to the MHRA's Defective Medicines Reporting Centre (DMRC) by email, at dmrc@mhra.gsi.gov.uk .

The initial report from the Sponsor/delegate should try to have as much information as possible, however, it should not delay initial notification to the DMRC. Information required includes:

- The brand or the non-proprietary name of product
- The name of the manufacturer, supplier or parallel importer
- The strength and dosage form of the product
- The product license number
- The batch number or numbers of the product
- The expiry date or dates of the product
- The nature of the defect
- The account of any action taken in consequence, including clinical incidents/actions

Alternatively, a verbal report should be made, if the report concerns a critical or major defect or is outside of office-hours. The DMRC are available 24 hours a day.

In response, an auto-reply email will be received, followed by an email from the DMRC giving the Medicines Defect Report (MDR) reference number, which should be used in all further correspondence.

Any missing information should be provided when available. Further information regarding production, distribution and batch details will be requested by the DMRC directly from the IMP manufacturer or license holder. Any other updates following investigations should be documented in a final report.

If the IMP is recalled, a reconciliation report must also be provided. An investigation is only officially closed after the DMRC issues a closing response. Copies of all reports and correspondence must be filed in the TMF.

The DMRC will use the following internationally agreed classification of risk to create an alert/decide on a recall:

- Class 1: The IMP defect presents a life threatening or serious risk to health. Action must be taken now including out of hours.
- Class 2: The IMP defect may cause mistreatment or harm to the participant, but it is not life-threatening or serious. Action must be taken within 48 hours.
- Class 3: The IMP defect is unlikely to cause harm to the participant, and the recall is carried out for other reasons, such as non-compliance with the marketing authorization or specification. Action must be taken within 5 days
- Class 4: 'Caution in Use notice'. No threat to participants or no serious defect likely to impair product use or efficacy. These are generally used for minor defects in packaging or other printed materials.

The timescales specified on Drug Alerts are for advice to indicate the priority with which action should be taken.

Drug alerts classed 1-3 usually require affected batches of the IMP to be recalled. Please see appendices B-E for examples of drug alerts [Include appendices from SOP CR004 IMP Release Management and Accountability.

The DMRC is also responsible for disseminating drug safety warnings or messages to healthcare professionals. These must be filed in the Pharmacy File, ISF and TMF.

For commercially available IMPs used within clinical trials, a drug recall or alert is usually cascaded via the site Pharmacy departments who have an appropriate system in place to cascade this information to healthcare professionals/research staff on site.

For IMPs without a marketing authorization, a recall or drug alert may be received by the CI, whose responsibility it will be to contact/notify site PIs and their pharmacy departments, or to delegate this to a member of the study team i.e. Trial Manager. This should be done within 24 hours.

If a research member becomes aware of a recall or drug alert first, they must inform the CI and cascade the information as above.

For alerts with classification 1-3, sites should be advised to ascertain whether the affected batch is in stock and in use by checking their IMP inventory and accountability logs. Where IMP is stored outside of Pharmacy, this stock must also be checked along with their relevant accountability logs. Any affected product within stock must be quarantined immediately, until further instruction is received from the Sponsor/delegate or manufacturer.

5.11.3 Alerting participants

An alert may instruct to recall an IMP to patient/participant level. In this instance, sites may be instructed to identify participants using their accountability logs. If batch numbers cannot be identified, then all participants must be contacted.

A reasonable number of attempts should be made to contact the participants however possible (telephone, email, post etc.), and if this is not possible or is unsuccessful, this must be documented as a File Note.

The CI, PI or delegate will be responsible for contacting participants. Timely and accurate information should be supplied to affected participants. This may include:

- Definition of symptoms
- What to do if symptoms are experienced
- What to do with their supply of IMP (return to Pharmacy/trial team member)
- Arrangements for re-supply/treatment

5.11.4 Replacing defective IMP stock

The CI/PI or delegate will order new stock for participating sites, as required. The CI is responsible for communicating any further actions, as a result of the recall, to all participating sites i.e. additional participant monitoring/study visits that may be required.

6. Version History

Version	Date Effective	Reason for Update
V2.0	22.04.2024	Changes to sections 5.2.1 Packing and 5.3.1 IMP Site Supply and Stock