



# SISTER

## STRATEGY FOR IMPROVING STROKE TREATMENT RESPONSE

### (SISTER) TRIAL

#### Pharmacy Manual

#### INVESTIGATOR-SPONSORED STUDY PROPOSAL

IND Number: 122550

Protocol # TS23/DS9231-U202

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## Abbreviations and Definitions

CPS	Clinical Performance Site
IP	Investigational product
MUSC	Medical University of South Carolina
NCC	National Coordinating Center
NCC Central Pharmacy	StrokeNet National Coordinating Center Central Pharmacy
NDMC	National Data Management Center at MUSC
NS	Normal Saline (sodium chloride 0.9% in water)
PM	Project Manager
TERF	Temperature Excursion Report Form
TS	Translational Sciences, Inc
WebDCU™	Web based Clinical Trial Management System (CTMS) containing a web-based study drug shipping and management component, which allows for study drug management at the CPS.
MAR	Medication Administration Record

## Contact Information

<b>SISTER Primary Study Contact List</b>			
<b>Title and Responsibility</b>	<b>Name</b>	<b>Contact Information</b>	<b>When to Contact</b>
StrokeNet Central Pharmacist	Noor Sabagha R.PH, MPH	<a href="mailto:SISTERtrialRX@ucmail.uc.edu">SISTERtrialRX@ucmail.uc.edu</a> 513-584-3166	Pharmaceutical questions/issues, study drug shipments, handling, and maintenance.
StrokeNet Central Pharmacist	Christian Unger PharmD	<a href="mailto:SISTERtrialRX@ucmail.uc.edu">SISTERtrialRX@ucmail.uc.edu</a> 513-584-3166	Pharmaceutical questions/issues, study drug shipments, handling, and maintenance.
StrokeNet Central Pharmacy Technician	Brittany Dornheggen CPhT	<a href="mailto:SISTERtrialRX@ucmail.uc.edu">SISTERtrialRX@ucmail.uc.edu</a> 513-584-3166	Study drug shipments, handling, maintenance, and pharmacy regulatory documents.
StrokeNet Central Pharmacy Technician	Carla Jones CPhT	<a href="mailto:SISTERtrialRX@ucmail.uc.edu">SISTERtrialRX@ucmail.uc.edu</a> 513-584-3166	Study drug shipments, handling, maintenance, and pharmacy regulatory documents.
Principal/ Protocol Investigator	Eva A. Mistry, MBBS, MSCI	<a href="mailto:mistryea@ucmail.uc.edu">mistryea@ucmail.uc.edu</a> 513-558-1291	Protocol inclusion/exclusion questions, medical management treatment and any SAEs or unanticipated problems.
Principal/ Contact Investigator	Pooja Khatri, MD, MSC	<a href="mailto:Pooja.khatri@uc.edu">Pooja.khatri@uc.edu</a>	Protocol inclusion/exclusion questions, medical management treatment and any SAEs or unanticipated problems.
Principal Investigator Biostatistician	Jordan Elm, PhD	<a href="mailto:elmj@musc.edu">elmj@musc.edu</a>	Please route all questions to Protocol or Contact PI
Principal Investigator	Guy Reed, MD, MS	<a href="mailto:guyreed@arizona.edu">guyreed@arizona.edu</a>	Please route all questions to Protocol or Contact PI
NCC Project Manager	Pam Plummer, MSN, RN, CCRC	<a href="mailto:plummepa@ucmail.uc.edu">plummepa@ucmail.uc.edu</a> 513-885-2437	Study related clinical or trial operations questions, regulatory and cIRB submissions, site payments.
WebDCU™ Data Manager	Katie Stever, MPH	<a href="mailto:steverca@musc.edu">steverca@musc.edu</a> 843-792-2077	WebDCU™ interfacing and troubleshooting
WebDCU™ Data Manager	Riley Luckmann	<a href="mailto:luckmann@musc.edu">luckmann@musc.edu</a>	WebDCU™ interfacing and troubleshooting
Site Monitoring Manager	Aaron Perlmutter, MPH, MSW	<a href="mailto:perlmutt@musc.edu">perlmutt@musc.edu</a> 843-792-2784	Study related monitoring management questions.

## Introduction and General Study Drug Information

SISTER is a Phase-2, prospective, randomized, placebo-controlled, blinded, dose finding trial that aims to determine the safety and preliminary efficacy of TS23, a monoclonal antibody against the alpha-2 antiplasmin ( $\alpha$ 2-AP), in acute ischemic stroke.

## Study Drug Formulation

The IP or study drug, TS23, is an IgG2 monoclonal antibody that inactivates human  $\alpha$ 2-antiplasmin,  $\alpha$ 2AP (also known as serpin f2 (Sf2),  $\alpha$ 2-plasmin inhibitor, plasmin inhibitor). TS23 prevents the inhibition of plasmin by  $\alpha$ 2AP and has been shown to significantly enhance dissolution of thromboemboli without causing bleeding in pre-clinical experimental studies. It was constructed by chimerizing the variable regions of a mouse monoclonal antibody against  $\alpha$ 2AP with a human IgG2 constant region. It is produced in Chinese hamster ovary (CHO) cells with a molecular mass of 148 kDa.

TS23 is formulated at a concentration of 10 mg/mL in a buffer consisting of 10 mM sodium phosphate, 50 mM sodium chloride and 5% sorbitol at pH 6.0; it is a clear mostly colorless solution. For purposes of this pharmacy manual, the IP or “study drug” refers to TS23. The expiration date for the IP (TS23) will be provided and updated by Translational Sciences, Inc. based on stability testing.

## Study Drug Supply, Packaging, and Labeling

### Supply

Translational Sciences, Inc. has and will be responsible for manufacturing TS23 according to cGMP. TS23 study drug is provided in 10 ml vials at a concentration of 10 mg/ml. The manufactured drug substance is shipped to the University of Iowa pharmacy for packaging and labeling. Packaged and labeled vials are then shipped to the StrokeNet National Coordinating Center Central Pharmacy (NCC Central Pharmacy) located at the University of Cincinnati. NCC Central Pharmacy will prepare and label study drug boxes, which will then be distributed to the Clinical Performance Sites (CPSs). Translational Sciences will be responsible for manufacturing and supplying the study drug to accommodate a maximum of 300 study subjects.

*CPSs Pharmacies to provide supplies:*

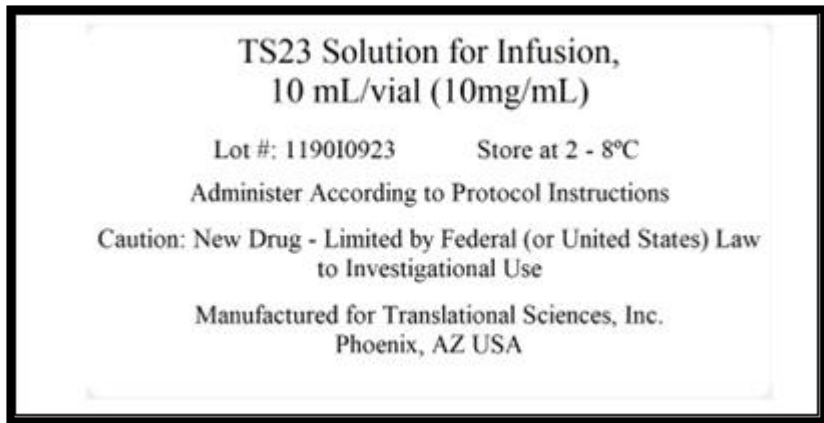
1. IV extension set with 0.22-micron filter, Non DEHP
2. 250 ml NS infusion bag, Non DEHP (Used for placebo and TS23 compounding)

\* Note: Placebo will not be sent to sites by the StrokeNet Central Pharmacy. For preparation of placebo doses, sites will use a standard 250 ml NS infusion bag.

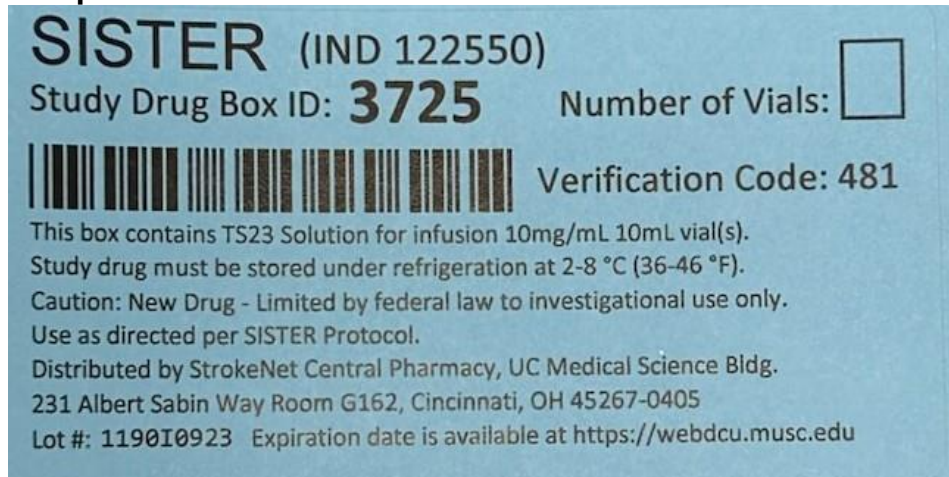
## Packaging and Labeling

The study drug vials will be shipped in white boxes measuring approximately 5"x3"x2.5", with each box capable of holding 1-6 vials. Both the vials and boxes will have an open label that includes essential information such as product description, box/vial ID number, strength, lot number, storage conditions, and an Investigational New Drug (IND) caution statement.

### Sample of Vial Label:



### Sample of Box Label:



## Study Drug Ordering, Shipping, and Receipt

### Shipping and Ordering

CPSs must upload a valid institutional pharmacy license into WebDCU™ before study drug can be shipped. The CPS pharmacy shipping address entered into WebDCU™ must match the address on the institution's pharmacy license uploaded in WebDCU™. If the shipping address of the CPS pharmacy entered into WebDCU™ does not match the address listed on the institution's pharmacy license, please email the NCC Central Pharmacy at [SISTERtrialRx@ucmail.uc.edu](mailto:SISTERtrialRx@ucmail.uc.edu) stating the reason why they do not match.

Study drug boxes will be shipped in a 6L insulated shipper, with a USB temperature logger, cold packs, and enough insulation to maintain a temperature range of 2-8°C (36-46°F).



When a CPS is released to receive study drug, an initial study drug shipment will automatically be submitted to NCC Central Pharmacy by WebDCU™. The initial study drug shipment will contain a total of two study drug boxes.

All study drug shipment resupply requests will be automated by WebDCU™ and will be triggered when a subject is randomized, or study drug is wasted/damaged/expired and after the CPS enters the information into WebDCU™. Initially, each site will receive a box containing 6 vials of active TS23. Replacement of used study drug will vary from 1-6 vials in the restocking shipment. As the trial progresses, the maximum number of boxes that a CPS is expected to keep in inventory will be adjusted based on the individual CPS dispensing volume and escalation phase.

The StrokeNet Central Pharmacy will receive an automated email notification from WebDCU™ when a study drug request is triggered. The StrokeNet Central Pharmacy will refer to WebDCU™ regarding the number of study drug boxes to be shipped to a CPS. StrokeNet Central Pharmacy will ship study drug boxes Monday through Wednesday for next day delivery Tuesday through Thursday. No shipments will take place for receipt on Friday, Saturday, Sunday, or holidays, except under extenuating circumstances.

A packing slip will be generated by WebDCU™ and will be included with each shipment. The packing slip will contain the expiration/retest date of each individual study drug box and should be retained by the CPS; the expiration date will also be available in WebDCU™ (Drug Tracking>Site Drug Removing). The study drug expiration date will not be printed on the study drug box label.



## SISTER Investigational Product Packing Slip



---

**Ship From:**  
StrokeNet Central Pharmacy  
231 Albert Sabin Way, Room G162  
Cincinnati, OH 45267 - 0405

**Ship To:**  
WebDCU Test Site 2, Charleston, SC

---

**Packing Slip No.:** 1121.20240130

**Shipment Tracking No.:**

---

SISTER Investigational Product Shipping Contents

Site ID: 2348    Site Name: WebDCU Test Site 2, Charleston, SC

---

No.	Drug Box ID	Drug Box Type	Vial 1	Vial 2	Vial 3	Vial 4	Vial 5	Vial 6	Expiration Date	Shipping Date
1	9951	6 vials	15139	17177	29042	44831	57322	21042	12/31/2025	1/30/2024

---

Generated by WebDCU on 2/15/2024 10:12:30 AM EST

[Back to previous page](#)

**WebDCU™ Study Drug Shipping Email**

CPS will receive an automated email from WebDCU™ when a study drug box is processed out of WebDCU™ for shipment via UPS®.

**UPS® Shipping Notification Email**

CPS will also receive an email from UPS® that includes a tracking number and any updates to shipment during transit for every shipment.



UPS Delivery Notification, Tracking Number 1Z576F708499106737




UPS <pkginfo@ups.com>  
To StrokeNetcpharm (strokenetcpharm)

Reply Reply All Forward

Thu 8/24/2023 9:51 AM

If there are problems with how this message is displayed, click here to view it in a web browser.



**Hello, your package has been delivered.**  
Delivery Date: Thursday, 08/24/2023  
Delivery Time: 9:47 AM  
Left At: OFFICE  
Signed by: BRITTANY D

**JAMA OLSEN WEBDCU**

Tracking Number:	<a href="#">1Z576F708499106737</a>
Ship To:	STROKINET CENTRAL PHARMACY 231 ALBERT SABIN WAY MEDICAL SCIENCE BUILDING ROOM G162 CINCINNATI, OH 452672827 US
Number of Packages:	1
UPS Service:	UPS Next Day Air®
Package Weight:	4.5 LBS
Reference Number:	LABELS

The CPS can track their shipments on the UPS® website ([https://www.ups.com/WebTracking/track?loc=en\\_US](https://www.ups.com/WebTracking/track?loc=en_US)). If a CPS has a group pharmacy email address, they would like to have receive their UPS shipment notifications, please email the StrokeNet Central Pharmacy at [SISTERtrialRX@ucmail.uc.edu](mailto:SISTERtrialRX@ucmail.uc.edu)

## Study Drug Receiving

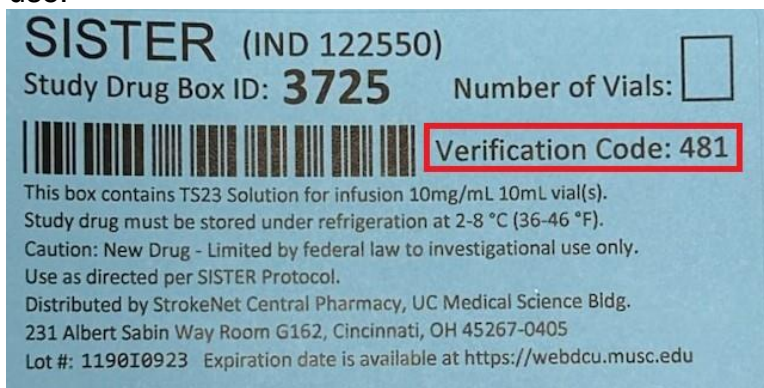
Upon arrival of the study drug shipment, the following steps should be taken as soon as possible within 48 hours of receipt:

1. Open the insulated shipper.
2. Locate the USB temperature logger.
3. Stop the USB temperature logger. Refer to “How to View and Retrieve the Temperature Curve from the USB Temperature Data Logger Instructions” section.
  - a. If the temperature logger shows the check mark symbol, the shipment has not been exposed to a temperature excursion during transit. Proceed to step 4.
  - b. If the temperature logger shows the X symbol, this shipment has been exposed to a temperature excursion during transit.
    - i. All temperature excursions must be reported to the Prime and NCC PM and StrokeNet Central Pharmacy prior to receiving drug into WebDCU™.
      - See the Temperature Excursion section for instructions on how to handle a temperature excursion.
    - ii. If the study drug boxes received in the shipment are deemed suitable for use, proceed to step 4.
    - iii. If the study drug received in the shipment are deemed NOT suitable for use, refer to the instructions for removing of study drug unfit for use section.
4. Carefully inspect the received study drug boxes ensuring all the boxes are received in good condition; and the materials received match the enclosed packing slip. The CPS should retain the packing slip for their records.
5. Promptly store the study drug boxes in the appropriate storage temperatures (2-8°C/36-46°F) in a location with continuous temperature monitoring.
  - a. Temperatures should be recorded daily on a temperature log with comments, if applicable. The monthly temperature logs should be filed into the pharmacy regulatory binder section.
  - b. See additional information regarding temperature excursions below on page 14.
6. Confirm receipt of all study drug boxes in WebDCU™ within 2 days of receipt. To do this, click [Drug Tracking] then [Drug Box Site Receiving]. Click the blue number of the box you are receiving. Click [Edit Record] at the top right-hand corner, choose receiving status, and enter the drug box 3-digit verify code. Then click [Save Record] at the bottom of the page.

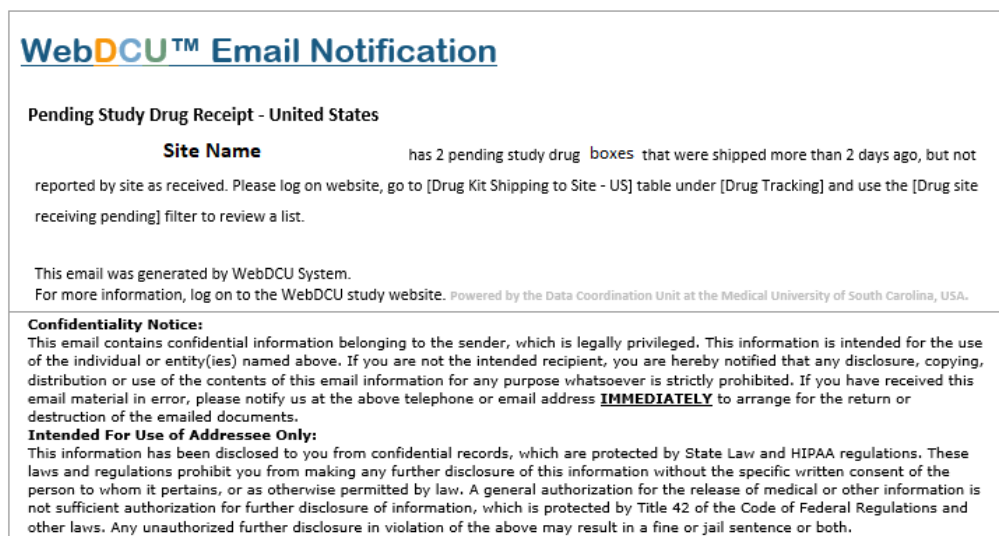
No.	Item Description	Data Value
1	Site ID	2347
2	Site name	WebDCU Test Site 1, Charleston, SC
3	Drug box ID	3871
4	Drug box type	6 vials
5	Lot ID	1
6	Expiration date	31-Dec-2025
7	Date shipped	16-Jan-2024
8	Receiving status	<input type="radio"/> Pending <input checked="" type="radio"/> Confirm received <input type="radio"/> Lost in shipping
10	Date received	17-Jan-2024
11	Drug box 3-digit verify code	164
12	Receiving notes	
13	Receiving status reported by	Aaron PERLMUTTER
14	Receiving status reported on	16-Jan-2024 13:01

Last updated by Aaron PERLMUTTER on 16-Jan-2024 13:01

7. Each box in the shipment will need to be marked as received in WebDCU™ individually.
  - a. Each box in the shipment will include a unique 3-digit verification code on the box label. This code will be entered into WebDCU™ to confirm receipt and make the box available for use.
  - b. Only after a study drug box is confirmed as received by the CPS into WebDCU™ will it be available for use.



8. If study drug boxes are not marked as received in WebDCU™ within 2 days of shipment, the CPS will receive an automatic email notification prompting them to receive the study drug boxes in WebDCU™.



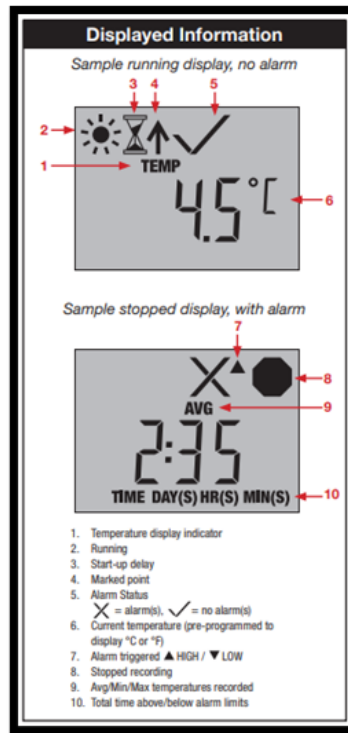
### To mark the study drug box as received in WebDCU™:

1. From the main menu page, click [Drug Tracking] and then [Drug Site Receiving]. A list of all study drug shipments that have been shipped to your site will appear.
  - a. Note: Use the 'Drug Site Receiving Pending' system filter located in the 'Page Actions' dropdown menu to filter for the shipments that need to be received.
2. Select the study drug box that needs to be received by clicking on the blue number link in the left-hand column.
3. Click on 'Edit Record' at the top of the screen.
4. Verify that the code on the box matches the drug box code listed in WebDCU™.
  - a. If the box codes do not match, contact the study's Data Manger.
5. Edit the receiving status radio button to indicate 'Confirm received.'
6. Enter the date received, the 3-digit drug box verification code, and any receiving notes.
7. To finish, click 'Save Record'. You will need to repeat this process for each box received.

## How to View and Retrieve the Temperature Curve from the USB Temperature Data Logger

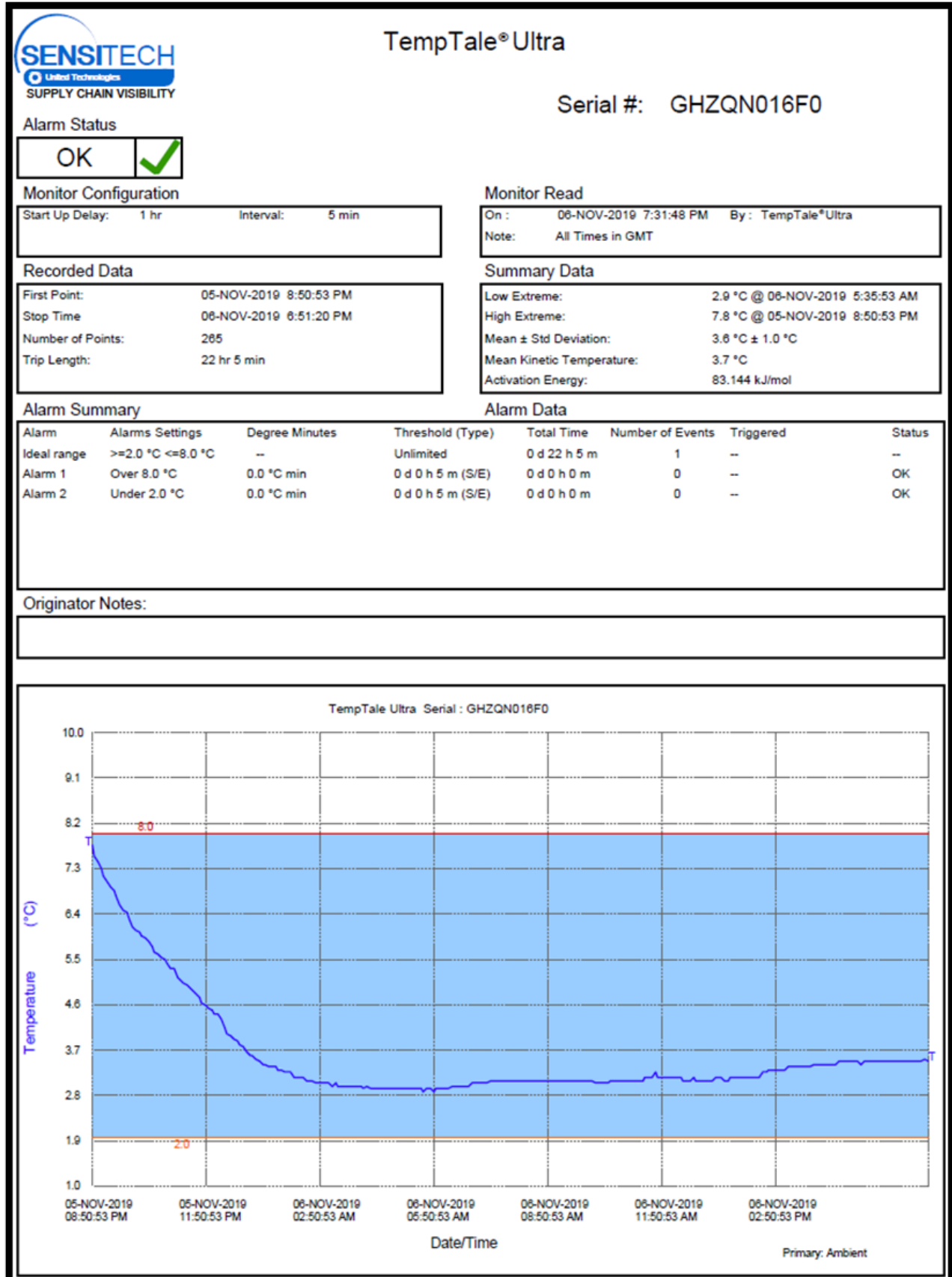
The USB temperature data logger will be activated by the StrokeNet Central Pharmacy at the time the shipment is ready to be shipped from the StrokeNetC Central Pharmacy. The sun logo in the top left corner of the LCD display indicates that the data logger is recording data.

1. Once the data logger arrives at the CPS, the CPS will stop the data logger by pressing the red STOP button for 1-3 seconds until the stop sign logo appears in the top right corner of the LCD display. This indicates that the data logger has stopped recording data.
  - a. *Note: The data logger may also be stopped by plugging it into a USB port of a computer at the CPS instead of pressing and holding the stop button.*
2. Insert the data logger into a USB port of a computer at the CPS.
3. View the PDF temperature data log and review the data log for temperature excursions.
4. Print and file the temperature data log in the SISTER trial binder to be available during monitoring visits; if an excursion has occurred, please refer to “*In-Transit Temperature Excursion*” reporting instructions
5. Site can discard the USB data logger afterward.



# Example Data Logger Report

Note: all times will be in GMT(Greenwich Mean Time)



## Storage, Temperature Monitoring, and Temperature Excursions

### Storage

Study drug must be stored in a secure location with limited access by authorized personnel only.

Study drug must be stored at 2-8°C (36-46°F).

DO NOT FREEZE TS23 Study drug must be protected from excessive exposure to light.

### Temperature Monitoring

The CPS will maintain study drug storage temperature between 2-8°C (36-46°F) at all times.

All areas where study drug will be stored must be monitored continuously for temperature excursions and the temperature monitoring system, at a minimum, must provide a daily minimum and maximum temperature. It is preferable to have:

- Automated and continuous temperature monitoring with an alarm system in place.
- Temperature alarm systems linked to the monitoring system(s) with high and low alarm set points.
- A visual alarm and preferably an audible alarm (automatic telephone dial-up, SMS text warnings, or email messages to key personnel recommended).

A sample Study Drug Temperature Log is provided for the CPSs to use (Appendix A). The CPSs may use their own institution-specific or electronic study drug temperature monitoring log to document temperature readings if such temperature log is deemed equivalent. The original Study Drug Temperature Log must be filed in the master file at the CPS and available for monitoring visits.

### Temperature Excursions

A temperature excursion occurs when in-transit or on-site drug storage temperatures fall outside of the acceptable temperature range.

- A temperature excursion must be reported if temperature falls below 2°C (36°F) and/or rises above 8°C (46°F).
- US Pharmacopeia (USP) rounding rules do apply for the temperature excursion (i.e., 35.5°F is rounded up to 36°F and 46.4°F is rounded down to 46°F). Both examples are not reportable excursions.
- Temperature excursions with the duration up to a maximum of 30 minutes and with no previous excursions, do not need to be reported.

Any temperature excursion affecting SISTER study drug must be reported immediately, at least within 48 hours of occurrence. Any study drug exposed to a temperature excursion should be quarantined in the designated storage temperature until StrokeNet pharmacy provide further instruction. Instruction on how to quarantine study drug in WebDCU™ can be found in Appendix C.

### In-Transit Temperature Excursion:

If study drug experiences a temperature excursion in-transit, the CPS should follow these steps:

1. Do NOT receive study drug into WebDCU™ inventory. Study drug boxes are available for use once they are marked as received in WebDCU™, thus, if not received into WebDCU™, subjects cannot be randomized to an affected box and enrollment is allowed to continue using the current inventory at the CPS.
  - a. *If the shipment that experienced an in-transit temperature excursion is accidentally received in WebDCU™, please follow the directions for temperature excursion during on-site drug storage below and include the Temperature Data Log from the USB Temperature Logger.*

2. The CPS must submit the SISTER Temperature Excursion Report Form (TERF) (Appendix B) and the Temperature Data Log from the USB Temperature Logger to the Prime PM and StrokeNet Central Pharmacy for review.
  - a. *If the study drug box that is not yet in WebDCU™ inventory is deemed usable after review, mark the study drug boxes received in WebDCU™.*
  - b. *If the study drug box that is not yet in inventory is deemed unusable after review, mark the study drug box as received in WebDCU™ and then immediately mark the study drug box as destroyed in WebDCU™ (Drug Tracking>Site Drug Removing) and enter in the comments “Temperature excursion per TERF.” Removing Instructions can be found on Page 20.*
    - i. Sites should destroy unusable study drug per institutional policy. Once the study drug is marked as destroyed in WebDCU™, an automatic email notification will be sent to the StrokeNet Central Pharmacy to resupply the site.

### **On-Site Temperature Excursion / Daily Assessment:**

If a temperature excursion occurs during daily assessment of the storage area(s), the CPS should follow these steps:

1. Immediately quarantine all affected study drug at the appropriate storage temperature AND in WebDCU™, instructions in Appendix C.
2. The CPS must submit the SISTER Temperature Excursion Report Form (TERF) (Appendix B) and the Temperature Data Log from the USB Temperature Logger to the Prime PM and StrokeNet Central Pharmacy for review.
3. The excursion will be reviewed once the TERF and all pertinent temperature monitoring logs are received.
  - a. If the study drug box is deemed usable after review:
    - i. Remove study drug box from quarantine; the study drug(s) may be used for enrollment.
  - b. If study drug box is deemed unusable after review:
    - i. Mark the study drug box as destroyed in WebDCU™ (Drug Tracking>Site Drug Removing) and enter in the comments “Temperature excursion per TERF.”
    - ii. Sites should destroy unusable study drug per institutional policy. Once the study drug is marked as destroyed in WebDCU™, an automatic email notification will be sent to the StrokeNet Central Pharmacy to resupply the site.

## **Ordering, Dispensing, Infusion Preparation, and Administration of Study Drug**

### **Subject Specific Ordering**

A subject-specific order should be placed for study drug per the CPS institutional policy. Subject-specific orders should be entered or written by an authorized provider consistent with the local CPS regulations and institutional policy.

The CPS subject-specific ordering process should generate the necessary labeling to support appropriate compounding and dispensing per SISTER protocol and CPS institutional policy. Subject-specific orders should allow the CPS medication administration record (MAR) to be used as final source documentation of administration for study drug dose. All documentation in the medication administration record should be blinded.


If using an electronic medical record, the use of an “order set” (i.e., compilation of orders in a single listing) should be considered to promote timely and standardized entry of all study drug doses and necessary labs per the SISTER protocol. If not using an electronic medical record, a standardized order form consistent with the SISTER protocol and WebDCU™ randomization format should be considered.

## Dispensing

The study team and subjects will be blinded in this study, while the pharmacy team responsible for preparing the study drug will remain unblinded. To determine the assigned arm for each subject, SISTER will use a Randomization Code List, which will be provided to each site pharmacy by the NDMC.


To access the "site randomization code" in WebDCU, navigate to WebDCU > SISTER trial > Drug Tracking > 'Site randomization code' tab. You can organize the randomization code alphabetically or by the 'dose level' column. The list must be printed and saved in an unblinded folder with access limited to unblinded pharmacists in the central pharmacy for after-hours randomizations. Only unblinded pharmacists and pharmacy personnel specified in the DOA will be able to view the "site randomization code" list in WebDCU.

After a subject is randomized, a SISTER study team member will obtain a copy of the Randomization Verification Form from WebDCU™ and deliver it to the CPS pharmacist or designated personnel for dispensing. This form will contain subject weight, a 4-letter randomization code that corresponds to the assigned treatment arm for the subject. The pharmacist will then match the 4-letter randomization code on the form with the 4-letter code on the SISTER Randomization Code List. A visual example is provided below:



**SISTER Subject  
Randomization Code Confirmation Form**

This form should be completed prior to study drug preparation and filed in the SISTER pharmacy binder.



---

Site Name: WebDCU Test Site 1, Charleston, SC

Subject ID: **106**

Assigned Randomization Code: **ABCD**

Weight: **63.5 (kg)**

Randomized By: Wenle ZHAO

Randomized On (local 24 hour time): 2/13/2024 12:11:04 PM

Weight-adjusted TS23 dose (mg)					
Weight (kg)	Placebo	3 mg/kg	5 mg/kg	7 mg/kg	10 mg/kg
<b>60 to &lt;70</b>	0	210	350	490	700

Below section to be completed by Site Pharmacist.

I attest that I referred to the Randomization Code List in my pharmacy binder and identified the treatment assignment which corresponds to the randomization code above.

I understand that this study is blinded and that I should NOT unblind any non-pharmacy study team members.

Signature of the pharmacist attesting to the statements above: \_\_\_\_\_

PRINT Name: \_\_\_\_\_

Date: \_\_\_\_\_

Form generated by WebDCU on 2/13/2024 12:11:04 PM

EXAMPLE SISTER Randomization Code List	
4-Letter Randomization Code	Treatment Arm
JDVS	PLACEBO
FDOG	PLACEBO
JAND	3.0 mg/kg (Max. 3 Vials)
OISD	3.0 mg/kg (Max. 3 Vials)
LKDG	5.0 mg/kg (Max. 5 Vials)
OURY	5.0 mg/kg (Max. 5 Vials)
NMSH	7.0 mg/kg (Max. 7 Vials)
<b>ABCD</b>	<b>7.0 mg/kg (Max. 7 Vials)</b>
NATS	10.0 mg/kg (Max. 10 Vials)
RQYW	10.0 mg/kg (10 Vials)



## TS23 Infusion Preparation

The study drug infusion must be prepared under sterile conditions in accordance with your site's local policies and guidelines for compounding intravenous compounds. Below is a step-by-step guide for preparing a TS23 infusion.

1. Obtain the SISTER randomization verification form from the SISTER study team member who randomized the subject. Match the 4-letter randomization code on the SISTER Randomization Verification Form with the 4-letter code on the SISTER Randomization Code List to determine the assigned treatment arm for the subject.
2. Using the subject's weight and assigned treatment arm, determine the TS23 dose from the TS23 Dosing Table (Table 1) below. Obtain the appropriate number of vials required for the TS23 dose from a SISTER study box. The TS23 study drug is provided in 10 ml vials at a concentration of 10 mg/ml. For example, if subject 123 was assigned to the 7.0 mg/kg arm and weighs 75 kg, they will receive a TS23 infusion of 560 mg. To compound the infusion, 6 vials of TS23 will be needed.

**Table 1:** Dosing Based on Subject Weight (mg/kg)

Weight (kg)	TS23 dose (mg)				
	placebo 0 mg/kg	3 mg/kg	5 mg/kg	7 mg/kg	10 mg/kg
<60	0	180	300	420	600
60 to <70	0	210	350	490	700
70 to <80	0	240	400	560	800
80 to <90	0	270	450	630	900
≥90	0	300	500	700	1000

3. Obtain a 250mL 0.9% sodium chloride infusion bag from your local inventory.
4. Using aseptic technique, remove the required volume from the 250 mL 0.9% sodium chloride IV bag based on Table 2 below. The remaining volume in the IV bag will be used as diluent for the final TS23 infusion. Do **not** remove the overfill in the 250ml sodium chloride bags. Advise the study team that the Prepared IP Bags might contain a slightly higher volume than 200 ml. After the infusion, study team to confirm that the full contents of the IP bag have been administered.

**Table 2:** 0.9% Saline 250 mL IV Bag Preparation

Weight (kg)	0.9% NaCl Volume to be Removed from 250 mL IV Bag (ml)				
	placebo 0 mg/kg	3 mg/kg	5 mg/kg	7 mg/kg	10 mg/kg
<60	50	68	80	92	110
60 to <70	50	71	85	99	120
70 to <80	50	74	90	106	130
80 to <90	50	77	95	113	140
≥90	50	80	100	120	150

5. Visually inspect each vial to ensure absence of particulates in solution.
6. The appropriate weight-based dose of TS23 (see Table 3) will be sterilely withdrawn from the TS23 vials and added to the IV bag containing the 0.9% saline to make a final solution for infusion (200

mL total volume). For example, subject 123 assigned to the 7mg/kg arm and weighing 75kg will need 56ml of TS23.

**Table 3:** Dosing of TS23 and 0.9% Saline (mL) Based on Subject Weight (kg)

Weight (kg)	Placebo 0 mg/kg		3 mg/kg		5 mg/kg		7 mg/kg		10 mg/kg	
	TS23 (mL)	0.9% saline (mL)	TS23 (mL)	0.9% saline (mL)	TS23 (mL)	0.9% saline (mL)	TS23 (mL)	0.9% saline (mL)	TS23 (mL)	0.9% saline (mL)
<60	0	200	18	182	30	170	42	158	60	140
60 to <70	0	200	21	179	35	165	49	151	70	130
70 to <80	0	200	24	176	40	160	56	144	80	120
80 to <90	0	200	27	173	45	155	63	137	90	110
≥90	0	200	30	170	50	150	70	130	100	100

7. Mix the IV bag by slowly inverting the IV bag 5 times, do not shake the bag.
8. An IV label should be applied to the prepared bag in accordance with local policy and should include the following information as a minimum: protocol number (TS23/DS9231-U202), subject initials, subject ID, total volume (200 mL), infusion rate/ duration, time/date prepared and expiration information (i.e., 12 hours following the start time of preparation). There is to be no difference between active and placebo bag appearance or label. An infusion set with a downstream in-line, 0.22-µm, protein-sparing filter will be used for administration. The infusion set should be primed at bedside following the instructions for administration of study drug.
9. Once properly compounded, blinded, and labeled, the resulting study drug infusion can be provided to the study team and infused over 15 minutes. At the highest dose of TS23, this corresponds to the maximum rate of ≤0.67 mg/kg/min.
10. Each vial of TS23 will have a unique 5-digit numerical code. This number should be recorded before any used vials are discarded. These numbers should be recorded such that only unblinded pharmacy staff at the site have access and should not be accessible to anyone else without the expressed consent of the SISTER primary investigator.
11. Once the vial numbers are recorded, the vial numbers should be entered into WebDCU™ on the Subject Study Drug Mixing form no later than 72 hrs. post study drug mixing:
  - a. Go to [Drug Tracking]
  - b. Click [Subject Study Drug Mixing]
  - c. Select the blue number in the row of the subject you mixed the drug for
  - d. Select [Edit Record] on the top right-hand corner of the screen.
  - e. Complete the form and press Save Record at bottom of the screen; if you receive an error message indicating wrong Randomization code, Dose level, or Weight-adjusted TS23 dose, double check that you have entered the data correctly. If you still get an error or have an improper number of vials to enter for the number of fields open, please contact NDMC explaining your issue.
12. The used TS23 vials can be discarded and documented per site's local guidelines for destruction once the vial numbers have been recorded at the site level and in WebDCU™

## **Placebo Infusion Preparation**

Subjects assigned to the placebo group will receive a 200ml infusion of 0.9% sodium chloride. The infusion bag will be sourced from the local inventory of the site. Using aseptic technique, remove 50 mL from the 0.9% NaCl solution to create a final infusion volume of 200 mL (as indicated in Table 2). The labeling and administration procedures should adhere to the same criteria as the active study drug.

\*\*\*Preparing the active drug takes longer than the placebo bag. When delivering it, be cautious to prevent unblinding (i.e., if preparing the active drug takes 15-20 minutes compared to < 5 min for the placebo, the time gap might unintentionally reveal treatment details to the team)

## Administration of study drug

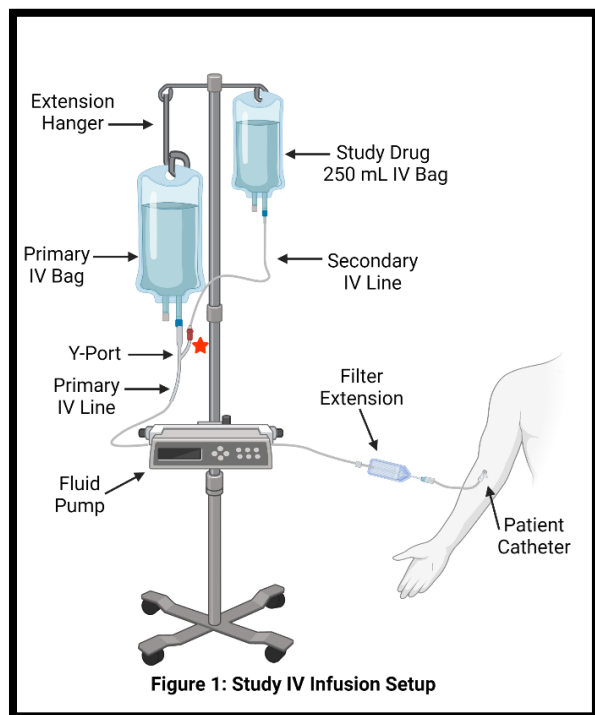
After preparation, the 200ml study drug infusion in a 250ml bag will be delivered to the subject's bedside by a study team member or pharmacy member. Follow the listed steps below for administration of study drug:

1. Study drug will be infused intravenously through a peripheral vein at a constant rate over 15 minutes.
2. Study drug should be administered in a dedicated secondary IV line. An intravenous piggyback (IVPB) system should be used, with the 0.9% NaCl as the primary bag/flush fluids. The secondary line should be primed with the study drug and should NOT be back primed.
3. Study drug will be administered via IV infusion using an infusion set, sterile filter, and an IV piggyback flush.
4. An infusion pump should be used to control the rate of infusion. See attached Figure 1 "Study IV Infusion Setup" for reference.
5. Total infusion volume with the primary/flush IV fluids and study drug (200mL) will be 240 mL, given at a rate of 13.3 mL/minute, with total duration of 18 minutes (~15 minutes of study drug, ~3 minutes for priming and flushing the IV lines).

**NOTE:** If a hypersensitivity reaction develops, the infusion of the study drug should be stopped, and the study drug bag/tubing disconnected from the subject. A separate saline bag and line may be started to administer medications as required, and the subject treated accordingly. An adverse event (AE) should be immediately reported by the study staff via the electronic database.

6. When the study drug administration has been completed, discard the empty study drug bag/tubing in accordance with local protocol.

**\*\*The Prepared IP Bags may have a volume slightly exceeding 200 ml. Following infusion, the study team should verify that the entire contents of the IP bag have been administered**





# Study Drug Accountability, Expiration/Damage, and Destruction/Return

## Study Drug Accountability

The CPS pharmacist/designee is responsible for documenting the dispensing and destruction of study drugs using the IP Drug Accountability Log (refer to Appendix D for an example). Additionally, the pharmacist/designee should update the drug inventory logs in WebDCU™. CPSs may utilize their own drug accountability forms as long as they are deemed equivalent to the supplied log and document all of the information required on the example log found in Appendix D.

## Study Drug Expiration/Damage

If the CPS has expiring study drug in their inventory, StrokeNet Central Pharmacy will send replacement study drug prior to local inventory expiration. The CPS will mark all study drug vials that are expiring in WebDCU™ as 'expired' after receiving the replacement study drug. StrokeNet Central Pharmacy will send directions on this process to CPS. 7 days prior to the expiration of a study drug, CPS will receive an automated email from WebDCU™ notifying them of the upcoming expiration of the study drug in inventory. CPS will receive this email daily until the expiring study drug is removed from WebDCU™ inventory.

WA Thu 3/18/2021 4:01 AM  
WebDCU Automated Mailer (No-Reply) <webdcu@musc.edu>  
(NEW) Study Name : Expiring Study Drug in 14 days  
To webdcu@musc.edu  
Cc

**WebDCU™ Email Notification**

**Expiring Study Drug in 14 days**  
**Site Name** has 2 study drug kits expiring within 14 days.

This email was generated by WebDCU System.  
For more information, log on to the WebDCU study website. Powered by the Data Coordination Unit at the Medical University of South Carolina, USA.

**Confidentiality Notice:**  
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WA Fri 3/12/2021 4:01 AM  
WebDCU Automated Mailer (No-Reply) <webdcu@musc.edu>  
(NEW) Study Name Pending Study Drug Removing  
To webdcu@musc.edu  
Cc isideeds@wustl.edu; XTR-Elm, Jordan (Jordan.Elm); Vandergriff, Lindsay (vanderly); Dornheggen, Brittany (gebelby); UCH-Mueller, Eric (Eric.Mueller); trosclak@musc.edu; UCH-Sabagha, Noor (Noor.Sabagha); JPortogues@jhsiami.org

**WebDCU™ Email Notification**

**Pending Study Drug Removing**  
**Site Name** has 1 study drug kit(s) that are already expired. Go into WebDCU [Drug Removing from Inventory] to view which drug kits are expired and remove the kits from your inventory.

This email was generated by WebDCU System.  
For more information, log on to the WebDCU study website. Powered by the Data Coordination Unit at the Medical University of South Carolina, USA.

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This email contains confidential information belonging to the sender, which is legally privileged. This information is intended for the use of the individual or entity(ies) named above. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or use of the contents of this email information for any purpose whatsoever is strictly prohibited. If you have received this email material in error, please notify us at the above telephone or email address **IMMEDIATELY** to arrange for the return or destruction of the emailed documents.

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**\*\*Updating drug accountability logs and WebDCU™, drug tracking systems is crucial following any instance of dispensing and/or destruction.**

## To remove study drug in WebDCU™:

1. From the main menu page, click [Drug Tracking] and then [Drug Site Removing]. A list of all study drug previously removed and currently in inventory will appear.
  - a. **Note:** Use the 'Last dispensable date passed, removal pending' system filter located in the 'Page Actions' drop-down menu to filter for study drug that is past its last dispensable date and need to be removed.
2. Select the study drug that needs to be removed by clicking on the blue number link in the left-hand column.
3. Click on 'Edit Record' at the top of the screen.
4. Edit the removing confirmed radio button to indicate 'Yes.'
5. Enter the date removed, the removing type, and any removing notes.
  - a. For expiring drug, select 'Expired' and add the comment 'Expiring MM/DD/YYYY.'
  - b. Other removing options include Damaged, Missing, Returned, Recall, Quarantined, Temperature excursion, Site closing, and Other.
6. To finish, click 'Save Record'. You will need to repeat this process for each study drug you would like to remove.
7. Once the study drug is confirmed as destroyed, update the following:
  - a. Edit the study drug destroyed confirmed radio button to indicate 'Yes.'
  - b. Enter the method of destruction and date destroyed.

## Study Drug Destruction/Return


For damaged, expired, or unused study drug, once study drug is accounted for and all documentation is appropriately completed, including WebDCU™, study drug must be destroyed per the CPS policy and procedures. Study drug may be returned to the StrokeNet Central Pharmacy, at the site's expense, if required by CPS institutional policy.

If study drug is being returned to the StrokeNet Central Pharmacy, the following steps must be followed:

1. The Study Drug Return Form (Appendix E) must be completed and returned with the shipment.
2. The study drug should be addressed and shipped to the StrokeNet Central Pharmacy via the institution's preferred postal carrier.
3. If study drug is being returned per institutional policy, shipping costs will be at the expense of the CPS.
4. Package tracking information must be provided to the StrokeNet Central Pharmacy via email at [SISTERTrialRX@ucmail.uc.edu](mailto:SISTERTrialRX@ucmail.uc.edu).
5. Returned study drug does not require temperature monitoring during transit, therefore, a temperature logger does not need to be included with the shipment.
6. Returned study drug to the StrokeNet Central Pharmacy may not contain any patient/subject identifiers.

**Appendix A** Temperature Monitoring Log Example

Current Versions of Appendices can be found on WebDCU™ > SISTER >Toolbox> Project Documents



**SISTER**

**SISTER Study Drug Temperature Monitoring Log**

Protocol: TS23/DS9231-U202

Temperature Range: 2°C to 8°C (36°F to 46°F)

Site ID:	Site Address:					
Site Name:						
PI:						
<p>Instructions: Under the appropriate date record time of the temperature reading, the current temperature, minimum temperature, maximum temperature, conformation of resetting of the thermometer if applicable and initials. Report any excursions promptly to study sponsors.</p>						
Month/Year:						
Date	Time of Reading (24 hour clock)	Current Temp (°C)	Minimum Temp (°C)	Maximum Temp (°C)	Confirmation of Reset of Reading	Reader's Initials
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
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# Appendix B Temperature Excursion Report Form

Current Versions of Appendices can be found on WebDCU™ > SISTER >Toolbox> Project Documents



## Study Drug Temperature Excursion Report Form

Protocol # TS23/DS9231-U202

Allowable Storage Range per USP Controlled Room Temperature: 2° to 8°C (36° to 46°F)

Date of Excursion:	Site ID #:	Site Name:	Investigator's Name:
--------------------	------------	------------	----------------------

**Instructions:**

- Please complete this form in its entirety.
- Email this form and all relevant temperature logs to the StrokeNet Central Pharmacy at [SISTERtrialRX@ucmail.uc.edu](mailto:SISTERtrialRX@ucmail.uc.edu) and NCC and PRIME Project manager at [plummepa@ucmail.uc.edu](mailto:plummepa@ucmail.uc.edu) [baile2sh@ucmail.uc.edu](mailto:baile2sh@ucmail.uc.edu)
- Quarantine the affected study drug until StrokeNet Central Pharmacy's review is complete.
- US Pharmacopeia (USP) rounding rules are applied for temperature excursions. i.e., 1.5°C is 2°C and 8.4°C is 8°C, both examples are not reportable temperature excursions.
- Temperature excursions with the duration maximum of 30 minutes and with no previous excursions, do not need to be reported.

<input type="checkbox"/> <b>Low Extreme (Below 2°C)</b>	<input type="checkbox"/> <b>High Extreme (Above 8°C)</b>
Temperature: _____ °C	Duration of Excursion: _____ Hours _____ Minutes
Temperature: _____ °C	Duration of Excursion: _____ Hours _____ Minutes
Description of Excursion: _____	
_____	
_____	
Has the issue been resolved? <input type="checkbox"/> Yes <input type="checkbox"/> No	

Vial Code	Box Code	Lot #	Involved in Previous Excursion?
			Yes, Date: _____ No
			Yes, Date: _____ No
			Yes, Date: _____ No
			Yes, Date: _____ No
			Yes, Date: _____ No
			Yes, Date: _____ No
			Yes, Date: _____ No
			Yes, Date: _____ No
			Yes, Date: _____ No
			Yes, Date: _____ No
			Yes, Date: _____ No
			Yes, Date: _____ No
			Yes, Date: _____ No

Reporter's Name (Print): \_\_\_\_\_ Contact Phone Number: \_\_\_\_\_

Reporter's Signature: \_\_\_\_\_ Date: \_\_\_\_\_

StrokeNet NCC Central Pharmacy Use Only		
The StrokeNet NCC Central Pharmacy has evaluated the data made available by the Clinical Practice Site regarding the temperature excursion details listed on this form. Please follow these instructions regarding the SISTER study drug		
<input type="checkbox"/> Affected study drug listed above is suitable for use and may be returned to inventory. <input type="checkbox"/> Affected study drug listed above is <b>NOT</b> suitable for use. Please follow instructions in WebDCU Toolbox to remove study drug from inventory.		
Data Reviewed:	Reviewing Official's Name (Print):	Signature of Reviewing Official:

Version 1

### WebDCU Instructions to Quarantine Study Drug

If your study drug is quarantined due to a temperature excursion or some other reason, you will need to temporarily remove the Box/Vial from inventory in WebDCU.

1. From the main menu page, click on [Drug Tracking].



2. Then click on [Drug Vial Removing]



3. Click the **blue number** in the first column of the 'List Record' table adjacent to the kit code you are reporting as quarantined.



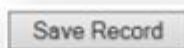
4. Click [Edit Record] at the top of the screen.



5. Enter the required information. For removing type, select '**Quarantined**'

Removing type  Expired  Damaged  Missing  Returned  Recall  Quarantined  Temperature excursion  
 Site closing  Other

6. To finish, click [Save Record].

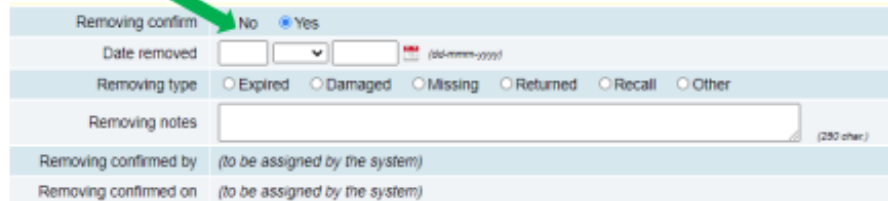


## WebDCU Instructions for Quarantined Study Drug: Study Drug deemed Fit for Use

**If the study drug is deemed fit for use after quarantine, the study drug must be put back into inventory in WebDCU.**

Repeat step 1-4 as above

5. Change 'Removing Confirm' to 'No.'



Removing confirm	<input type="radio"/> No <input checked="" type="radio"/> Yes
Date removed	<input type="text"/> <input type="text"/> <input type="text"/> <small>MM (dd-mm-yyyy)</small>
Removing type	<input type="radio"/> Expired <input type="radio"/> Damaged <input type="radio"/> Missing <input type="radio"/> Returned <input type="radio"/> Recall <input type="radio"/> Other
Removing notes	<input type="text"/> <small>(250 char.)</small>
Removing confirmed by	<small>(to be assigned by the system)</small>
Removing confirmed on	<small>(to be assigned by the system)</small>

6. To finish, click [Save Record].

Save Record

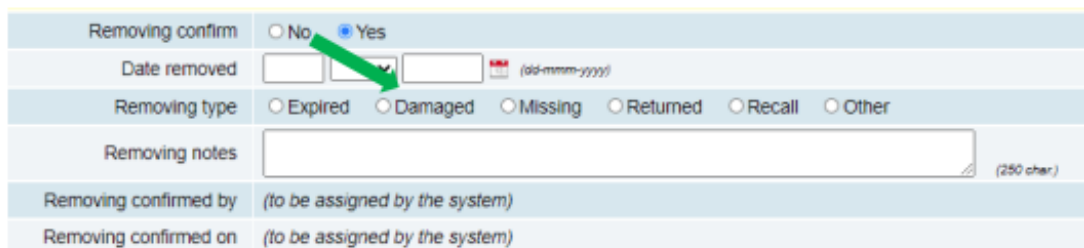
7. Repeat for all IP being removed from quarantine.

## WebDCU Instructions for Quarantined Study Drug Study Drug deemed NOT Fit for Use

**If the study drug is deemed NOT fit for use after quarantine:**

Repeat step 1-4 as above

5. Change 'Removing Type' to Damaged.



Removing confirm	<input type="radio"/> No <input checked="" type="radio"/> Yes
Date removed	<input type="text"/> <input type="text"/> <input type="text"/> <small>MM (dd-mm-yyyy)</small>
Removing type	<input type="radio"/> Expired <input checked="" type="radio"/> Damaged <input type="radio"/> Missing <input type="radio"/> Returned <input type="radio"/> Recall <input type="radio"/> Other
Removing notes	<input type="text"/> <small>(250 char.)</small>
Removing confirmed by	<small>(to be assigned by the system)</small>
Removing confirmed on	<small>(to be assigned by the system)</small>

6. To finish, click [Save Record].

Save Record

7. Repeat for all IP deemed not fit for use.





## Changes in Version 2.0

Sections Affected	Changes in the MOP
Title Page	Added new version number and date
Page 4	Update Contact information
Page 5	Added "Non DEHP" to 250 ml NS infusion bag
Page 10	Added instructions to #6 under Study Drug Receiving
Page 16	Added guidance on accessing the "site randomization code"
Page 17	<ul style="list-style-type: none"><li>• Use "&gt;= 90" instead of "&gt;90" for the infusion preparation in tables 1, 2, and 3</li><li>• Additional instructions for bullet #4 in infusion preparation regarding overfill.</li><li>• Additional instructions for Subject Study Drug Mixing form to #11</li></ul>
Page 19	Added guidelines for placebo infusion preparation concerning preparation timing