York Foundation Trust R&D Unit
Standard Operating Procedure
Pharm/S48

Temperature Monitoring (Clinical Trials)

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the R&D Unit's website and R&D Newsletter for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.

The definitive versions of all R&D Unit SOPs appear online. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the R&D Unit website: www.northyorksresearch.nhs.uk/sops.html

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This SOP will normally be reviewed every 2 years unless changes to the legislation require otherwise

Version History Log

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of significant changes
1.0	16th March 2009	
2.0	27th July 2009	
3.0	1st January 2010	Pharmacy SOP put into revised template, temperature excursion section added
4.0	2nd July 2012	Change of SOP Controller. Removal of references to the North and East Yorkshire Alliance. Updated to reflect addition of freezer temperature monitoring form, addition of temperature excursion notification form
5.0	24th February 2014	Inclusion of Scarborough Hospital as a site working to this SOP. Removal of guidance relating to Comark temperature loggers. Addition of central Temperature excursion record file.
6.0	19th October 2015	Inclusion of new forms. Change of author. Process of cold chain transport to offsite units and other minor changes.

Contents

1 Introduction, Background and Purpose

All refrigerators used for the storage of Investigational Medicinal Products (IMPs) must be temperature controlled and continually monitored to ensure compliance with the appropriate temperature range of 2°C and 8°C.

All areas used for the storage of IMPs at ambient temperature also require temperature monitoring (limits are usually between 15°C and 25°C - or occasionally up to 30°C depending on the drug stability data).

All freezers used for the storage of IMPs require continuous temperature monitoring whilst in use during a clinical trial to ensure the temperature is maintained between the appropriate ranges as defined by the protocol (limits are usually between -15°C and -25°C).

2 Who Should Use This SOP

This SOP should be followed by all members of the clinical trials team within Pharmacy at York and Scarborough hospitals, which form part of York Teaching Hospital NHS Foundation Trust.

3 When this SOP Should be Used

This SOP covers:

- Temperature monitoring systems and devices
- Daily temperature recording
- Maintaining electronic temperature records
- How to complete the temperature monitoring forms and associated documentation
- What to do if any of the temperature readings are out of range. This includes below 2°C or above 8°C for refrigerated products, or below 15°C or above 25°C for ambient products, or above -15°C or below -25°C for frozen products.
- Fridge alarm fault reporting
- Hospital alarm system activation
- Cold chain transport to offsite units

4 Procedure(s)

Temperature monitoring ensures that products are fit for use and that the quality of the product has not been compromised before its expiry date. A nominated member of the Pharmacy clinical trials team should monitor these storage conditions on each working day (except weekends and Bank Holidays). In this way, a continuous daily record of the storage temperature for all IMPs is available for the Sponsor if requested. A graph showing the temperatures of each of the areas where IMP is stored should also be printed when the temperature loggers are downloaded.

Where IMP is stored outside Pharmacy, a study specific SOP will be in place describing the responsibilities and arrangements for temperature monitoring. As described in Pharm/S76 (Storage and dispensing of Investigational Medicinal Products outside of Pharmacy), this may be delegated to the research team.

In Scarborough, this SOP should be followed in conjunction with SOPSCQA1 (Daily Fridge Temperature Monitoring in Pharmacy) and SOPSCQA4 (Responding to a Fridge Alarm Following a Temperature Deviation).

4.1 Temperature Monitoring Systems and Devices

Temperature logging systems or devices used for temperature monitoring IMPs should be UKAS certified where possible. They should be calibrated annually by the manufacturer, and a calibration certificate should be obtained and stored in the Pharmacy Clinical Trials Dispensary to confirm this.

In order to calibrate the temperature loggers used at York Hospital you will need to contact the person responsible for orders in the admin office with your request. You will then be provided with a purchase reference number which you will need to reference in your letter to the manufacturer detailing your request for the loggers to be re calibrated.

4.2 Daily Temperature Recording

Manual temperature records should be checked daily using electronic temperature monitoring systems (excluding weekends and bank holidays) for all areas within Pharmacy where IMP is stored.

The following form should be used to document temperature readings in Scarborough;

- Pharm/F108 (Daily Clinical Trials Temperature Checks)

The following forms should be used to document the readings of the various storage locations in York;

- Pharm/F36 (Temperature Monitoring Form – Fridge Temperature)
- Pharm/F54 (Temperature Monitoring Form – Ambient Temperature)
- Pharm/F78 (Temperature Monitoring Form – Frozen Temperature)
- Pharm/F112 (Ambient temperature monitoring form for studies where IMP is stored outside of Pharmacy)

In York, completion of the forms involves recording the month, year, and storage area. Against the correct date, the electronic temperature monitoring system should be used to record the time, current temperature, maximum temperature, and minimum temperature. The alarm status of the temperature monitoring system should be checked, and the form should ticked to confirm this. The entries should be signed to confirm completion. There is also space on the form to document what action has been taken if the temperature is outside of the acceptable range.

A new form for each location should be started at the beginning of each month, and the form should be handed to the Pharmacy Clinical Trials Manager/Senior Pharmacy Technician at the end of the month for review to ensure the IMP storage areas have been temperature monitored daily, and the temperature has remained within an acceptable range.

4.3 Maintaining Electronic Temperature Records

Electronic temperature monitoring systems are used to continuously monitor the areas where IMP is stored. Where applicable all temperature monitoring systems within Pharmacy should be downloaded on a fortnightly basis. For studies outside of Pharmacy the temperature monitoring systems will be downloaded at the frequency described in the study specific SOP. The electronic temperature graph produced should be saved on the Pharmacy X Drive and a paper copy should be filed within the Temperature Records file held in the Pharmacy Clinical Trials Dispensary.

The paper copy should be annotated to confirm whether the temperature remained within an acceptable range, and the signature and date of the person checking the data should be added.

4.4 Temperature Records Outside of Acceptable Limits

A temperature excursion occurs if the temperature range for a storage location is outside of its acceptable limits. The processes described below are to be followed for an ambient, fridge, or freezer temperature excursion.

Once a temperature excursion has been discovered, it is important to communicate with the relevant Research Nurse(s) for the affected trials as soon as possible to ensure they are aware of any IMPs affected by the temperature excursion. They may have to re-arrange patient visits if confirmation has not been received (from the trial Sponsor) that the product is still suitable for use.

4.4.1 Ambient Temperature Excursion

If the temperature graph or daily temperature reading from the temperature monitoring system shows that the temperature has been out of range (below 15^{o}C or above 25^{o}C), you must inform all members of the Pharmacy Clinical Trials team so that they are aware that the stock cannot be used. Inform all the trial Sponsors whose supplies are stored in

that area. This is to request confirmation that the product is fit for continued use. This should be in writing via email with a copy of the relevant graph. Follow any study specific procedures for reporting temperature excursions detailed in the study-specific Pharmacy clinical trial file. Check the study-specific Pharmacy trial file for products that are stable up to 30ºC. Trial Sponsors of these products still need to be informed of the temperature excursion, but the products can remain stored in that area.

The affected IMP supplies should be placed in quarantine. Follow the procedures outlined in Pharm/S59 (Quarantine of IMP).

Discuss the reason for the temperature being out of range with the appropriate member of staff managing the area. If the reason has not been identified, or has not been corrected, contact the Facilities department to check the air conditioning system. Record the job reference number and any actions taken on the appropriate temperature monitoring form (Pharm/F54).

If the temperature fails to return within normal limits, move the supplies to an alternative area (e.g. Pharmacy Stores). Keep a record of the temperature in any area used for storage.

Once the temperature returns within normal limits, and the trial Sponsor has confirmed the product is safe for use, remove the supplies from quarantine and place the supplies back in their designated area.

Document all actions taken in the 'Temperature Excursion Record Form (Clinical Trials)' (one form per trial affected, Pharm/F79) and place the completed form in the temperature section of the Pharmacy file for each study affected.

A file note (R&D/T20) should also be written referring others to the temperature excursion record form (Pharm/F79). The file note should be attached to a copy of the relevant temperature graph, and filed within the Temperature Records file held in the Pharmacy Clinical Trials Dispensary. **The File note log should be updated accordingly so there is a Master list of all Temperature excursions.**

4.4.2 Fridge Temperature Excursion

If the temperature graph or daily temperature reading from the temperature monitoring system shows that the temperature has been out of range (below 2^{o}C or above 8^{o}C), you must inform all members of the Clinical Trials team so that they are aware that the stock cannot be used. Inform all the trial Sponsors whose supplies are stored in that area. This is to request confirmation that the product is fit for continued use. This should be in writing via email with a copy of the relevant graph. Follow any study specific procedures for reporting temperature excursions provided by the Sponsor detailed in the study-specific Pharmacy clinical trial file. Check the study-specific Pharmacy trial file for products that are stable outside of this temperature range. Trial Sponsors of these products still need to be informed of the temperature excursion, but the products can remain stored in that area.

The affected supplies should be placed in quarantine. Follow the procedures outlined in Pharm/S59 (Quarantine of IMP).

If the reason for the excursion is unknown and the temperature has not returned to within the acceptable ranges, move the supplies to another refrigerated area within Pharmacy, which is temperature monitored.

Report the fridge fault to the Facilities department. Record the job reference number and any actions taken on the appropriate temperature monitoring form (Pharm/F36).

Once the fridge is repaired and before the supplies are returned to it, validate the fridge temperature (arrange via the Pharmacy Quality Assurance team) for at least 48 hours using an electronic temperature recording device. Ensure the fridge maintains a temperature between 2°C and 8°C. File validation documentation in the current temperature graphs file.

Document all actions taken in the 'Temperature Excursion Record Form (Clinical Trials)' (Pharm/F79, one form per trial affected) and place the completed form in the temperature section of the Pharmacy file for each study affected.

A file note (R&D/T20) should also be written referring others to the temperature excursion record form (Pharm/F79). The file note should be attached to a copy of the relevant temperature graph, and filed within the Temperature Records file held in the Pharmacy Clinical Trials Dispensary. **The File note log should be updated accordingly so there is a Master list of all Temperature excursions**

4.4.3 Freezer Temperature Excursion

Freezers should be calibrated to a suitable temperature as defined by the protocol for which it is being used (usually between -15°C and -25°C).

If the temperature graph or daily temperature reading from the temperature monitoring system shows that the temperature has been out of range, you must inform all members of the Clinical Trials team so that they are aware that the stock cannot be used. Inform the trial Sponsors whose supplies are stored in that area regarding the temperature excursion. This is to request confirmation that the product is still suitable for use. This should be in writing via email with a copy of the relevant graph. Also follow any study specific procedures for reporting temperature excursions provided by the Sponsor detailed in the study-specific Pharmacy clinical trial file.

The affected supplies should be placed in quarantine. Follow the procedures described in Pharm/S59 (Quarantine of IMP).

If the reason for the excursion is unknown and the temperature has not returned to within the acceptable ranges, move the supplies to another suitable area, which is temperature monitored.

Report the freezer fault to the Facilities department. Record the job reference number and any actions taken on the appropriate temperature monitoring form (Pharm/F78).

Once the freezer is repaired and before the supplies are returned to it, validate the freezer temperature (arrange via the Pharmacy Quality Assurance team) for at least 48 hours using an electronic temperature recording device. Ensure the freezer maintains an appropriate temperature as defined by the trial protocol. File validation documentation in the current temperature graphs file.

Document all actions taken in the 'Temperature Excursion Record Form (Clinical Trials)' (Pharm/F79, one per trial affected) and place the completed form in the Pharmacy file of each study affected

A file note (R&D/T20) should also be written referring others to the temperature excursion record form (Pharm/F79). The file note should be attached to a copy of the relevant temperature graph, and filed within the Temperature Records file held in the Pharmacy Clinical Trials Dispensary. **The File note log should be updated accordingly so there is a Master list of all Temperature excursions**

4.4.4 Fridge and Freezer Alarm Fault Reporting

Any suspected fridge or freezer alarm faults within Pharmacy clinical trials should be reported to the Quality Assurance department within Pharmacy. If they cannot determine the cause, the fault should be reported to the Facilities department.

In these circumstances, any IMP stored in the affected fridge or freezer should be moved to an alternative location ensuring that it is still continually monitored and stored under the correct conditions.

4.4.5 Hospital Alarm System Activation

Each Pharmacy clinical trials fridge and freezer is also connected to the hospital alarm system, as well as having its own internal alarm. These activate if the temperature is below 2^{o}C or above 8^{o}C in the fridges and if the temperature is below -25.5°C or above -10.0°C for more than 10 minutes in the freezer.

If an alarm activates, check that the fridge or freezer is plugged in and the door is properly closed. If not, correct the fault and reset the alarm. Check after 30 minutes that the temperature has returned to normal.

If no reason is found for the alarm to activate, move all supplies into another refrigerated or frozen area within Pharmacy that is temperature monitored. Print out the temperature monitoring device graph and data sheet to see how long the temperature has been out of range. Telephone the Facilities department to see if the fridge or freezer can be adjusted or repaired/serviced.

4.5 Cold Chain Transport to offsite units

When transporting cold chain items from Pharmacy to offsite units e.g. GUM clinic a validated process must be followed in order to avoid temperature excursions occurring during packing and transporting the cold chain items. To do this you need to follow the method outlined below. You will need to use this SOP alongside procedures detailed in the study specific SOP for the relevant trial if appropriate.

1. Locate the clinical trial vaccine porter and 7 cool packs (which can be found in the cold room). These should be stored at 2 to 8°C for 24 hours prior to use.
2. Pack the vaccine porter, refer to manufacturer's instructions in illustration in Appendix 1, as follows; use 7 cool packs; place one on the bottom and one at each side. Keep two to one side for inside and on top of the cardboard box that will house the vaccines.
3. Put a cardboard box (which will be holding the stock) into the vaccine porter and place a small cool pack (wrapped in a small bag) inside.
4. Program a temperature logger as follows; set it to record every minute with alarm points set between 2 and 8°C. Delay the start by ONE hour.
5. Place the temperature logger inside the cardboard box in the vaccine porter.
6. Store the vaccine porter (that has been packed as above) in the cold room for 24 hours with the lid open.
7. The next day (day of transfer), ensure small cool pack is still inside the cardboard box and is cold to the touch. Ensure the logger has not registered any temperature excursion.
8. Close the cardboard box and put the one cool pack on top. Close the vaccine porter.
9. Check the temperature of the logger after it has been recording for ONE hour to ensure no excursions have occurred.
10. If no excursions have occurred, transfer the stock from its location (already placed into a sealed bag to protect during transport) and then place into the cardboard box inside the vaccine porter. Ensure the cool pack is placed on top of the vaccines within the cardboard box.
11. Place the remaining cool pack on top of the cardboard box and seal the vaccine porter by putting the lid on. Transport to the offsite unit recording the time of transfers on the Pharm/F91 transfer form.
12. On arrival at the offsite unit, locate the relevant fridge, and promptly transfer the stock to the fridge (2 to 8°C). Note time of placing in the fridge on the Pharm/F91 transfer form.
13. After returning from the offsite unit, download the temperature logger as per local work instructions.
14. Compare the resulting graph/data against the times noted on the Pharm/F91 transfer form.
15. If the temperature has stayed in range during those times, file the graph/data with the transfer form in section 8 of the Pharmacy file. No further action is required and the vaccines are ready for use.
16. If the temperature has gone out of range, contact the Sponsor to report the temperature excursion, and follow section 4.4.2 of this SOP.
17. The research team should also be contacted so that they can quarantine the IMPs by completing a Pharm/F43 quarantine log and an Pharm/F42 quarantine notice until they receive further instruction from the Sponsor.

4.6 Validation of offsite transfer using a vaccine porter

This transport method will need to be validated twice yearly; once during winter and again during summer. To do this a 'Validation Document for Good Distribution Practice' document must be acquired from QA. Two loggers will be required; one recording the ambient temperature outside the porter and another recording the temperature inside the vaccine porter. Once the journey has been made to the GUM clinic and the loggers have been downloaded a copy of the temperature graphs and completed document can then be given to the QA team.

5 Related SOPs and Documents

Pharm/F36	Temperature Monitoring Form – Fridge Temperature
Pharm/F54	Temperature Monitoring Form - Ambient Temperature
Pharm/F78	Temperature Monitoring Form – Frozen Temperature
Pharm/F79	Temperature Excursion Record Form (Clinical Trials)
Pharm/F91	Transfer of IMP from Pharmacy to a storage location outside of Pharmacy
Pharm/F112	Ambient temperature monitoring form for studies where IMP is stored outside of Pharmacy
Pharm/S59	Quarantine of IMP
Pharm/F42	Quarantine Notice
Pharm/F43	Quarantine Log
Pharm/F108	Daily Clinical Trials Temperature Checks
Pharm/S76	Storage and dispensing of Investigational Medicinal Products outside of Pharmacy
SOPQA9	Refrigerated storage of medicines on wards/departments
SOPQA8	Responding to the Pharmacy fridge alarm
	MHRA Good Clinical Practice Guide (2012)
SOPSCQA1	Daily Fridge Temperature Monitoring in Pharmacy
SOPSCQA4	Responding to a Fridge Alarm Following a Temperature Deviation
R&D/T20	File Note Template
R&D/F59	File Note Log

6 Appendix 1- Packing instructions for vaccine porter