PRE-SITE / SITE INITIATION VISIT PACKET
ONCOLOGY IDS PHARMACY

Updated 18 MAY 2022

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Introduction

Cancer Investigational Drug Pharmacy (Cancer IDS) at the University of North Carolina Hospitals is located at the North Carolina Cancer Hospital (NCCH).

Hours are Monday through Friday, 08:00 am until 04:30 pm

We are closed all major holidays.

Cancer IDS Pharmacy has controlled access granted by secure ID badge.

All cancer investigational products are prepared on the 3rd floor of the North Carolina Cancer Hospital (NCCH).

Cancer IDS Pharmacy requires all documentation from the sponsor to be supplied in electronic format. The current protocol/amendment, IB and pharmacy manual, when supplied, will be stored in Oncore. Oncore is maintained and updated by Lineberger Comprehensive Cancer Center (LCCC) Regulatory Department. LCCC regulatory department maintains previous protocol documents in the protocol regulatory file.

Cancer IDS Pharmacy will receive and store all information electronically. We do not retain paper documents.

Cancer IDS Pharmacy has an onsite destruction policy for investigational drugs. A copy of the destruction policy is included.

Cancer IDS Pharmacy receives and processes all investigational products in our 3rd Floor Oncology Infusion pharmacy. The shipping address is:

UNC Healthcare
101 Manning Drive
NC Cancer Hospital Infusion Pharmacy, RM C3247-5
Chapel Hill, NC 27514

Phone Number: 984-974-8236
Fax Number: 984-974-8560

NCOncologyids@unchealth.unc.edu

Staff Information

Cancer IDS pharmacist's names, titles, and e-mail addresses are as follows:

- Sharon Guerry, RPh Sharon.Guerry@unchealth.unc.edu
- Kristen Gray, PharmD Kristen.Gray2@unchealth.unc.edu
- Jamie Chuu, PharmD Jamie.Chuu@unchealth.unc.edu
- Jordan Smith, PharmD Jordan.Smith4@unchealth.unc.edu
- Donna Topping, PharmD Donna.Topping@unchealth.unc.edu

Equipment Information

Cancer IDS Pharmacy Utilizes (temps also noted in IDS SOP-05)

- Controlled Room Temperature Drug Storage (20°C – 25°C with excursions permitted 15°C – 30°C)
- Refrigerator Storage (2°C – 8°C)
- Freezer (-25°C – -10°C)
- Ultra Low Freezer (-90°C – -60°C)
- Refrigeration equipment is certified annually by a third party contractor and this documentation is available upon request.
- Temperature is recorded daily every 15 minutes by the UNC Healthcare Hospital Engineering Department and provided daily to Cancer IDS

Closed System Information

Cancer IDS Pharmacy utilizes the BD PhaSeal system for any drug prepared in the hazardous cleanroom

Inventory Control and Temperature Monitoring SOP

UNC HEALTH	Procedure Name	**Investigational Drug Services Inventory Control and Temperature Monitoring**
	SOP #	**IDS SOP-05**
	Date this Version Effective	**01 Jul 2020**
	Responsible for Content	**IDS Manager**

I. Description

This SOP describes inventory control processes. Ordering, accountability, storage, temperature monitoring, and processes for control of investigational product (IP) when temperature excursions happen are also described.

II. Rationale

Clear workflow process for inventory management ensure that IP is appropriately received, stored, transferred, and accounted for at each step along the way.

The goal of this SOP is to create standard processes and consistency in inventory control processes and temperature monitoring.

III. Procedure

A. IP Inventory

1. IP labeled “Investigational Drug: Limited by Federal Law to Investigational Use” will not be used as regular pharmacy stock.
2. UNC Investigational Drug Services (IDS) will not provide IP supplied for a clinical use to a laboratory for non-clinical use unless the sponsor and/or IND holder authorize the release of that IP. If verbal authorization is obtained from a sponsor, written documentation shall be completed and retained.

B. Ordering IP

1. IP is typically obtained from the National Cancer Institute (NCI), pharmaceutical industry, study sponsor, or wholesaler.
    a. Ordering process should be discussed with IDS at least several weeks in advance of the need to order IP.

b. If requested to order IP by the primary investigator (PI), IDS will verify protocol approval by IRB prior to ordering IP.

c. Protocol inventory must be received in IDS before study activation can take place. Exceptions will only be made for those protocols that require patient registration prior to shipment of inventory by the sponsor or supplier.

2. If the sponsor supplies IP for the study, they shall supply sufficient IP to enroll patients, but not more than sufficient inventory for six months' duration of the trial at our institution. Please see UNC IDS SOP-13 for additional details.

3. IDS can order IP provided by NCI only after the study has received full approval from both the IRB and NCI.

    a. IDS will place an order through NCI's system once a study is activated and IDS is allowed to order IP (often only after patients are already enrolled/randomized).

4. When the initial supply is sent automatically from the sponsor, if requested in advance IDS will notify the study team when IP is available on site.

5. IDS will be responsible for ordering and reordering all drug supplies for research protocols with inventory managed by IDS. IDS will not order or reorder inventory that is managed outside of IDS (i.e. a sponsor utilizing an electronic system that automatically generates orders).

    a. If IDS is to be responsible for managing inventory levels, this must be communicated to and confirmed by IDS in advance of study startup.

    b. IDS reserves the right to refuse to be responsible for managing inventory levels.

    c. If IDS agrees to manage inventory levels, this will be done through a par and re-order level system. IDS will work with the study team to determine what inventory levels to use as par and re-order points. No other inventory management methods will be used and IDS will not proactively anticipate patient volume or use any other method for predicting need for study medication.

    d. If par and re-order levels prove to be insufficient to keep enough stock on hand, IDS will work with the study team to revise the par and re-order levels.

    e. At any time, study teams may request a revision of the par and re-order levels.

6. In rare scenarios, including investigator-initiated trials (IITs) and when the sponsor will reimburse the wholesale acquisition cost, IDS will order commercially available IP from a wholesaler.

    a. Purchases are based on package size and the study will be charged for the entire package size ordered at the time of purchase plus a small percentage of the purchase cost as a processing fee.

    b. Unused IP at study closure cannot be returned for a refund.

C. Vestigo Accountability

1. Drug accountability of receipt, inventory transfer, dispense, and returns are all recorded and kept in Vestigo. IDS will perpetually maintain inventory stored in both central and satellite locations within Vestigo.
2. Used vials and their remainders will not be accounted separately in Vestigo. All used vials are immediately destroyed, including their remnants, immediately after use. For more detail on destruction of IP, please see UNC IDS SOP-08.
3. Elements of drug accountability records (DARs) include, but are not limited to: institution name, primary investigator name, protocol title and number, agent name, agent strength, agent formulation, dispensing location, recorder initials and date, transactions, lot number, and quantity on hand.
4. Accountability will be maintained for IP supplied by the sponsor or procured by IDS. No accountability will be completed for non-study-supplied commercial agents, standard of care medications, or other medications involved in a study not maintained or dispensed by IDS.
5. No sponsor-based forms will be utilized for drug accountability.
6. Satellite DARs will be maintained at each location where IP is stored other than the central location, refer to UNC IDS SOP-03 for additional details.
7. Some studies may request double accountability. IDS should not be assumed to be performing double accountability for all studies. If double accountability is requested for a protocol, the sponsor or study team must make this clear to IDS in writing prior to study opening.
    a. IDS will only agree to perform double accountability in cases where a compelling argument, in the view of IDS, can be made why double accountability is necessary.
    b. If double accountability is performed, two individuals will check accountability. As accountability is different than dispensing, different individuals may be involved in these processes.

        a. Double accountability does not have to be completed by two pharmacists and a pharmacist does not have to be the second check for accountability.

D. Storage of IP

1. IP will be stored in a secure manner with sufficient back up procedures to address and maintain proper storage of IP in an emergency such as a power outage. Please refer to UNC IDS SOP-01 for additional details.

E. Temperature Monitoring

1. IDS will monitor temperature conditions in all storage locations continuously. Data from temperature monitoring will be maintained by IDS in an accessible format.
2. IDS will not utilize sponsor-provided temperature logs/data capture systems.

3. Official recorded temperatures will be recorded from devices which have been calibrated. The calibration documents can be made available upon request. Frequency of calibration will be determined by IDS but calibrations will not be allowed to expire.
4. IDS will use only our own temperature monitoring equipment and will not accept or operate temperature monitoring equipment provided by sponsors or study teams.
5. IP temperatures will be maintained in compliance with standard temperature ranges as defined by United States Pharmacopeia (USP) standards within USP Standard 33-NF28 Sections 10.30.10, 10.30.40, 10.30.60 and according to USP <1079>.
    a. Any temperatures recorded in Fahrenheit will be converted to Celsius.
    b. Though temperature data will be measured to tenths or hundredths of degrees, official recorded temperatures will be rounded to the nearest whole Celsius degree.
    c. Room temperature: temperature prevailing in a working area, 20°C – 25°C with excursions permitted between 15°C – 30°C.
    d. Refrigerated temperature: 2°C – 8°C.
    e. Freezer temperature: -25°C – -10°C.
    f. Ultra-low freezer temperature: -90°C – -60°C (the standard temperature ranges for ultra-low freezer temperatures are not included in the USP Standard 33-NF28 or USP <1079>).
    g. Any request to comply with temperature conditions or temperature limits other than the above standard ranges will be denied unless the request is supported by robust data to justify the request. This determination will be made at the discretion of the IDS manager.
6. IDS will notify the sponsor of temperature excursions.
    a. Deviations of less than ±5°C from room temperature (20°C – 25°C) that are maintained for 24 hours or less will not be reported to the sponsor; only deviations of >5°C maintained for at least 30 minutes, or excursions of less than ±5°C for greater than 24 hours contiguously will be considered a reportable temperature excursion and reported to the sponsor.
    b. For refrigerated and frozen medications, excursions will be considered reportable and reported if a temperature deviation of ±1°C or greater is sustained for a contiguous time period of 30 minutes or longer. Excursions from refrigerated or frozen temperatures of less than 1°C for any period of time or excursions of any magnitude of less than 30 minutes will not be reported.
    c. If a refrigerator or freezer malfunctions causing temperatures to exceed the acceptable range, IDS will transfer IP to a similar working, monitored unit. The temperature and condition of the malfunctioning unit will be observed prior to returning IP to that unit.
    d. In the event of a temperature excursion, IP in question will be quarantined in the appropriate storage conditions until the IP is deemed acceptable for use by the

sponsor and/or sponsor representative. The quarantined inventory will be separated from other IP and clearly marked as not for patient use.

e. Relevant temperature data will accompany any notification of excursion in order to support decision making regarding the viability of any affected IP.

f. Monitors, sponsors, or the study team are expected to respond to temperature excursion notifications within two business days.

g. IDS will use their own temperature excursion reporting form. Sponsor-provided forms for reporting temperature excursions will not be utilized.

7. IDS will maintain an on-call response to temperature alarms.
8. IDS will monitor temperature during any IDS controlled or initiated shipping or transfer that leaves the interior of our buildings. If the transfer of IP occurs between two locations where the transfer path does not exit a UNC-controlled facility, temperature will not be monitored. Refer to UNC IDS SOP-07 for additional details.
9. IDS will not monitor the temperature of IP after it has been dispensed and picked up by a study team, research patient, or their representative.
10. Laboratory specimens and food are not permitted in IDS refrigerators or freezers.

F. Study Specific Time Points

1. IDS will not duplicate source documentation information such as nursing infusion start and stop times that are recorded elsewhere (Epic, etc.).
2. For study-specific time points and documentation not collected in source documentation work, IDS will work with the sponsor to identify an acceptable place to document the information.

IV. Original Procedure Date and Revisions

31 Jan 2020, 25 Mar 2020, 15 Jun 2020 – DRAFTS

01 Jul 2020 - Live

Returns and Destruction of IP SOP

UNC HEALTH	Procedure Name	**Investigational Drug Services Returns and Destruction of IP**
	SOP #	**UNC IDS SOP-08**
	Date this Version Effective	**17 Mar 2021**
	Responsible for Content	**IDS Manager**

I. Description

This SOP describes the process and documentation of returns of investigational product (IP) as well as the process and documentation of the destruction of IP returns and materials used in the dispensing of IP.

II. Rationale

All pharmacy personnel, both at Central IDS and at satellite locations, involved in the handling, preparation, and returns of IP must be aware of procedures and proper documentation of their activities.

The goal of this SOP is to produce consistent practice to ensure compliance.

III. Procedures

A. USP <800> and Hazardous Medications

1. USP <800> establishes practices to protect health care employees from the dangers of repeated and extended exposure to hazardous medications. The standards will be considered to apply to employees as well as to any visitors to IDS who will handle medications that are considered hazardous—monitors, coordinators, and nurses, etc.
2. At the time of protocol review by the assigned lead pharmacist, a determination will be made whether the IP to be handled by IDS will be considered hazardous or not. To make this determination, the lead pharmacist will use any available source they deem relevant, including, but not limited to, guidelines from USP <800>, NIOSH, sponsor-provided guidance, and any institutional hazardous medication lists or policies.
3. If IP is deemed to be hazardous, it will be handled according to the local hazardous medication policies and any federal or state statute or regulation.

B. General Destruction Guidelines

1. All destruction of IP is documented in the electronic accountability system.

2. IDS will not log patient returns into any IRT system. For further detail on the roles of IDS or activities that IDS does not perform, please see UNC IDS SOP-01.
3. Controlled substances are exempted from this SOP. For guidance on the handling of controlled substances by IDS, see UNC IDS SOP-16.

C. Destruction of IP

1. All IP is placed into black Resource Conservation and Recovery Act (RCRA) pharmaceutical waste bins located in each pharmacy. These are then collected by local environmental health and safety staff for destruction.
2. After collection, IP is shipped to an incinerator where it is incinerated for final destruction.
3. Supplies, PPE, and other materials used in the preparation of IP or dispensing of IP are placed into red hazardous waste bags. These bags are collected by local environmental health and safety staff for destruction. These items may either be incinerated for final destruction or autoclaved prior to wasting.

D. IP Containers After Use

1. Immediately after use to prepare IP for dispensing, any containers, vials, boxes, or other empty or partially used containers will be disposed of in the appropriate waste streams.
2. Any containers storing oral IP with remaining dosage units to be dispensed at a later time will be retained until all dosage units have been dispensed and the container is empty. Once emptied, oral dosage containers will be disposed of in the appropriate waste stream.
3. Separate or duplicate records of destruction outside of our electronic accountability system will not be maintained for any partially used or fully emptied vials used during the preparation and dispensing of IP.
4. Any IV bags, syringes, filter sets, infusion lines, patches, topical products, or other materials used in the process of administering prepared doses of IP to patients will be considered hazardous waste and will be immediately disposed of into the appropriate waste stream.

E. Oral, Topical, Transdermal IP Returns

1. Study coordinators will perform a count of the product to be returned and provide documentation of their count to IDS. IDS staff will then perform a second, blind count of the returned product.
2. If both counts are in agreement, returns will be destroyed by being placed into the appropriate waste stream. Returns will be considered destroyed at the time of placement into waste bins.
3. If counts are discrepant, IDS will work with the coordinator to resolve the discrepancy and document any relevant information. If the discrepancy can be resolved, the final count will be documented and returns will be destroyed as described in section C above.
4. IP returned to the pharmacy by the study coordinator will be accounted for in the electronic accountability system. Aside from documentation provided by study coordinators and data in the electronic accountability system, no other documentation of returns will be maintained.

5. If a study wishes to request that returns be retained for monitor review, it is the responsibility of the study team, sponsor, or the monitor to notify IDS prior to study opening. IDS will keep returns for monitor review for an additional fee, if approved, at the discretion of the IDS manager. Maintenance of returns for monitor review will only be approved if required by law/regulation or if a compelling argument for the need to maintain returns is made (again, at the discretion of the IDS manager).
6. If returns are kept, they will only be kept for 90 calendar days or until the next monitoring visit, whichever is sooner, and then they must be accounted for and destroyed or sent back to the sponsor. If a monitor neglects to appropriately destroy or send any returns to the study sponsor at a monitor visit, IDS will destroy any and all returns for the applicable protocol(s) within 30 calendar days of monitor visit.
7. Hazardous drug returns will be immediately destroyed after accounting for their return in the electronic accountability system. Under no circumstances will hazardous returns be stored by IDS.
8. Per section D above, no returns of any intravenous, intradermal, topical, or subcutaneous product will be accepted by IDS.

F. Tear-Off Labels

1. IDS will not save tear-off labels from dispensed IP. Sponsors may request that tear-off labels be retained for an additional fee if there is additional information on the tear-off label compared to other sources and at the discretion of the IDS system clinical manager.
2. If tear-off labels are retained with paper dispensing documentation, they will be affixed to the dispensing record and then stored electronically as a part of the dispensing record. The paper record of dispensing nor the tear-off label will be guaranteed to be kept in paper form. (For further information on IDS practices regarding the storage of documents, please see UNC IDS SOP-11 and UNC IDS SOP-10.)

G. Temperature Monitoring Devices Sent to IDS

1. Devices for monitoring the temperature of shipments will be stopped immediately upon opening the shipment, and the data from the monitoring device will be downloaded and saved electronically. (For further information on temperature monitoring devices and procedures for temperature excursions, see UNC IDS SOP-05.)
2. Once temperature data is confirmed to be stored appropriately, the temperature monitoring device will be destroyed. Multi-use monitoring devices that have been requested be returned with shipping containers will be returned.
3. If the temperature monitoring device is not downloadable, then it will be kept until the next monitor visit. At their next visit, the monitor will review the device, remove it from the paper it is affixed to (if this is applicable), replace it with the tear-off label from the temperature monitoring device (if applicable), and then destroy the device. If the monitor neglects to review and destroy the devices which were made available to them at their visit, IDS will destroy them on behalf of the monitor.

H. Quarantined IP

1. IP that has been placed into quarantine will be stored for up to 90 calendar days to allow for a decision to be reached regarding returning the IP to normal stock or wasting the IP.
2. If IP is supplied to IDS, then at the time of quarantine study sponsor will be notified and be requested to investigate and provide instruction for next steps. If a decision is not reached within 90 calendar days, IDS will destroy the IP into the appropriate waste stream.
3. If IP is acquired by IDS, then IDS will communicate with the study coordinator and assist the coordinator in making a determination of how to proceed.
4. All IP received by IDS that is not properly labeled will be immediately quarantined. For proper labeling requirements, please see UNC IDS SOP-13

I. IP Dispensed and Not Picked Up

1. If the IP never left the pharmacy and is not an IRT-assigned product, it may be returned to stock.
2. If IRT-assigned, then it will be accounted for as a subject return. Because no coordinator count will be available in this case, a blind double count will be performed by IDS staff.

J. Expired IP

1. Expired IP will be retained for up to 90 calendar days after expiration or until the next monitor visit, whichever is sooner. Arrangements can be made by the sponsor for expired IP to be retained for longer periods of time at the discretion of the IDS system clinical manager. After 90 calendar days or the agreed upon extension period, expired IP will be destroyed per the waste destruction policies of the local institution.

K. Unused IP at Time of Study Close

1. IP remaining in possession of IDS at time of study closure will be destroyed or returned to the sponsor by the monitor at the study close-out visit.
2. Any IP not destroyed or returned by the monitor at the study close-out visit will be accounted for and destroyed within 30 calendar days.
3. If the study sponsor or monitor neglect to perform a close-out visit within 90 days of study closure with IDS, IDS will destroy all unused IP within 90 days of study closure with IDS.

IV. Original Procedure Date and Revisions

01 Jul 2019 – SOP live.

15 Jun 2020 – Updated period of retention of expired medications. Clarified language to be more specific. Expanded criteria for quarantine to include improperly labeled IP. Clarified the reasons why requests for maintenance of patient returns may or may not be approved. Inserted details for destruction process.

17 Mar 2021 – Simplified language in destruction description to address misunderstanding of practice by IDS.

Vestigo Information

a) Vestigo™ is a web-based software system that is the method of electronic documentation for all research protocols with oversight by IDS at UNC Health.

b) Data is secured via VPN tunnel or 128-bit SSL by connection. All back-up data is encrypted using 256-bit AES encryption.

c) Vestigo™ software meets the compliance standards for HIPAA and the Code of Federal Regulations 21 Part 11. There is no field for the storage of social security numbers.

d) All users will have a unique user name and password. The use of shared or common account is not allowed.

e) Vestigo™ software will be used for the following:

   i) Scheduling of monitor visits, if applicable

   ii) Availability of documents for monitor visits

   iii) Study drug inventory management and electronic drug accountability logs, including a record of all dispensations and returned medications

   iv) Printing of patient specific labels for dispensing medications

   v) Scanned shipping documents for monitor review

Monitor Visit Communication

PLEASE NOTE: Monitor visits to the pharmacy are available by appointment only. The following document outlines the process for scheduling and flow for the monitor's visit.

Making an appointment:

1. The sponsor monitor calls their designated UNC Clinical Research Associate (CRA) at Lineberger for each scheduled appointment. (Blinded Monitors may Contact the Pharmacy Directly)
2. The UNC CRA emails IDS pharmacy a completed Monitor Request form for best possible Date/Time for monitor to visit. (see page 9)
    a. Select Date/Time from Monitor Request form for visits to the pharmacy.
    b. Include monitor name, phone, email address.
3. Pharmacy replies with verification of Date/Time availability.
4. UNC CRA confirms Date/Time with Monitor and IDS Pharmacy. Please note: delayed responses may lead to the verified times being filled by other monitors that have completed the verification process.
5. The sponsor monitor will be emailed a Vestigo login/password to access documents prior to site visit (see Day of Visit below).

Table 1. Available Appointments*

Days	**Type of Visit**	**Time Slot**
Monday -Friday	Visit	30 minutes
	Closeout	2 hours
	Audit	Half-day (4 hours) or Full-day (7 hours)

*Variations in allotted time will be accommodated as necessary when notified at point of scheduling for closeouts and audits.

Monitor Visits	
Day	**Time Available (30min)**
Monday - Friday	0830; 0900; 0930
	1400; 1430; 1500

Day of Visit:

1. The monitor will only have access to the IDS pharmacy during their designated appointment time.
2. The monitor is given Vestigo access beginning at 4pm the day before his/her visit. The monitor needs an appointment with IDS pharmacy to be given access to Vestigo, even if they do not plan to come to the IDS pharmacy.
3. Vestigo will send a one-time email to the monitor with the details of their access once the visit is scheduled. **Please note: the Monitor will not receive any further Vestigo emails prior to or after the visit is scheduled to remind him/her of their visit** The monitor will need to view and print relevant Vestigo documents or records in a location separate from the IDS pharmacy.
4. If the sponsor has issues with Vestigo, they should contact the company directly. Contact information for Vestigo is in the Vestigo email sent at the time the visit is scheduled.
5. In the unlikely event that Vestigo is experiencing downtime during the monitor's visit, pharmacy will send the monitor the Drug Accountability Record Forms (DARFs) and shipping documents when the system is available.

Monitor Request Form

Contact Information

Monitor Name: _____
Monitor Email: _____
Monitor Phone #: _____
Company Associated with: _____
All Studies Monitored: _____

Vestigo access request

Study: _____
Date: _____
*All monitor access to Vestigo is scheduled for **4PM to 4PM***
24 hours of access is standard but can be extended upon request

WebEx Request

WebEx meetings are available upon request, priority given to closing studies or for expiring IP reconciliation. Fees may apply.
Study: _____
Date: _____
Time: _____

Please note available times for 30 minute WebEx
Monday -Friday
Morning: 8:30AM-9AM, 9AM-9:30AM
Afternoon: 2PM-2:30 PM, 2:30PM-3PM, 3PM-3:30PM*
*All times Eastern

Please email completed form to
NCOncologyIDS@unchealth.unc.edu

Training Process

Study Specific Training

1. For each study, the lead pharmacist creates a protocol information sheet to meet the needs of the given study using the protocol and other resources provided by the sponsor. This protocol information sheet contains instructions on the handling, storage requirements, receiving, dispensing, preparation and labeling of the investigational study material(s).

2. The lead pharmacist will distribute this initial document to all cancer IDS and cancer hospital infusion pharmacy staff via email. The document will be kept electronically by cancer IDS and hard copies will be placed in the cancer IDS dispensing area and in the clean room of the cancer hospital infusion pharmacy.

3. The clean room technician, IDS technicians, cancer IDS pharmacists, and cancer hospital infusion pharmacists will access this document any time drugs are received, dispensed or prepared per the specific protocol. Each staff member is trained in real time by being required to read the document when doing any of these tasks.

4. Updates and amendments will be reviewed by the lead pharmacist and the protocol information sheet will be updated. Updated protocol information sheets will be kept electronically by cancer IDS and hard copies will be placed in the cancer IDS dispensing area and in the clean room of the cancer hospital infusion pharmacy. Updated protocol information sheets will not be emailed to each individual staff member because real time training is done each time tasks related to the protocol are done.