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Pharmacy
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SUBJECT: Investigational Drugs Services (IDS)

As a planned audit for Fiscal Year 2015, Audit and Advisory Services (AAS) conducted a review of the management and oversight of investigational drugs used in clinical studies.

Our services were performed in accordance with the applicable International Standards for the Professional Practice of Internal Auditing as prescribed by the Institute of Internal Auditors (the "IIA Standards").

Our preliminary draft report was provided to department management in February 2015. Management provided us with their final comments and responses to our observations in March 2015. The observations and corrective actions have been discussed and agreed upon with department management and it is management's responsibility to implement the corrective actions stated in the report. In accordance with the University of California audit policy, AAS will periodically follow up to confirm that the agreed upon management corrective actions are completed within the dates specified in the final report.

This report is intended solely for the information and internal use of UCSF management and the Ethics, Compliance and Audit Board, and is not intended to be and should not be used by any other person or entity.

Sincerely,

Irene McGlynn
Director
UCSF Audit and Advisory Services

EXECUTIVE SUMMARY

I. BACKGROUND

As a planned audit for Fiscal Year 2015, Audit and Advisory Services (AAS) conducted a review of the management and oversight of investigational drugs used in clinical studies.

An investigational drug is one that is under study which meets one of the following requirements:

- Not approved by the U.S. Food and Drug Administration (FDA) for commercial distribution in the United States;
- Approved by the FDA for distribution under Treatment Investigational New Drug (IND) status; or
- Approved for commercial distribution, but is under investigation for an unapproved indication subject to a commercial or investigator-sponsored IND.

Federal requirements for investigational drugs which investigators must follow are contained under Code of Federal Regulations (CFR) Part 312 of Section 21.

Studies involving investigational drugs are critical components for achieving UCSF's vision of being a world leader in scientific discovery and its translation into improved health. At the same time, improper handling of investigational drugs can pose risks to study participants, cause non-compliance with regulations, and undermine confidence with study sponsors.

At UCSF, all clinical trial studies that involve the administration of investigational drugs with human subjects must be reviewed and approved by the Committee on Human Research (CHR), UCSF's Institutional Review Board (IRB). The UCSF Human Research Protection Program (HRPP) has oversight responsibility for all human subject research projects conducted by UCSF investigators. HRPP has established guidelines for investigational new drugs and biologics in accordance with current federal regulations.[1] All studies are registered and documented in iRIS, a web-based system that enables online IRB application submission, real-time submission tracking, protocol review, post-approval compliance activities, and data management of studies.

UCSF Medical Center Pharmaceutical Services' Investigational Drug Services (IDS) assumes responsibility for the storage, accountability, preparation, dispensing, and security of investigational drugs to be used at Medical Center licensed facilities. IDS is located at Parnassus and Mt Zion campuses, and Mission Bay campus will be added in the near future. IDS is staffed by seven FTEs and currently manages investigational drugs for about 340 studies.[2] In fiscal year 2014, IDS generated approximately $613,000 in revenue from recharge fees for managing investigational drugs.

[1] UCSF Guidance on Research Topics and Issues, Investigational New Drugs and Biologics.
[2] Based on data obtained from iRIS and Vestigo (the web-based software used by IDS to record and manage investigational drugs) on 11/4/2014.

Alternatively, investigators may choose to directly manage investigational drugs for their studies. The number of investigational drugs studies directly managed by investigators at the various UCSF locations as of November 4, 2014, is shown below:[3]

UCSF Study locations	Number of Studies investigational drugs directly managed by Investigators	Oversight Responsibility
Medical Center licensed facilities	20	IDS
Langley Porter Psychiatric Hospital and Clinics (LPPI)	9	LPPI Pharmacy
Non-Medical Center licensed facilities (research units, Labs etc.)	13	No oversight responsibility defined

II. AUDIT PURPOSE AND SCOPE

The objectives of this review were to:

- Evaluate the adequacy of controls for receiving, storing, documenting, preparing, and dispensing of investigational drugs;
- Determine if handling and management of investigational drugs complies with regulatory standards;
- Determine if there is recovery of pharmacy expenses for management of investigational drugs; and
- Determine whether IDS has a process in place for the periodic quality assurance evaluation of investigational drugs not directly managed by IDS.

The scope of the review included investigational drugs managed by IDS and investigators within UCSF locations. It excluded studies with investigational drugs dispensed at San Francisco General Hospital, San Francisco Veterans Affair Health Care System, and San Francisco Department of Public Health.

Procedures performed as part of the review included interviews with IDS personnel; assessment of existing controls for handling investigational drugs; assessment of physical security controls; and review of a sample of studies managed by IDS and investigators. For more detailed steps, please refer to Appendix A.

Work performed was limited to the specific activities and procedures described above. As such, this report is not intended to, nor can it be relied upon to provide an assessment of compliance beyond those areas specifically reviewed. Fieldwork was completed in January 2015.

[3] This statistical information is based on a data extract from iRIS on 11/4/2014 for studies where investigators provided Investigational New Drug (IND) numbers and disclosed that the investigational drugs would be used for clinical trials. Seventeen studies for radioactive or cellular materials and eight studies for data analysis purpose only were excluded, as IDS does not manage or oversee these studies.

III. SUMMARY

Based on work performed, overall internal controls for receiving, storing, documenting, preparing, and dispensing of investigational drugs are in place and functioning appropriately.

Opportunities for improvement exist in the areas of oversight and responsibilities, and IDS operations.

The specific observations from this review are listed below.

Oversight and Responsibilities:

- Requirements for handling investigational drugs stored and dispensed at UCSF non-licensed facilities as well as corresponding oversight responsibilities are not defined;
- There is not an effective method to identify all studies involving investigational drugs conducted at UCSF locations;
- There are inconsistencies in documentation of investigational drugs administration; and
- Investigators did not seek waivers from IDS to directly manage the storage and dispensing of investigational drugs.

IDS Operations

- IDS expenses for providing research related services are not separately identified from Pharmaceutical Services operations costs for standard patient care causing inaccurate reporting on the Medicare Cost Report;
- Periodic reviews and inspections are not being performed by IDS as required by Medical Center Policy;
- IRB approval is not validated prior to dispensing of investigational drugs;
- IDS recharge fees do not cover total costs for providing the service;
- Physical security of the room where investigational drugs are stored is not sufficient; and
- Labels for investigational drugs generated in APeX do not meet FDA requirements.

General Observation

- IDS Pharmacists do not participate in the IRB protocol reviews.

IV. OBSERVATIONS AND MANAGEMENT CORRECTIVE ACTIONS

A. Oversight and Responsibilities

No.	Observations	Risks/Effect	Recommendations	MCA
1	***Requirements for handling investigational drugs stored and dispensed at UCSF non-licensed facilities as well as corresponding oversight responsibilities are not defined.*** The Medical Center and Langley Porter Psychiatric Hospital and Clinics (LPPI) investigational drugs related policies and procedures apply to only studies performed at Medical Center/ LPPI licensed facilities and do not cover investigational drugs directly managed by investigators outside of Medical Center/LPPI licensed facilities. Also, many investigators were not aware of the Medical Center policy and/or interpreted that it did not apply to the campus research community. Additionally, the oversight responsibility of investigational drugs directly managed by investigators in non-licensed facilities has not been defined. During the review, we also noted that there are no guidelines or procedures documented for non-investigational drugs being used for study purposes. [4]	Lack of defined processes and requirements for proper management of investigational drugs could lead to inconsistencies in the handling of investigational drugs and potential non-compliance with federal regulations and/or sponsor requirements.	a) Office of Research should work with Pharmaceutical Services in developing a comprehensive set of policies and procedures which covers the management and oversight responsibilities of investigational drugs stored and dispensed at all UCSF licensed and non-licensed locations. b) Guidelines for non-investigational drugs managed by investigators should also be taken into consideration when developing the new set of policies and procedures. c) Office of Research should evaluate whether all UCSF investigational drugs should be managed by the Medical Center IDS with exceptions allowing investigators to directly manage investigational drugs to be	a) By June 1, 2015, Office of Research will identify the appropriate committee or workgroup to discuss the following: Management and oversight responsibilities of investigational drugs stored and dispensed at all UCSF licensed and non-licensed. - Non-investigational drugs managed by investigators - Proposal for Medical Center IDS to manage all UCSF investigational drugs and development of criteria for exceptions allowing investigators to manage investigational drugs upon approval by IDS. b) By September 30, 2015, Office of Research and the workgroup will make recommendations on policy to be presented to the relevant governance committee for approval.

[4] Drugs that are approved by the FDA for commercial use and used for an approved indication during clinical research are not classified as "investigational". Therefore, these non-investigational drugs are not subject to the same review and oversight as IND status studies.

No.	Observations	Risks/Effect	Recommendations	MCA
			approved by IDS.	c) By March 31, 2016, Office of Research will communicate and implement the policy.
2	***There are inconsistencies in documentation of investigational drug administration.*** Review of a sample of investigational drug studies and discussions with IDS personnel identified that the administration of investigational drugs is documented in a variety of ways, both within and outside APeX. For inpatients, drug administration is documented in the APeX Medication Administration Record (MAR). For outpatients, documentation for drug administration vary, including locations such as: o Patient instructions or notes section in APeX o Paper documents in the study file managed by investigators o Paper documents and/or within Vestigo managed by IDS There is currently no policy or clear directive on whether investigational drugs administration should be documented within APeX or where to document (e.g. MAR, the medication list, treatment notes etc.). Additionally, there has been no decision made on whether all study drugs administered to	There is not a legal requirement to administer investigational drugs at a medical licensed facility, nor it is a requirement for investigational drug administered in non-licensed facilities to be documented within patients' medical records, However, the absence of or inconsistencies in record keeping of the administration of investigational drugs can create patient safety risks due to adverse drug reactions, as the treating provider may not know about any investigational drugs taken by the patient.	CTSI and Office of Research, in consultation with UCSF Health, should consider identifying the appropriate oversight committee to review and provide guidance on the overall UCSF standards for: a) Documenting the administrations of investigational drugs in the medical records dispensed at all UCSF locations. b) Based on the documentation requirements established, Office of Research should communicate these to all UCSF researchers.	a) By January 31, 2016, Office of Research, in consultation with UCSF Health, will identify the appropriate oversight committee to review and provide guidance on the overall UCSF standards for documenting the administrations of investigational drugs in the medical records dispensed at all UCSF locations. b) By March 31, 2016, based on the documentation requirements established, Office of Research will communicate these to all UCSF researchers.

No.	Observations	Risks/Effect	Recommendations	MCA
	research subjects, regardless of whether they are patients at UCSF should be recorded in APeX. Some investigators and/or research coordinators for clinical studies conducted at non-licensed facilities do not have access to APeX; therefore, documenting medication administration in APeX is not an option. Also, these investigators have concerns regarding documentation requirements compromising the confidentiality of study participants.			
3	***There is not an effective method to identify or track all studies involving investigational drugs conducted at various UCSF locations.*** Although all drug related studies are submitted through the iRIS system for IRB review and approval, information on the storage and dispensing locations of investigational drugs is not captured in the system or separately maintained within IDS. Therefore, IDS does not currently have a mechanism to easily identify investigational drugs directly managed by investigators both within and outside Medical Center licensed facilities.	The lack of an effective process to identify all investigational drugs managed by investigators at UCSF impedes IDS' ability to oversee investigational drugs and increases the risk of mis-management of drugs.	IDS, in conjunction with Human Research Protection Program (HRPP), should develop and implement a method for identification and tracking of all investigational drugs studies and their locations.	Effective February 6, 2015, an initial report of approved drug studies within the prior 30 days was provided to IDS for review. Further refinements to the report and development of a survey/process for review of the report are to be developed. IDS will complete this by May 30. 2015.
4	***For investigational drugs that are directly managed by investigators, the requirement of seeking waivers from IDS has not been enforced.*** Based on discussions with IDS, we noted that investigators who directly manage investigational drugs did not obtain	Without obtaining waivers and approvals from IDS, no assessment can be made on the drug pharmacology, dosage, and storage requirements or the	a) IDS should develop a website that includes IDS contact information, locations, services provided, or relevant Medical Center policy to educate the UCSF community on any	a) Pharmaceutical Services has developed an intranet website. By May 31, 2015, the new website will include content related to IDS. b) Upon completion of the

No.	Observations	Risks/Effect	Recommendations	MCA
	waivers/approvals from IDS as required by Medical Center Policy 6.07.05 IV B. Discussions with investigators noted that they were not aware of the existence of the policy; therefore, they did not know of the requirement to obtain waivers from IDS. Further, it was noted that IDS does not have a website that investigators can access in order to obtain IDS contact information, locations, services provided, or relevant Medical Center policy for proper management of investigational drugs.	appropriateness of investigators managing the drug. Insufficient communication and promotion of IDS services and guidance on managing investigational drugs to the research community can create conditions of non-compliance due to lack of awareness by investigators.	requirements or guidance on proper management of investigational drugs. b) Upon completion of the IDS website development, HRPP should disseminate the link to the IDS website and the requirement to investigators on seeking waivers/approvals from IDS if investigational drugs are to be directly managed by the investigators. c) IDS should use the newly developed report for active and approved investigational drug studies to monitor policy compliance on waivers	IDS website development, HRPP will disseminate the link to the IDS website and the requirement to investigators on seeking waivers/approvals from IDS if investigational drugs are to be directly managed by the investigators. This will be completed by June 30, 2015. c) By July 31, 2015, IDS will use the newly developed report for active and approved investigational drug studies to monitor policy compliance on waivers.

B. IDS Operations

No.	Observations	Risks/Effect	Recommendations	MCA
5	***IDS expenses for providing research related services are not separately identified from Pharmaceutical Services operations cost for standard patient care, causing inaccurate reporting on the Medicare Cost Report.*** IDS expenses are not recorded and tracked in a separate cost center account but are subsumed in the Pharmaceutical Services operations account. As a consequence, the Medical Center has been claiming the full	Failure to separate research costs from patient care costs creates risk of inaccurate reimbursement claims on the Medicare Cost Report. Also expenses and recovery of costs for IDS cannot be	a) Pharmaceutical Services should contact Medical Center Finance to create a separate cost center for IDS operations and to assess funding sources. b) Pharmaceutical Services should provide information on IDS expenses to Reimbursement Services for determination of	a) By March 31, 2015, Pharmaceutical Services will contact Medical Center Finance to create a separate cost center for IDS operations and to assess funding sources. b) By March 31, 2015, Pharmaceutical Services will provide information on IDS expenses to

No.	Observations	Risks/Effect	Recommendations	MCA
	cost of Pharmacy operations on the Medicare Cost Report including the IDS costs expended for providing services for research purposes which are unallowable costs for reimbursement claim on the Medicare Cost Report. The Centers for Medicare & Medicaid Services (CMS) Provider Manual Chapter 5 Research Costs stipulates that "costs incurred for research purposes, over and above usual patient care, are not includable as allowable costs for reimbursement claim on the Medicare Cost Report.	tracked and monitored.	adjustments to previously submitted Medicare Cost Reports.	Reimbursement Services for determination of adjustments to previously submitted Medicare Cost Reports.
6	***Periodic reviews and inspections of investigational drugs are not being performed as required by Medical Center Policy.*** Although requirements for periodic reviews by IDS and Pharmacy are defined in the Medical Center's Medication Management – Investigational New Drugs Policy 6.07.05 §IV.B and IDS operational procedures, reviews are not currently being performed. Discussions with IDS management noted that the lack of resources and the absence of a complete quality assurance program have been contributory factors for the lack of reviews conducted. Medical Center policy defines that investigational drugs managed by investigators will be subject to oversight and monthly inspection by Department of	Absence of periodic review increases the risk that improper handling of investigational drugs will go undetected and can potentially lead to non-compliance with FDA regulations.	a) Pharmaceutical Services should develop and implement a process to include reviews of investigational drugs as a part of the monthly departmental inspection reviews conducted by assigned Pharmacists. b) IDS should develop processes for periodic reviews of documentation, data records, and fee recharges for investigational drugs managed by investigators and IDS, as well as the frequency of these reviews.	a) By March 31, 2015, IDS will develop a comprehensive quality assurance program plan to include reviews of documentation, data records, and fee recharges for investigational drugs managed by investigators and IDS, as well as the frequency of these reviews. b) By June 30, 2015, IDS will operationalize its quality assurance program.

No.	Observations	Risks/Effect	Recommendations	MCA
	Pharmaceutical Service personnel and that IDS will perform periodic evaluation on a yearly basis. Additionally, IDS internal operational procedures require quarterly data review of pharmacy records for the Phase I studies managed by IDS for data quality measures.			
7	***IRB approval is not validated prior to dispensing of investigational drugs.*** IDS's current process does not include validation of study approval by IRB prior to dispensing investigational drugs. Investigators are not required to submit a copy of the IRB approval to IDS. In addition, IRB number and approval/expiration dates are not entered in Vestigo, the system used by IDS to track and manage investigational drugs. Therefore the control functionality in Vestigo to prevent IDS from dispensing investigational drugs without an IRB approval is not utilized. Medical Center policy requires investigators to submit a copy of the protocol and a copy of the approval notification to IDS.	Dispensing investigational drugs to participants for studies that may not be approved by the IRB creates risks to study subjects.	IDS should implement a process to ensure that an IRB approved study protocol is submitted by investigators prior to any dispensing of drugs. The IRB approval document should be retained and the IRB number and approval/expiration dates should be documented in Vestigo.	IDS has implemented a process to document the IRB number and approval/expiration dates in Vestigo. By June 30, 2015, IDS will implement a process to ensure that an IRB approved study protocol is submitted by investigators prior to any dispensing of drugs. The IRB approval document will be retained.
8	***IDS recharge fees do not cover total costs for providing the service.*** Review of the IDS recharge fees and billing process identified that the recharge fees do not cover the IDS total costs for managing and handling investigational drugs. In fiscal year 2014, IDS recharges covered less than 50% of IDS personnel expenses (salaries and benefits). The under-recovery of cost is	By not recovering the full cost of the IDS service, Medical Center is bearing costs that should be borne by the sponsors, which is contrary to University Policy and can jeopardize	Pharmaceutical Services should review and assess its fee structure to assure that costs are fully recovered. Any decision to subsidize the costs to research studies should be approved by Medical Center Senior Leadership.	By June 30, 2015, Pharmaceutical Services will discuss with Medical Center Senior Leadership and Office of Research about additional funding to support research studies, especially for non-sponsored studies that Pharmaceutical Services has been subsidizing.

No.	Observations	Risks/Effect	Recommendations	MCA
	funded by Pharmaceutical Services operations contrary to University policy requiring all costs for extramurally funded projects to be recovered from the sponsor(s). Campus Administrative Policy 400-10 "Academic, Legal and Financial Policies of Contracts and Grants" stipulates that "It is the policy of The Regents that extramurally funded projects are conducted at no cost to the University. All direct and indirect costs for extramurally funded projects must be recovered from the sponsor(s)".	the long-term financial viability of IDS services.		
9	***Physical security of the room where investigational drugs are stored is not sufficient.*** Some investigational drugs are stored in locked refrigerators in a room shared by Pharmacy, Material Services, and Hospitality Services. Investigational drugs are visible through the glass doors of the refrigerators. While there is a keypad entry system installed for the room, the PIN code has not been changed for several years. Additionally, we found the PIN code being written down on the wall by the keypad entry during the audit inspection of physical security.	Lack of sufficient physical security to the storage area increases risks of theft and/or loss of investigational drugs.	There are plans to remodel the storage room and its surrounding areas and security features will be incorporated in the remodeling. However, resources for this will not be available until fiscal year 2017. As an interim plan, Pharmacy has changed the current PIN code. In addition, Pharmacy should implement procedures to change the PIN code when employees with access to the room separate from the University.	There are plans to remodel the storage room and its surrounding areas and security features such as badge reader access will be incorporated in the remodeling. However, resources for this will not be available until fiscal year 2017. As an interim plan, Pharmacy has changed the current PIN code and will ensure it is changed when employees with access to the room separate from the University.
10	***Labels for investigational drugs generated in APeX do not meet FDA requirements.*** Labels are generated from APeX for investigational drugs managed by IDS and administered for all inpatients and limited	Insufficient caution statement on medication labels may not provide the necessary information to	APeX IT should modify the label template for investigational drugs to include the required caution statement.	At the completion of the audit test work and upon notification to APeX IT team, a change was made to include the required caution statement on the labels. No

No.	Observations	Risks/Effect	Recommendations	MCA
	outpatient clinics. Our review identified that labels generated from APeX state "For Investigational Use Only" and do not have the complete caution statement as required by FDA. FDA requires that the immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug--Limited by Federal (or United States) law to investigational use."[5]	protect study participants.		further action is required.

C. General Observation

No.	Observations	Risks/Effect	Recommendations	
11	***UCSF IDS Pharmacists do not review the IRB protocols for investigational studies.*** HRPP recognizes the benefits and importance of having IDS Pharmacists in the IRB protocol review and currently the IDS Pharmacist at SFGH participates in the review of investigational drug studies reviewed by the SFGH IRB Committee. However, due to limited available resources, the UCSF IDS Pharmacists are not able to participate in the IRB protocol reviews of investigational drug studies conducted at UCSF sites. IDS Pharmacist participation in the initial protocol review is important for ensuring that	The absence of IDS Pharmacist review of the protocol increases the risks that investigators may not possess sufficient understanding on the management of investigational drugs. Additionally, research subjects may not be given complete and accurate information on the drug.	Pharmaceutical Services, in conjunction with Clinical Pharmacy should consider adding resources or re-assessing workloads so that IDS Pharmacists can participate on a rotational basis in IRB protocol reviews.	By June 30, 2015, Pharmaceutical Services and HRPP will evaluate and identify the extent of IDS participation on IRB Committees based on the risks in research to make effective use of IDS limited resources.

[5] 21 Code of Federal Regulations (CFR) 312.6(a).

	complete information for the medication is included in the protocol; risks from the medications are accurately described; and guidelines for reporting adverse medication reactions are outlined. The IDS Pharmacist's review is especially important with in-house or investigator-initiated clinical trials, as investigators may be unaware of the complexity of the drug interactions and federal regulatory requirements.			

APPENDIX A – Procedures Performed

To conduct our review the following procedures were performed for the areas in scope:

- Reviewed relevant University policies and regulatory requirements for control of investigational drugs;
- Interviewed IDS personnel to gain an understanding of IDS processes for procurement, receiving, storage,
- accountability, preparation, and dispensing of investigational drugs;
- Selected a sample of six studies that had investigational drugs managed by IDS and tested for the following controls:
  - Documentation supporting receipt of drugs
  - Temperature monitoring
  - Physical security of the drugs storage areas
  - Drugs inventory controls
  - Record keeping and accountability of drugs dispensed
  - Complete and accurate recharges for IDs services
- Reviewed a sample of five studies with investigational drugs directly managed by investigators to verify that investigational drugs are properly managed; and
- Reviewed documentation on how the fees for handling and management of investigational drugs are determined to ensure all costs are included.