

**UNIVERSITY OF CALIFORNIA, SAN FRANCISCO  
AUDIT & ADVISORY SERVICES**

**Investigational Drugs Review  
Project #23-012**

**November 2022**



University of California  
San Francisco

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**DESI KOTIS**  
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**SUBJECT: Investigational Drugs Review**

As a planned internal audit for Fiscal Year 2023, Audit & Advisory Services (“A&AS”) conducted a review of the management of investigational drugs used in clinical studies. The purpose of this review was to validate that processes and controls over the management of investigational drugs used in clinical studies are operating effectively.

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 review was completed and the preliminary draft report was provided to department management in September 2022. Management provided their final comments and responses to our observations in November 2022. 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. A&AS 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 Committee, and is not intended to be and should not be used by any other person or entity.

Sincerely,

Irene McGlynn  
Chief Audit Officer  
UCSF Audit and Advisory Services



## EXECUTIVE SUMMARY

### I. BACKGROUND

As a planned audit for Fiscal Year 2023, Audit & Advisory Services (A&AS) conducted a review of processes and controls over the management 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) § 312.21.

Studies involving investigational drugs are critical to achieving UCSF's mission and vision of advancing healthcare through research and discovery. At UCSF, researchers must receive approval from the Committee on Human Research (CHR), which is UCSF's Institutional Review Board (IRB), before conducting research involving human subjects. In conjunction to this, the UCSF Human Research Protection Program (HRPP) reviews and monitors research involving human subjects at UCSF and several affiliate institutions to ensure the ethical and equitable treatment of the research participants. 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.

Another integral component of managing investigational drug is UCSF Investigational Drugs Services (IDS) Pharmacy; it is integrated into the Department of Pharmaceutical Services at UCSF Medical Center. IDS services three main medical center campuses: Mount Zion, Parnassus Heights and Mission Bay (Benioff Children's Hospital, Precision Cancer Medicine Building, and in the future Weill Institute for Neurosciences). IDS pharmacy manages and dispenses all investigational drugs for trials conducted within UCSF Health Medical Center and clinics and when investigational drug management has been delegated to IDS pharmacy by the study investigator. When the IDS pharmacy manages the drugs for a particular study, all necessary drug control and record keeping functions are conducted for the investigator. More specifically, IDS will adhere to record keeping requirements, maintain investigational drug inventory, track dispensed doses, maintain temperature control of investigational medications, dispense and prepare oral, injectable, hazardous and non-hazardous investigational agents (including blinded doses), assist with clinical trial budget development for IDS pharmacy fees, develop chemotherapy drug order templates, participate in site qualification, initiation, close-out, other monitoring visits, and site committee meetings.

IDS is staffed by 25 FTEs and currently manages investigational drugs for about 814 studies. To manage the studies, IDS uses a web-based platform called Vestigo to manage investigational drug products that allows for the tracking of all details including

protocols, inventory and expiration dates, patient enrollment, generate prescription labels, and recharge for services rendered. In fiscal year 2022, IDS generated approximately \$2.59 Million in revenue from recharge for managing investigational drugs.

Alternatively, investigators may choose to directly manage investigational drugs for their studies. In order for investigators to directly manage their investigational drugs, a waiver must be obtained from IDS. During the review period of February 2022 to June 2022, there were only two waivers reported in iRIS.

## **II. AUDIT PURPOSE AND SCOPE**

The purpose of this review was to assess the controls over the management of investigational drugs. Procedures performed as part of the review include: (1) review policies, procedures, and regulatory requirements for control of investigational drugs; (2) interview key stakeholders in IDS to assess IDS processes for procurement, receiving, storage, accountability, preparation, and dispensing of investigational drugs; (3) evaluate processes and controls in place for fees associated with investigational drugs through approved study budgets and recharges; (4) review copies of signed informed consent forms in APeX<sup>1</sup>; (5) analyze notification of protocol amendment dates for proper lead time to prepare for dispensing; (6) examine recording and reconciliation between Vestigo and the General Ledger; (7) review waivers in the iRIS system; and (8) evaluate the tracking of external IRB amendment approval dates for adequacy.

The scope period included transactions and activities from February 1, 2022 to June 30, 2022. 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 September 2022.

## **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 and the IDS team is highly focused on improvement efforts. In November 2019, IDS had a third-party consultant, Visante conduct a review of its processes. From that review, there were eighteen recommendations that IDS continue to implement. As of July 2022, IDS completed three recommendations and is on track to complete 80% of the remaining recommendations that are centered around strengthening communication and information technology, financial strength, employee and training, patient experience, quality and safety, and strategic growth.

The specific observations from this review are listed below:

1. There is no current practice of Pharmacy oversight and monthly inspection of studies where investigators have been given permission to manage the storage and dispensing of investigational drugs in their own clinical trials. Additionally, there is not a mechanism to verify the completeness of studies being captured in the waiver program due to data limitations.

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<sup>1</sup> APeX is the Electronic Health Record (EHR) used by UCSF Health.

2. The investigational drugs policy contains inconsistencies and does not reflect current practices.
3. There is no regular reconciliation between Vestigo and the General Ledger to ensure that recharges are appropriate and IDS billing issues are timely resolved.
4. A copy of a signed patient consent form specific to the current research study protocol in question could not always be found in the patient's medical record, resulting in difficulty in locating records and incomplete medical record documentation.
5. IDS is not always notified of external IRB amendment approvals to evaluate the need to make changes to the dispensing protocols.
6. IDS is not always given sufficient time by the study team to get trained on protocol amendments.
7. Not all approved study budgets could be located and there were instances of IDS not charging based on the approved study budgets.

**IV. OBSERVATIONS AND MANAGEMENT CORRECTIVE ACTIONS (MCAs)**

No.	Observation	Risk/Effect	Recommendation	MCA
1	<p><b><i>There is no current practice of Pharmacy oversight and monthly inspection of studies where investigators have been given permission to manage the storage and dispensing of investigational drugs in their own clinical trials. Additionally, there is not a mechanism to verify the completeness of studies being captured in the waiver program due to data limitations.</i></b></p> <p>Per Policy 6.07.05 Medication Management: Investigational New Drugs, Investigators given permission to manage the storage and dispensing of investigational drugs in their own trials will be subject to oversight and monthly inspection by Department of Pharmaceutical Services personnel. This practice is currently not performed by IDS.</p> <p>While there were only two waivers for the managing of investigational drugs that were provided during the scope period, the full population is not currently known due to data limitations in reporting/reconciliation between iRIS and Vestigo to determine the completeness of the waiver population. Discussions with Office of Research noted the perspective that the risk of lacking this reconciliation may be low due to the oversight provided by sponsors of trials, and that the effort required to identify if studies fall outside of the populations managed by IDS or having obtained waivers would be significant and may not generate a complete accounting.</p>	<p>Without monthly inspections, IDS cannot ensure investigators are complying with the standard operating procedures for storage and dispensing of investigational drugs.</p>	<p>IDS should have oversight and perform regular inspections of studies where investigators have been given permission to manage the storage and dispensing of investigational drugs in their own trials.</p>	<p><b>Action:</b> IDS will implement a process to allow Principal Investigators to self-audit against the Waiver requirements.</p> <p><b>Responsible Party:</b> IDS Manager</p> <p><b>Target Date:</b> 1/31/2023</p>
2	<p><b><i>The investigational drugs policy contains inconsistencies and does not reflect current practices.</i></b></p> <p>The policy language around the frequency of monitoring of studies where investigators are managing the storage and dispensing of the investigational drugs is inconsistent in the Policy 6.07.05 Medication Management: Investigational New Drugs; different sections of this</p>	<p>Without a clear and thorough policy setting expectations, the IDS cannot ensure its</p>	<p>A) IDS should clarify its frequency of oversight and monitoring and update its policy</p>	<p><b>Action:</b> A) IDS will update its Medication Management Policy to indicate that the monitoring will</p>

No.	Observation	Risk/Effect	Recommendation	MCA
	<p>policy require IDS to perform monitoring at varying timeframes, including:</p> <ul style="list-style-type: none"> <li>• monthly inspections</li> <li>• periodic quality assurance</li> <li>• yearly evaluation</li> </ul> <p>Also, per the policy, in cases when the same protocol requires investigational drug dispensing at two or more UCSF Medical Center locations, the Investigational Drug Pharmacist at each location shall develop protocol-specific procedures as described. The practice of developing location specific protocol when dispensing at two or more UCSF Medical Center locations is discouraged by IDS and not currently being performed due to safety risks of enrolling patients into two separate protocols.</p>	<p>objectives are being met.</p>	<p>and website accordingly.</p> <p>B) IDS should update its policy to reflect current practice where safety is an issue.</p>	<p>occur on a quarterly basis. B) IDS will update its Medication Management Policy to reflect current practice where safety is an issue.</p> <p><b>Responsible Party:</b> IDS Manager</p> <p><b>Target Date:</b> 4/28/2023</p>
<p>3</p>	<p><b><i>There is no regular reconciliation between Vestigo and the General Ledger to ensure that recharges are appropriate and IDS billing issues are timely resolved.</i></b></p> <p>During the review, it was noted that Finance performs the recording of IDS charges from Vestigo to the GL; however, the function of reconciling from Vestigo to the GL for accuracy and completeness is not being performed. As a result, charges where awards have expired went into a suspense account and accumulated at fiscal year-end, causing inefficiency to clear, and IDS to not recover its cost timely.</p>	<p>Without a reconciliation between Vestigo and the GL, the IDS cannot ensure charges are accurate and complete for its financial.</p>	<p>IDS should assess what personnel needs required to perform the reconciliation between Vestigo and the GL.</p>	<p><b>Action:</b> IDS has hired a billing analyst and will train the analyst on the reconciliation between Vestigo and the GL.</p> <p><b>Responsible Party:</b> IDS Manager</p> <p><b>Target Date:</b> 1/31/2023</p>

No.	Observation	Risk/Effect	Recommendation	MCA
4	<p><b><i>A copy of a signed patient consent form specific to the current research study protocol in question could not always be found in the patient’s medical record, resulting in difficulty in locating records and incomplete medical record documentation.</i></b></p> <p>In a sample of 20, it was noted that 20% of the consent forms could not be located in the patient’s medical record in APeX which does not comply with Policy 6.07.05 which states that a copy of the signed informed consent form for the protocol in question must be in the patient’s medical record as a requirement for order processing. Of the four that could not be located, one was from a 2021 study, whereas the other three came from studies in prior years ranging from 2012-2019.</p> <p>While the informed consent form is required to be scanned into APeX, the lead pharmacist relies on the confirmation in OnCore by the Clinical Research Coordinator (who updates in OnCore with a “yes” or a “no” to indicate whether a signed consent form was obtained) to begin dispensing. If the confirmation is not present, the pharmacist should not dispense and should contact the Clinical Research Coordinator to ensure a signed consent form is obtained, which may cause a delay. Note, if the copy of the signed consent form is not scanned into APeX, it may reside with the study team.</p> <p>This issue was also noted in a 2021 review<sup>2</sup>, and management initiated a campaign to educate and raise awareness for the research community of the need to scan informed consent forms in APeX, including holding townhall meetings for education and awareness and creating guides and tip sheets (such as an APeX Job Aid and Study Start Up Checklist) to clarify how to upload informed consent forms into the patient’s chart in APeX to educate Clinical Research Coordinators (CRC).</p>	<p>Without a copy of a signed informed consent form in the medical record, the IDS cannot ensure patients were aware of their rights, and the study risks. Patient safety risk can occur if dispensing occurs before obtaining consent.</p>	<p>The Office of Research should work with the APeX Research team to implement a report to ensure participants enrolled in investigational studies have a signed informed consent form in APeX.</p>	<p><b>Action:</b> APeX does not currently have functionality that would allow for reporting on the scanning of informed consent forms for clinical research studies; however, the Office of Research will continue the discussion at the upcoming EPIC Research Refuel to consider incorporating controls over the patient informed consent for participants enrolled in investigational studies and determine priority and appropriate inclusion of key stakeholders.</p>

<sup>2</sup> In fiscal year 21, A&AS conducted a review of Clinical Research Billing (Project 21-045) and the scope of this audit included the review of informed consent documentation.



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				<p><b>Responsible Party:</b> Program Manager, CTO</p> <p><b>Target Date:</b> 1/31/2023</p>
<p><b>5</b></p>	<p><b><i>IDS is not always notified of external IRB amendment approvals to evaluate the need to make changes to the dispensing protocols.</i></b></p> <p>The study team is not required to update the HRPP of external IRB amendment approvals. Therefore, no record of external IRB amendment approval is collected in iRIS or conveyed to IDS. Without a consistently followed process, IDS does not always know when there is an external IRB amendment approval and if there is a need to start dispensing based on the updated protocols.</p>	<p>Without an updated IRB protocol amendment, IDS may not be dispensing based on the approved protocol version creating patient safety risks and regulatory non-compliance.</p>	<p>HRPP will work with its external IRBs to add IDS as a recipient of all protocol amendments. In the future, HRPP will explore the feasibility of capturing external IRB amendments in iRIS.</p>	<p><b>Action:</b> IDS has sent a list of emails for all the sites to HRPP to ensure it can receive the external IRB amendment approval notifications.</p> <p><b>Responsible Party:</b> IDS Manager</p> <p><b>Target Date:</b> 11/30/2022</p>
<p><b>6</b></p>	<p><b><i>IDS is not always given sufficient time by the study team to get trained on protocol amendments.</i></b></p> <p>Six out of thirty internal IRB amendments (20%) reviewed provided less than two weeks' notice to IDS for preparing and getting trained to dispense on the updated protocol. Ideally, the entire workflow requires a four-week lead time to take necessary steps and make appropriate preparations.</p>	<p>Without adequate lead time, IDS may release a wrong order, or there may be a delay in dispensing</p>	<p>IDS should work with Office of Research to develop a process to obtain the amendment submission date to the IRB from the</p>	<p><b>Action:</b> IDS will work with Office of Research to implement a plan to ensure amendments are given to lead</p>

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	<p>Upon notification of an amendment, IDS submits a ticket, and it usually takes two weeks for Willow Informatics to build a drug to be added to the electronic medical record (APeX), so this can become an electronic orderable file. Additionally, the lead pharmacist needs to be trained on the updated protocol in order to comply to IDS-Standard Operating Procedure (SOP) 01: Investigational Drug Training and Documentation. Per IDS-SOP 01, Ongoing Lead Pharmacist training will be completed with new amendments or updates throughout the study conduct, as provided by the Primary Investigator, study coordinator, or Sponsor.</p>	<p>based on the amendment. Also, the lead pharmacist does not have enough time to update and train on the amendment changes.</p>	<p>study team to allow for review of those protocols ahead of time to prepare for training and monitor the approval dates to prepare to dispense.</p>	<p>pharmacists in a timely manner.  <b>Responsible Party:</b> IDS Manager  <b>Target Date:</b> 4/28/2023</p>
7	<p><b><i>Not all approved study budgets could be located and there were instances of IDS not charging based on the approved study budgets.</i></b></p> <p>During testing, it was noted that three out of twenty (15%) of approved study budgets could not be located. Therefore, the accuracy of the billing could not be substantiated. Additionally, there were two instances where the pharmacist charged based on the proposed budget and not the approved budget, leading to one instance of undercharging by \$1,180, and one instance of overcharging by \$1,700.</p>	<p>Without adequate record keeping, IDS cannot ensure it is billing accurately. Also, by using the proposed budget and not the final budget, the IDS is not working from the negotiated and approved budget.</p>	<p>IDS should have a consistent method of storing all approved IDS budgets and train its pharmacist to only bill based on the approved budgets.</p>	<p><b>Action:</b> IDS will work with Office of Sponsor Research to ensure approved budget is available and will store the budget in an IDS repository.  <b>Responsible Party:</b> IDS Manager  <b>Target Date:</b> 12/30/2022</p>