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0052

Subject: ***Investigational Drug and Research Medication Inventory Management***
AMAS Audit Project 2011-37

Audit & Management Advisory Services (AMAS) has completed a review of research unit investigational drug and research medication inventory management as part of the approved audit plan for Fiscal Year 2010-2011. This report summarizes the results of our review.

Background

Investigational drugs and research medications may be administered to study participants, in accordance with applicable Food and Drug Administration (FDA) and Office of Human Research Protections (OHRP) regulations. At UCSD, all studies that involve the administration of investigational drugs or research medications must be reviewed and approved by the UCSD Institutional Review Board (IRB). The IRB Administrator of Record also serves as the Director of the UCSD Human Research Protections Program (HRPP), which has oversight responsibility for all human subject research projects conducted by, or under the supervision of, UCSD physicians, faculty, or staff. The HRPP has established guidelines for obtaining human subjects informed consent, adverse event reporting, and other related topics in accordance with current federal regulations.

Specific review criteria apply to clinical research involving non-approved ("off-label") uses of FDA approved drugs, or single use of an investigational drug in an emergency setting. When an investigational drug is used in clinical research, or a marketed product is used in the context of a clinical research protocol (research medication), an approved Investigational New Drug (IND) application must be on file with the FDA, unless certain exclusion conditions are met[1].

It is critical that investigational drug inventory be appropriately secured, and drugs received and dispensed be documented to increase accountability for the accuracy of research results. The UCSD Investigational Drug Service (IDS) assumes responsibility for maintaining and dispensing investigational drugs for inpatient studies in accordance with UCSD Medical Center Policy (MCP) 341.1, *Investigational Drugs, Devices and Procedures*. For outpatient studies, the Principal Investigator (PI) may choose to maintain control of the investigational drug at the

[1] Examples of exclusion conditions include:

- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug; and
- If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

Other circumstances which need to be met for an investigation to be exempt from the requirement for an IND application are described in 21 Code of Federal Regulations (CFR) 312.2(b)

research site, or utilize the IDS. If the PI chooses to manage the drug or medication inventory, applicable state and federal regulations as well as related University policies must be observed.

Audit Objective, Scope and Procedures

The objectives of this review were to (1) evaluate the efficacy of controls over investigational drug and research medication inventories maintained outside of the IDS by PIs or their designee(s); and (2) determine whether changes to the current IDS model would result in greater number of drug studies utilizing the service. We performed the following audit procedures to achieve project objectives:

- Reviewed the Food and Drug Administration (FDA) website to obtain current information pertaining to investigational and humanitarian use drugs;
- Reviewed current HRPP Standard Operating Policies and Procedures, and Research Compliance Office (RCP) guidance on PI controlled investigational drug and research medication inventories;
- Discussed UCSD IDS inventory management processes with the IDS Director;
- Obtained information about the UCSD Antiviral Research Center (AVRC) Pharmacy, and the RCHSD IDS to verify the adequacy of drug inventory controls in those environments;
- Obtained a listing of all IRB approved studies involving investigational drugs for the period April 1, 2010 to April 1, 2011, and selected a judgmental sample of eight studies for focused review;
- Reviewed the study research plan, approval letter, and consent forms available from the e-IRB system for each of the studies in the sample; and,
- Conducted research unit site visits for the eight studies in the audit sample, and documented the results of the inventory management assessment using a standard audit template.

When selecting studies to be included in the audit sample, we exempted certain projects from further evaluation if (1) the study did not have any subjects enrolled as of the date that audit fieldwork, and (2) the study did not maintain an investigational drug or research medication inventory. In addition, studies that utilized the services of the UCSD IDS, the AVRC Pharmacy, Rady Children's Hospital, San Diego (RCHSD) IDS, or the Veteran's Administration San Diego Health System (VASDHS) Pharmacy were excluded from the sample of studies selected for focused review, based on the strong inventory management controls present in those entities.

IRB Project #101577 was specifically excluded from the scope of this review because it was evaluated during AMAS Project #2010-109.

Sample Set Selection

The UCSD IRB approved 135 investigational drugs studies during the period April 1, 2010 to April 1, 2011. Ninety four (70%) of the 135 studies were managed by an IDS and were therefore

excluded from our review. The table below identifies which IDS or other licensed research unit Pharmacy was managing investigational drug inventories.

Total Number of Active Studies	*Inventory Managed by the UCSD IDS*	*Inventory Managed by the RCHSD IDS*	*Inventory Managed by AVRC Pharmacy*	*Inventory Managed by VASDHS Pharmacy*	*Studies Available for Selection*
135	53	21	11	9	41

From the remaining 41 studies, AMAS judgmentally selected a sample of eight (20%) studies for review, with preference given to PI initiated studies selected for individual PIs in various medical specialties. The tables below classify the studies in the sample by funding source. Funding information was obtained from the Study Bio Sheets or Face Pages submitted to the IRB.

	Commercially Sponsored	**Federally Funded**	**Internally Funded**	**Total**
Studies Available for Selection	34	2	5	**41**
Number of PIs	14	2	5	**21**
Selected for Testing	6	-	2	**8**

IRB #	**Department**	**Funding**
101880	Medicine	Unfunded
100938	Pediatrics	Internal funding
100942	Pediatrics	Commercially sponsored
101020	Medicine	Commercially sponsored
101040	Medicine	Commercially sponsored
101441	Anesthesiology	Commercially sponsored
101069	Psychiatry	Commercially sponsored
101450	Psychiatry	Commercially sponsored

Conclusion

Based on our review procedures, we concluded that investigational drug inventory controls were generally adequate to help to ensure compliance with FDA regulatory requirements and University policy. PIs that chose to maintain study drug inventories on site, rather than utilize an IDS, typically made that decision based on cost considerations and/or operational issues. Six of the eight studies reviewed were commercially sponsored, and were subject to periodic review by an external study monitor. Drug accountability records were verified at scheduled monitor visits, which provided greater assurance that drug inventories maintained by the PI and or Study Coordinators met regulatory and policy requirements.

We noted that the two studies did not include an appropriate label on the drug or medication being tested, two studies had not maintained appropriate inventory records, and one study had not submitted FDA required reports within the required timeframe.

Opportunities for improvement are discussed in the remainder of this report.

Observations, Management Corrective Action, and Recommendations

A. Investigational Drug Labeling Requirements

Investigational drug containers labeling details needed improvement.

FDA Code of Federal Regulation, *Section 312.6, Labeling of investigational new drug,* states 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." Site visits for two studies (IRB# 100938 and #101040) revealed that a drug kit and a bottle label did not reference the investigational use of the drug. Although IRB #100938 related to an "off-label" use of a marketed drug, identifying the investigational use on drug containers would ensure study subjects are better informed on drug usage and risks.

In addition, AMAS was unable to verify whether drugs were labeled appropriately as there was no inventory on site for one additional study (IRB #101880). The Study Coordinator was unable to confirm whether the label on the drug had included an investigational use statement.

Management Corrective Action:

HRPP management will issue a letter to IRB Projects #100938 and #101040 to alert the PIs that drug labels must be modified to reference the investigational use of the drug.

B. Drug Receipt and Dispensing Documentation

Drug accountability records were inadequate to support drug inventory levels for two studies.

Although both studies maintained drug inventory logs, AMAS was unable to verify the number of doses/bottles received at the study site for two studies (IRB #100938 and #101880) due to the absence of supporting documentation.

In addition, AMAS was advised by the Study Coordinator for IRB #101880 that there were no drugs on site because all drugs had been dispensed to the study subject. However, because the drug dosage was not included on the drug inventory log, AMAS was not able to compare the inventory log to the research file to verify that all drugs received were dispensed. Consistent documentation showing drugs received and dosages dispensed would allow an external reviewer to verify that investigational drugs or research medications were appropriately distributed.

Management Corrective Actions:

1. HRPP management will issue a letter to IRB Projects #100938 and #101880 to alert the PIs that adequate documentation for the investigational drugs or research medication inventories must be maintained.

2. HRPP management will coordinate with the RCP Director to include a recurring article on investigation drug and research medication inventory documentation in the RCP bi-monthly newsletter.

C. FDA Reporting Requirements

We noted that FDA reporting requirements were not met for one study.

IRB #101880 was a PI initiated study with one enrolled subject. The subject opted to discontinue using the drug in March 2011, and the study has been closed.

FDA 21 *CFR 312.33, Annual Reports* requires that the sponsor submit annual progress reports within 60 days from the date the IND went into effect. During AMAS' site visit, we observed that the Investigational New Drug (IND) Application for the drug went into effect in December 2010. However, a progress report had not been submitted to the FDA as required by regulations.

The IRB was informed of the study closure in May 2011. However, during audit fieldwork, the required final report to the FDA that includes the treatment results had not been submitted by the research unit.

Management Corrective Action:

The PI was preparing the required documentation and the required report to the FDA.

Audit & Management Advisory Services appreciates the cooperation and assistance provided during the review. Because we were able to reach agreement regarding corrective actions to be taken in response to the audit recommendations, a formal response to the report is not requested.

The findings included in this report will be added to our follow-up system. We will contact you at the appropriate time to evaluate the status of the corrective actions. At that time, we may need to perform additional audit procedures to validate that actions have been taken prior to closing the audit findings.

UC wide policy requires that all draft audit reports, both printed and electronic, be destroyed after the final report is issued. Because draft reports can contain sensitive information, please either return these documents to AMAS personnel, or destroy them, at the conclusion of the audit exit conference. AMAS also requests that draft reports not be photocopied or otherwise redistributed.

Please contact me at (858) 534-3913 or by email at shburke@ucsd.edu if you have any questions about the issues discussed in this report.

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