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***Subject: Clinical Research Compliance – IND Program and Protocol Registration System
Project 2014-18***

The final audit report for the above referenced audit is attached. We would like to thank all members of the department for their cooperation and assistance during the audit.

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 (copied on tan paper for ease of identification) 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 this time. We also request that draft reports not be photocopied or otherwise redistributed.

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Attachment

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UC San Diego

AUDIT & MANAGEMENT ADVISORY SERVICES

Clinical Research Compliance – IND Program and Protocol Registration System March 2015

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Project Number: 2014-18

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Attachment 1: Summary of Audit Findings

***Clinical Research Compliance - IND Program and Protocol Registration System
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I. Background

Audit & Management Advisory Services (AMAS) has completed a review of *Clinical Research Compliance - IND Program, and Protocol Registration System* compliance as part of the approved audit plan for Fiscal Year (FY) 2014-15. This report summarizes the results of our review.

Investigational New Drug (IND) Program

The United States Food and Drug Administration's (FDA) role in the development of a new drug begins when a drug sponsor wants to test its diagnostic or therapeutic potential in humans. At that point, the drug becomes subject to the Federal Food, Drug, and Cosmetic (FDC) Act in Section 21, Part 312 of the Code of Federal Regulations (CFR). The FDA evaluates Investigational New Drug (IND) applications for safety, and to ensure that research participants are not subjected to unreasonable risk. An IND may also serve as an exemption to current federal law precluding transportation of a drug that is not subject to an approved marketing application before it is transported or distributed across state lines.

When determining responsibility for complying with IND requirements, it is important to know the roles that may be assumed by the institution and/or the Principal Investigator (PI). The following role definitions are associated with an IND:

- An IND sponsor is a person or agency that initiates the clinical investigation.
- An IND holder is the person or entity who initiates the clinical investigation and, therefore, assumes responsibilities equal to the IND sponsor.
- An IND sponsor-investigator is an individual who initiates and conducts a clinical investigation, and cannot be a corporation or agency.

Protocol Registration System

Clinical trials that meet the criteria for being an "applicable drug clinical trial" as defined in Food and Drug Administration Amendments Act (FDAAA 801) are required to register, provide periodic status updates, and enter study results at www.ClinicalTrials.gov. This requirement was enacted on September 27, 2007 and establishes penalties for failure to comply with registration or results submission requirements. Penalties include civil monetary penalties of up to \$10,000; and for federally funded studies, the withholding of grant funds. Registration is also required for journal publication and some other laws and policies.

Registration of clinical trials is intended to:

- Fulfill ethical obligations to study participants and the community;
- Provide information to potential study participants and referring clinicians;
- Reduce publication bias;
- Help editors and others understand the context of study results;
- Promote more efficient allocation of research funds; and

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- Help Institutional Review Boards (IRBs) determine appropriateness of a research study.

Reporting of clinical trial results is intended to:

- Provide a public record of basic study results in a standardized format;
- Promote the fulfillment of ethical responsibility to participants;
- Use of research results to contribute to medical knowledge;
- Mitigate “publication” and “outcome reporting” biases; and
- Facilitate systematic reviews and other analyses of the research literature.

The University of California (UC) San Diego Human Research Protections Program (HRPP) assists researchers in complying with federal, state, and University policies regarding experimentation involving human subjects, and supports six federally registered IRBs. IRB oversight is required for INDs.

The Health Sciences Research Compliance Program (RCP) assists Health Sciences investigators and research support staff maintain institutional compliance by providing staff training, and monitoring clinical studies. The RCP general research helpline is a valuable resource for research coordinators to obtain answers to questions about Good Clinical Practice (GCP) and regulatory compliance topics. In addition, RCP maintains an Intranet site that provides a number of University or external agency references that are relevant to the conduct of clinical trials at UC San Diego.

II. Audit Objective, Scope, and Procedures

The objective of our review was to determine whether PIs were complying with the requirements of the Investigational New Drug (IND) Program, and the Protocol Registration System via www.ClinicalTrials.gov. The project scope focused on active IND applications in which UC San Diego or the PI was the sponsor-investigator/sponsor of the IND based on information available in the HRPP database.

We completed the following audit procedures to achieve the project objective:

- Reviewed applicable federal regulations and guidance for the IND Program and the Protocol Registration System; and
- Selected a sample of nine PI initiated studies associated with a PI held IND for focused review and completed the following additional procedures for each study in the sample:
 - Interviewed HRPP, selected PIs and study coordinators;
 - Evaluated the IND application, Form FDA 1572: *Investigator Statements*, financial interest disclosures, information on investigator qualifications, study drug accountability documents, annual reports and other communications with the FDA, UCSD IRB documents, agreements associated with selected clinical trials and UC delegations of authority; and

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- Analyzed supporting documents, www.ClinicalTrials.gov information, and IRB database information to assess compliance with selected FDAAA 801 IND sponsor requirements and compliance with selected provisions of 21 CFR 312 (*Attachment I*).

Sample Selection Criteria

AMAS obtained a list of studies from the HRPP database for which the PI had an active IND. There were 49 active INDs associated with 32 PIs. AMAS selected nine PI initiated studies (18%) managed by eight PIs (25%) for focus review.

III. Conclusion

Based on our review procedures, we concluded that regulatory compliance for studies subject to ClinicalTrials.gov and PI held IND requirements needed improvement.

PIs complied with the requirement that approvals be obtained before initiating clinical trials, and the majority registered the clinical trial on www.ClinicalTrials.gov as required, or on a voluntary basis. However, we identified additional opportunities to improve the timeliness of reporting to and communicating with the FDA, and the maintenance of all required study documents.

These issues are discussed in more detail below.

IV. Observation and Management Corrective Actions

A. Non-compliance with Regulatory Requirements

1. Requirements for www.ClinicalTrials.gov under FDAAA 801

Required study registrations, updates, and results were not entered into www.ClinicalTrials.gov in some cases.

FDAAA 801 requires responsible parties of applicable clinical trials to register, provide annual updates, and report clinical trial results to the Director of the NIH. An applicable drug clinical trial is defined as meeting all of the following criteria:

- **Controlled Study:** A study designed to permit a comparison of a test intervention with a control to provide a quantitative assessment of the drug effect.
- **Clinical Investigation:** An experiment in which a drug is administered, dispensed, or used involving one or more human subject(s). An experiment is defined as any use of a drug except for the use of a marketed drug in the course of medical practice.
- **Other than a Phase I Clinical Investigation:** Phase I clinical investigations are excluded as they are designed to determine metabolism and pharmacologic

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actions of the drug in humans, the side effects associated with increasing the dose, and to gain early evidence on effectiveness.

- Drug subject to Section 505 of the FDC or Section 351 of the Public Health Service Act: A drug subject to an approved new drug application (NDA), a biologics license application (BLA) or a circumstance when an approved NDA or BLA would be required in order for that drug or biological product to be legally marketed.

Of the nine studies tested, we determined that all clinical trials were initiated after obtaining FDA IND and IRB approval. Only three of the nine studies were required to register based on the criteria. Of the seven studies (78%) that registered, five had registered voluntarily (55% of all studies), one (33%) registered within the required timeframe, and one (33%) registered late. One (33%) had not registered as required. In addition, the PIs of applicable clinical trials had not entered all required annual updates and/or reported results on the website. One life-threatening significant new drug related adverse effects had been reported, but not within the seven calendar days required. Detailed results are provided in the table below and in ***Attachment 1***.

2. IND Requirements under 21 CFR 312

Study documentation and communication to the FDA needed improvement for selected IND studies included in the test sample.

All IND applications we tested were submitted with either the PI or UC San Diego as the sponsor, and were executed by the PI. As such, the PI served as the sponsor or the sponsor's representative and obligated UC San Diego to meet IND sponsor requirements. Study documentation should be readily available to provide assurance that sponsor-investigator responsibilities and required notifications have been performed in a timely manner. For example, annual reports are required to be submitted to the FDA within 60 days of the IND anniversary date. Eight of the studies provided evidence of their annual reports. Two studies (25%) had completed all required annual reports; however, the remaining six studies (75%) had not met the annual reporting criteria (see ***Attachment 1***).

Some clinical trials are conducted utilizing discretionary funds only, and do not require the involvement of other UC San Diego contracting offices. UC San Diego contracting offices may participate in the negotiation of associated contracts or grants for other PI initiated INDs, but do not provide regulatory guidance or participate in IND sponsor monitoring responsibilities. In instances where a study is not periodically monitored by a commercial sponsor, a regulatory assessment may be conducted on a periodic basis by the RCP if selected for focused review. However, all studies are not periodically evaluated for compliance.

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Regulations governing IND clinical trials are designed to protect human subjects. IRB monitoring mitigates the risk of harm to subjects to a large degree. However, regulatory risk associated with sponsor responsibilities, the majority of which are designed to improve communication with the FDA, can be overlooked if the PI or study coordinator are not familiar with them. Non-compliance could potentially result in monetary penalties of \$10,000 and the withholding of federal grant funds if deficiencies are identified during an external review.

Several PIs and/or study coordinators we contacted indicated that additional resources and a point of contact would be useful to assist them with meeting IND related regulatory requirements.

Management Corrective Actions:

1. RCP management will:
 - a. Advise the PIs of non-compliant studies in the test sample to enter required registrations, updates, and results on www.ClinicalTrials.gov, and/or submit any required reports to the FDA.
 - b. Include articles about ClinicalTrials.gov and IND sponsor/investigator requirements in Research Compliance Newsletters periodically.
 - c. Include non-commercially sponsored IND clinical trials in the annual study monitoring plan to evaluate compliance with sponsor and PI regulatory requirements.
2. Clinical Translational Research Institute and RCP managements will consider providing a regulatory expert as a resource to provide guidance and clinical monitoring services for projects that must comply with such topics as sponsor-investigator requirements for INDs. This may be accomplished through use of a focused pre-study project manager or team, IND Service to PIs, or other means. In addition, CTRI will work toward requiring Good Clinical Practice (GCP) certification for all active personnel with direct research participant contact as a means to improve overall compliance with IND requirements.
3. HRPP management will:
 - a. Create a Fact Sheet for PI initiated clinical trials to be hosted at the HRPP website containing information on:

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- The process for IND application submissions;
 - The definition of an applicable clinical trial and the registration process; Sponsor IND requirements and guidance for registering, providing annual updates and/or verification of the record, and reporting results at www.ClinicalTrials.gov; and
 - Sponsor-Investigator IND documentation and notification requirements.
- b. If feasible, remind PIs conducting qualifying clinical trials of the requirement to register at www.ClinicalTrials.gov in IRB approval letters, and direct them to the Fact Sheet for PI initiated clinical trials and to other UCSD regulatory resources. Reminders regarding IND sponsor requirements will also be provided during continuing renewals. The department/person responsible for providing regulatory guidance will be copied on all approval and acknowledgement letters.

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Line	Requirement	Regulatory Reference	Results	Non-Compliant Sample Study Number	Results of Compliance Testing	Notes	Report Observation Reference
Requirements associated with ClinicalTrials.org registration and IND application							
1	Agreement associated with study drug was executed.	-	●	-	-		-
2	Clinical investigations began 30 days after FDA receipt of the IND.	21 CFR 312.40	●	-	-		-
3	Studies required to be registered at ClinicalTrials.gov were registered.	FDAAA 801(j)(2)(C)	◆	8	2 of 3 (67%)	Only 3 of 9 studies selected were required to be registered. Additional studies also registered voluntarily.	A.1
4	Studies required to be registered at ClinicalTrials.gov registered within 21 days of the first patient enrollment.	FDAAA 801(j)(2)(C)(ii)	■	5, 8	1 of 3 (33%)	One study did not register. One study registered in June 2012, but the first subject enrolled in October 2011.	A.1
5	Results were submitted to the ClinicalTrials.gov no later than 12 months after 1) estimated completion date or 2) the completion date.	FDAAA 801(j)(3)(E)(i)	■	8	0 of 1 (0%)	This requirement only applied to one of the three studies subject to clinicaltrials.gov disclosures. For that study, results were not submitted in accordance with the criteria.	A.1

- Requirements were met for all studies.
- ◆ Most studies met or substantially met this requirement.
- Most or all studies did not meet this requirement.

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Line	Requirement	Regulatory Reference	Results	Non-Compliant Sample Study Number	Results of Compliance Testing	Notes	Report Observation Reference
6	Studies meeting the ClinicalTrials.gov registration requirements met the annual update requirements at ClinicalTrials.gov, if applicable.	FDAAA 801(j)(5)(C)(i)(I)	■	5, 6, 8	0 of 3 (0%)	One study had not registered or provided updates. Two studies had provided some updates, but not annually or within 60 days of the IND effective date.	A.1
21 CFR 312 Requirements							
7	PI monitored the research activity of other participating sites.	21 CFR 312.50	●	-	4 of 4 (100%)		-
8	PI monitored the need to report an increased rate of occurrence of serious suspected adverse reactions.	21 CFR 312.32(c)(1)(iv)	●	-	9 of 9 (100%)		-
9	An investigator administered the drug only to subjects under his or her personal supervision or under the supervision of a sub-investigator responsible to the investigator.	21 CFR 312.61	●	-	8 of 8 (100%)	This requirement did not apply to one study, which was no longer recruiting subjects since being approved by the IRB.	-

- Requirements were met for all studies.
- ◆ Most studies met or substantially met this requirement.
- Most or all studies did not meet this requirement.

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Line	Requirement	Regulatory Reference	Results	Non-Compliant Sample Study Number	Results of Compliance Testing	Notes	Report Observation Reference
10	The Sponsor maintained adequate records for receipt, shipment, or other disposition of the investigational drug.	21 CFR 312.57, 312.59, and 312.62	◆	8, 9	6 of 8 (75%)	<ul style="list-style-type: none"> One study maintained these records, but the content of early study records was not entirely complete. The PI for one study stated that the Investigational Pharmacy was utilized and maintained the records. However, the Investigational Pharmacy stated that they were not involved in the study. One study was closed to accrual and not required to maintain drug management records. 	A.2
11	The PI reported significant protocol changes to the FDA.	21 CFR 312.30	◆	3	0 of 1 (0%)	For the one study to which this applies, the notification was not submitted timely.	A.2

- Requirements were met for all studies.
- ◆ Most studies met or substantially met this requirement.
- Most or all studies did not meet this requirement.




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Line	Requirement	Regulatory Reference	Results	Non-Compliant Sample Study Number	Results of Compliance Testing	Notes	Report Observation Reference
12	The PI monitored the need to report significant risks to subjects for other studies and animal or in vitro testing.	21 CFR 312.32(c)(1)(ii) and (iii)	◆	8	5 of 6 (83%) studies that responded.	<ul style="list-style-type: none"> • AMAS did not receive this information from two studies (#2, 7) in the sample. • One study did not enroll subjects. 	A.2
13	PI obtained a curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience.	21 CFR 312.53(c)(2)	◆	7	6 of 7 (86%) that responded.	<ul style="list-style-type: none"> • These documents were obtained by one study after we requested them during our review. • One study did not respond (#9). • One study was not tested for these criteria as it had been previously tested in another review. 	A.2

- Requirements were met for all studies.
- ◆ Most studies met or substantially met this requirement.
- Most or all studies did not meet this requirement.

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Line	Requirement	Regulatory Reference	Results	Non-Compliant Sample Study Number	Results of Compliance Testing	Notes	Report Observation Reference
14	Records of financial interest paid to clinical investigators by the sponsor of the covered study were maintained.	21 CFR 312.57	◆	1, 2, 3, 4, 6, 7, 8, 9	0 of 8 (0%) that responded.	AMAS did not receive this information for one study in the sample (#5). This item is recommended for INDs, but not required. Therefore, AMAS considered it to be an area for improvement, and not a deficiency.	A.2


-  Requirements were met for all studies.
-  Most studies met or substantially met this requirement.
-  Most or all studies did not meet this requirement.




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Line	Requirement	Regulatory Reference	Results	Non-Compliant Sample Study Number	Results of Compliance Testing	Notes	Report Observation Reference
15	The PI obtained signed investigator statements (Form 1572) from Co-PIs at other research sites.	21 CFR 312.53(c)(1)	■	5, 6	0 of 2 (0%) that responded.	<ul style="list-style-type: none"> • We did not receive this information for one study (#9). • Form 1572 was not obtained for one study. • A Form 1572 for one study was jointly completed and signed by the PI, which is precluded by FDA guidance. The separate forms required for other sites were obtained when the deficiency was brought to the PIs attention by AMAS. • One study had research conducted in alternative sites that were in close proximity to the primary sites, allowing the PI to 	A.2

- Requirements were met for all studies.
- ◆ Most studies met or substantially met this requirement.
- Most or all studies did not meet this requirement.

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Line	Requirement	Regulatory Reference	Results	Non-Compliant Sample Study Number	Results of Compliance Testing	Notes	Report Observation Reference
						<p>assume responsibility for all sites. Form 1572 guidance states that the FDA expects an investigator who has signed a 1572 to be available at each location to either personally conduct or supervise the study, and that responsibility cannot be delegated to a sub-investigator.</p> <ul style="list-style-type: none"> One study with other sites not in proximity to UCSD did not respond. 	
16	The PI notified the FDA in a timely manner of any significant new adverse effects or risk occurred.	21 CFR 312.32		3	0 of 1 (0%)	Notification was submitted, but not in accordance with time requirements.	A.2

-  Requirements were met for all studies.
-  Most studies met or substantially met this requirement.
-  Most or all studies did not meet this requirement.

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Line	Requirement	Regulatory Reference	Results	Non-Compliant Sample Study Number	Results of Compliance Testing	Notes	Report Observation Reference
17	The PI reported follow up information for an IND safety report to the FDA as soon as information was available.	21 CFR 312.32	■	3	0 of 1 (0%)	Notification was submitted, but not in accordance with time requirements.	A.2
18	Annual reports were submitted to the FDA within 60 days of the IND anniversary date.	21 CFR 312.33	■	3, 4, 6, 7, 8, 9	2 of 8 (25%) that responded.	<ul style="list-style-type: none"> AMAS did not receive this information for one study (#5) in the sample. An "annual report" may have been submitted, but not on an annual basis and not within 60 days of the IND anniversary date. 	A.2
19	Investigators were given an Investigator's Brochure and informed of adverse events.	21 CFR 312.32 and 312.55	N/A	-	-	Because the studies in the test sample were PI initiated, Investigator's Brochures were not available for most studies. PIs communicated through the research plan and meetings with investigators.	-

- Requirements were met for all studies.
- ◆ Most studies met or substantially met this requirement.
- Most or all studies did not meet this requirement.