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Director, Human Research Protection Program
0984

**Subject: *Ophthalmology Human Subjects Research Compliance
Report 2017-48***

The final report for *Ophthalmology Human Subjects Research Compliance*, Report 2017-48, is attached. We would like to thank all members of the department for their cooperation and assistance during the review.

Because we were able to reach agreement regarding management action plans 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 department personnel at the appropriate time to evaluate the status of the management action plans.

UC wide policy requires that all draft reports be destroyed after the final report is issued. We also request that draft reports not be photocopied or otherwise redistributed.

David Meier
Director
Audit & Management Advisory Services

Attachment

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AUDIT & MANAGEMENT ADVISORY SERVICES

Ophthalmology Human Subjects Research Compliance

Report No. 2017-48

February 2017

FINAL REPORT

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TABLE OF CONTENTS

I. EXECUTIVE SUMMARY	3
II. BACKGROUND.....	5
III. AUDIT OBJECTIVE, SCOPE, AND PROCEDURES	6
IV. CONCLUSION.....	7
V. OBSERVATIONS REQUIRING MANAGEMENT ACTION	7
A. Informed Consent and HIPAA Authorization	7
B. IRB Reporting	9
C. Subject Files Documentation	11
D. Enrollment Log Accuracy	13
E. Professional Fee Billing	14
F. Regulatory Documentation.....	14
G. Research Training.....	15

ATTACHMENT A - Study Audit Template

ATTACHMENT B - Summary of Findings by Study

I. EXECUTIVE SUMMARY

Audit & Management Advisory Services (AMAS) has completed a regulatory review of research projects conducted by a Principal Investigator (PI) in the Department of Ophthalmology (Department), at the request of the UCSD Human Research Protection Program (HRPP). The objective of our review was to evaluate the PI's active research studies overall compliance with regulatory requirements associated with study documentation, adverse event reporting, subject safety, and study monitoring.

We concluded that the study team research administration needed improvement to ensure that study files were complete and accurate, reporting obligations to the Institutional Review Board (IRB) were met, and research conducted was consistent with the approved protocol. We noted that consenting practices and HIPAA¹ Authorization completion were not consistently compliant with regulations and HRPP guidelines, particularly for initial subjects enrolled. IRB reporting of some protocol deviations and other study events was also not in compliance with HRPP guidelines. Documentation and completion of case report forms (CRFs), source documentation and adverse event assessment was also inadequate in some cases.

Professional fee billing errors totaling \$746 were identified for one study (#140173) that were improperly charged to the subject and/or their third party payor. Required regulatory documentation was generally adequate although some exceptions were noted. Research training was also incomplete for some study staff. It is possible that this contributed to the non-compliance described above. All staff have completed required training since the initiation of this review, however additional training or monitoring by the HRPP may be needed to promote future compliance.

Based on these findings, the IRB and Department may wish to consider additional strategies to improve the PI and study team's compliance with policies and regulations for conducting human subject research. For example, additional monitoring by the UCSD Research Compliance Program (RCP) may be requested. Management Action Plans to address these findings are summarized briefly below:

A. Informed Consent and HIPAA Authorization

1. The PI will notify the IRB of applicable consenting and HIPAA deviations as required by HRPP policy.
2. The study team will ensure that Section C and Section G of the HIPAA Authorization are completed as appropriate for future enrollment.

B. IRB Reporting

1. The PI will implement a Secondary Reviewer Screening Process for current and future trials requiring secondary verification of subject enrollment.
2. The PI will report adverse events and protocol deviations to the IRB for applicable studies; and ensure that events are reported to the IRB on a timely basis in the future to comply with HRPP guidelines.
3. The PI will consider modifying the recruitment criteria in the research plan for study #140090.

¹ Health Insurance Portability and Accountability Act of 1996

4. The PI will ensure that future enrollment is consistent with the IRB-approved inclusion/exclusion criteria.
5. The PI will ensure that Protocol, Informed Consent Forms (ICFs), and CRFs are consistent on the timeline for follow up contact.
6. The PI has filed a study closure report with the IRB for study #151667.

C. Subject Files Documentation

1. The study team will ensure that source documentation is filed for study #140173.
2. The study team will ensure that CRF's are completed or lack thereof is indicated for study #081041.
3. The study team will consider revising the adverse event log to capture PI sign-off for each event listed.

D. Enrollment Log Accuracy

1. The Study Coordinator has corrected the enrollment logs for study #081041 and #140090.
2. The study team will update the IRB with accurate enrollment information for studies #081041 and #140090.

E. Professional Fee Billing

1. Professional fee charges have been corrected for the three subjects.
2. The study team has reviewed all study visits for any other missed study procedure costs that may have led to inappropriate billing. Identified charges have been submitted to Revenue Cycle for correction.
3. The study team will re-train staff to ensure that professional fee billing documents are obtained and retained for all study procedures performed at study visits.

F. Regulatory Documentation

1. The study team will ensure that regulatory binders are complete for their clinical trials. The checklist on the UCSD Research Compliance website can assist with ensuring future compliance

G. Research Training

1. All three support staff completed the mandatory HRPP training module in November 2016.
2. The PI completed Stem Cell Ethics training in November 2016.
3. The PI and study team will pursue one-on-one training sessions with the IRB to help achieve regulatory compliance.
4. The PI will ensure that he and the study team are compliant with mandatory HRPP and Stem Cell Ethics training going forward.

Observations, related Management Action Plans are described in greater detail in section V. of this report.

II. BACKGROUND

Audit & Management Advisory Services (AMAS) has completed a regulatory review of research projects conducted by a Principal Investigator (PI) in the Department of Ophthalmology (Department), at the request of the UCSD Human Research Protection Program (HRPP). This report summarizes the results of our review.

The UCSD HRPP office assists researchers in complying with federal, state and University policies regarding experimentation involving human subjects, and oversees the review and conduct of research conducted through six federally registered Institutional Review Boards (IRBs).

The PI's clinical and research focuses are on novel disease gene targets and treatment, gene and stem cell based therapies in age related macular degeneration, diabetic retinopathy, and inherited retinal degeneration. The PI's Laboratory uses genetics to gain insights into the molecular mechanisms of macular degeneration and other eye diseases. As of October 2016, the PI had five active research projects with the IRB as summarized in the table below:

IRB #	Title	Sponsor/Funding	Enrollment
081041	Genetic and Molecular Studies of Eye/Human Diseases	Mix of departmental, grant and start-up funding used to support PI lab	Over 16,000
140090	Collection of Blood or Skin Biopsy Samples from Patients with Late-Life Blinding Eye Disorders and from Healthy Matched-Controls for a Stem Cell Bank (IT1-06601)	California Institute for Regenerative Medicine (CIRM) research grant	410
140173	EAGLE: Evaluating Genotypes Using Intravitreal Aflibercept Injection	Regenron Pharmaceuticals (PI-initiated)	47
151667	A Phase 2 Randomized, Double-masked, Multicenter, Active-controlled Study Evaluating Administration of Repeated Intravitreal Doses of hI-con1' in Patients with Choroidal Neovascularization Secondary to Age-related Macular Degeneration	Iconic Therapeutics (commercially sponsored)	None to date
160944	Prospective Case Crossover Study to Assess Whether PDE5 Inhibitor Exposure in Men with Erectile Dysfunction Increases the Risk for the Development of Non-arteritic Anterior Ischemic Optic Neuropathy (NAION)	Bayer (commercially sponsored)	None to date

One of the PI's inactive studies (#110567) was subject to a review by the Food & Drug Administration (FDA) in July/August of 2016 which found significant regulatory and study conduct noncompliance issues as summarized below:

- Failure to monitor investigational sites for an investigation conducted under an Investigational New Drug (IND),
- Failure to submit annual report to the FDA,
- Conducting enrollment during enrollment suspension period,
- Protocol Deviations - enrolling subjects that did not meet inclusion criteria and subjects not completing all protocol required study visits/examinations,

- Informed consent lacking required regulatory language,
- Inadequate retention practices and,
- Investigation drug disposition record discrepancies.

In response to the FDA report, the IRB placed an enrollment suspension on all of the PI's active studies, pending results of this audit of his active studies.

The PI's research projects are managed by three support staff: one Study Coordinator and two lab assistants. The support staff are funded through a combination of the PI's grants or unrestricted funding sources and other research projects conducted by another Department PI.

III. AUDIT OBJECTIVE, SCOPE, AND PROCEDURES

The objective of our review was to evaluate the PI's active research studies overall compliance with regulatory requirements associated with study documentation, adverse event reporting, subject safety, and study monitoring. The project scope included the five active studies, with a focused review of three studies with enrollment. The inactive study previously reviewed by the FDA was not further evaluated in the scope of this audit. A standard study audit template was used to document the focused reviews, which is provided in **Attachment A**.

In order to achieve our objective, we performed the following:

- Reviewed applicable IRB policy and Fact Sheets including reporting of protocol violations and/or unanticipated problems involving risks to subjects or others (UPRs), study closure, training requirements, and HIPAA compliance;
- Obtained and evaluated training records for the PI and his support staff for completion of mandatory research training;
- Met with the PI and Study Coordinator to understand study procedures, regulatory document management and reporting processes;
- Obtained enrollment logs for the three studies with enrollment (#081041, #140090 and #140193) and traced withdrawals listed on IRB submissions to the log to verify completion of logs;
- Reviewed regulatory binders and selected a judgmental sample of subjects for the three studies with enrollment (50 subjects for studies #081041 and #140090; 15 subjects for #140173) to complete a focused review of subject documentation;
- Verified subject eligibility for sampled subjects based on enrollment criteria on research plan;
- Verified hospital and professional fee billing for study procedures for study dates of service was in accordance with the research plan for a judgmental sample of subjects for the three studies with enrollment (#081041, #140090 and #140193); and
- Conducted a site visit to review study documentation and subject files for compliance with regulatory requirements and adverse event reporting.

IV. CONCLUSION

Based on our review, we concluded that the study team research administration needed improvement to ensure that study files were complete and accurate, reporting obligations to IRB were met, and research conducted was consistent with the approved protocol.

We noted that consenting practices and HIPAA Authorization completion were not consistently compliant with regulations and HRPP guidelines, particularly for initial subjects enrolled. IRB reporting of some protocol deviations and other study events was also not in compliance with HRPP guidelines. Documentation and completion of case report forms (CRFs), source documentation and adverse event assessment was also inadequate in some cases.

Professional fee billing errors totaling \$746 were identified for one study (#140173) that were improperly charged to the subject and/or their third party payor. Required regulatory documentation was generally adequate although some exceptions were noted. Research training was also incomplete for some study staff.

Investigational drug accountability records were maintained and study drug inventory was verified for one study (#140173). In response to the FDA audit, the study team indicated that they had taken steps to review subject files and regulatory binders for other active studies and this was evidenced through notes to file and PI sign offs in November 2016 to document missing data and PI assessments in subject files.

We noted that mandatory HRPP training was not completed by support staff. It is possible that this contributed to the non-compliance described above. All staff have completed required training since the initiation of this review, however additional training or monitoring by the HRPP may be needed to promote future compliance. These observations are described in further detail in the balance of this report and in **Attachment B**.

Based on these findings, the IRB and Department may wish to consider additional strategies to improve the PI and study team's compliance with policies and regulations for conducting human subject research. For example, additional monitoring by the UCSD Research Compliance Program (RCP) may be requested.

V. OBSERVATIONS REQUIRING MANAGEMENT ACTION

A.	Informed Consent and HIPAA Authorization
We noted instances when consenting practices were not fully compliant with policy and regulations. HIPAA Authorization forms Section C and G were not completed for several subjects.	
Risk Statement/Effect	
Inadequate consenting practices may negatively impact the rights, welfare, and safety of human	

subjects in clinical research.	
Management Action Plans	
A.1	The PI will notify the IRB of applicable consenting and HIPAA deviations as required by HRPP policy.
A.2	The study team will ensure that Section C and Section G of the HIPAA Authorization are completed as appropriate for future enrollment.

A. Informed Consent and HIPAA Authorization – Detailed Discussion

Informed Consent Form (ICF)

UCSD HRPP IRB Standard Operating Policies and Procedures (*Section 3.4, Informed Consent*) requires all investigators to obtain a legally effective informed consent from the subject or the subject's legally authorized representative, unless conditions for waiver of consent have been met. When children or minors are involved in research, the regulations require the assent of the child or minor and the permission of the parent(s) or legally authorized representatives, in place of the consent of the subjects.

We noted that two subjects (#16596001 and, #16973001) for study #081041 and two subjects (E023 and E043) for study #140173 did not sign the most current version of the ICF upon enrollment. The IRB was not informed of these discrepancies.

For study #081041, we noted that one subject's (#16587001) assent form was filed but was not signed by the subject. For study #140090, one subject (CW70350), signed an adult ICF when an adolescent assent was appropriate based on the subject's age.

In addition, we identified one instance where it appeared that research procedures were initiated prior to the informed consent date. The ICF for one subject (CW70354) for study #140090 was dated by subject for the day after study procedures were conducted. However, this appeared to be a date error on the part of the subject, as the Study Coordinator dated the ICF on the date the study procedures were performed.

HIPAA Authorization

The HIPAA Privacy Rule establishes a set of requirements for protecting the confidentiality of protected health information (PHI) arising as a result of health care services, and includes the requirement that authorization be obtained in most cases before this type of data is used for research purposes. Section C of the HIPAA Authorization form should be initialed by subjects if information specified (i.e. HIV/AIDS testing, genetic testing etc.) is being collected per study protocol. As of September 23, 2013, newly enrolled participants who sign a HIPAA Authorization must opt-in to allow the use of their PHI for optional research activity as well as for future secondary use of PHI (under Section G). By default, not addressing Section G indicates that the subject is opting out of the optional research activities.

Based on discussion with Study Coordinator and review of research activities, agreement for genetic testing (Section C) and additional optional testing (Section G) was applicable for the three studies. However, our review of study records identified several instances when Section C and/or Section G of the HIPAA form were not completed, as summarized in the table below:

IRB #	Section C	Section G
081041	15	25
140090	19	31
140173	1	4

The Study Coordinator indicated that they were not initially aware of the requirement to complete Section G of the HIPAA Authorization form but have taken measures to ensure this is appropriately completed by subjects.

In addition, upon review of subject files for study #140090, we noted that HIV testing was done at a central lab as a screening procedure to verify whether or not HIV or other blood borne diseases were found in the blood prior to generating cell-line for the samples submitted. The Study Coordinator indicated that subjects were not asked to initial agreement for release of HIV/AIDS testing information under Section C of the HIPAA Authorization form. However, obtaining approval for release of HIV/AIDS testing appears to be required for this study.

B.	IRB Reporting
We noted that selected minor protocol deviations, certain study events, and one study closure were not reported to the IRB as required by HRPP policy and guidelines.	
Risk Statement/Effect	
Incomplete or untimely reporting to the IRB of protocol deviations and adverse events may negatively impact the rights, welfare, and safety of human subjects in clinical research.	
Management Action Plans	
B.1	The PI will implement a Secondary Reviewer Screening Process for current and future trials requiring secondary verification of subject enrollment.
B.2	The PI will report adverse events and protocol deviations to the IRB for applicable studies; and ensure that events are reported to the IRB on a timely basis in the future to comply with HRPP guidelines.
B.3	The PI will consider modifying the recruitment criteria in the research plan for study #140090.
B.4	The PI will ensure that future enrollment is consistent with the IRB-approved inclusion/exclusion criteria.
B.5	The PI will ensure that Protocol, Informed Consent Forms (ICFs), and CRFs are consistent on the

	timeline for follow up contact.
B.6	The PI has filed a study closure report with the IRB for study #151667.

B. IRB Reporting – Detailed Discussion

Protocol Deviations

UCSD HRPP IRB Standard Operating Policies and Procedures (*Section 3.14, Protocol and Regulatory Violations and Exceptions*) requires major protocol violations to be reported to the IRB within 10 working days of awareness of the violation, and minor violations to be reported to the IRB at time of continuing review or study closure on the narrative summary of progress document. Major violations include instances that impact participant safety, substantially alter risks to participants, are non-compliant with applicable UCSD HRPP, federal, state and institutional policies and regulations, or any instance determined by the IRB Chair, HRPP Director, or HRPP Associate Director to require review by a convened IRB. Minor protocol violations include instances that do not impact participant safety or substantially alter risks to participants.

Our review of study #140090 identified seven subjects that did not meet the enrollment criteria as specified in the research plan. Recruitment criteria under Section 10 of the research plan specified subjects recruited will be 50+ years old (male or female) and that no minors will be studied. However, our review of 50 sampled subjects files identified seven subjects who were under 50 years, including one minor, who did not meet the enrollment criteria. The Study Coordinator indicated that the age should not be cause for exclusion in this study as long as eye disease or control requirements are met. However, this was inconsistent with the IRB-approved protocol and research plan.

For study #140173, we noted several instances of minor protocol deviations that had not been reported to the IRB. Most sampled subjects had some missed/delayed study procedures (Fundus Photography, Fluorescein Angiography (FR), follow up contact, and delayed blood draws). Subject records had notes to file (NTFs) for most of these procedures, although some missed or delayed procedures were not documented in NTFs. We noted that these events reflected minor protocol deviations, but none were reported to the IRB in the last two continuing reviews.

We also noted inconsistencies between the protocol, ICF, and CRFs for this study. The study #140173 CRF for follow up contact indicated 2-7 days after study injection but the ICF indicated 2-4 days after injection. The protocol did not specify timeline for follow up contact. The protocol, CRFs and ICF follow up timelines should be consistent to maintain compliance with the protocol and avoid confusion.

Non-Unanticipated Problems Involving Risks (UPRs)

UCSD HRPP IRB Standard Operating Policies and Procedures (*Section 3.13, Reporting Adverse Events and Unanticipated Problems*) requires an event classified as an unanticipated problem involving risks to subjects or others (UPR) to be reported to the IRB within 10 working days. Non-UPRs are required by policy to be reported to the IRB at least annually as part of the study continuing review report or study resubmission report.

During review of sampled subject study records for study #140173, we noted that five subjects had a total of seven non-UPRs that were not reported to IRB on the annual continuing reviews submitted.

Study Closure

Federal regulation [21 CFR 56.108(a)(3)] requires ensuring "prompt reporting to the IRB of changes in a research activity." The completion of the study is a change in activity and should be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report/notice to the IRB allows it to close its files as well as providing information that may be used by the IRB in the evaluation and approval of related studies. HRPP Face Sheets on Study Withdrawal/Closure requires PIs to "report closure of a research study to the IRB within 30 days."

Study #151667 was initially submitted to UCSD IRB in October 2015, seeking review and institutional jurisdiction waiver for Quorum IRB oversight. While the study was under review at UCSD, the sponsor's study enrollment goals were met, and UCSD was not established as a study site. The study team was informed of study enrollment closure by the sponsor on March 31, 2016, but a formal closure report was not submitted to UCSD IRB to reflect study status.

C.	Subject Files Documentation
Subject documentation was incomplete or inadequate in some cases.	
Risk Statement/Effect	
Reliable, accurate and adequate source documentation and case report forms are critical to ensure that study results are built on the foundation of credible and valid data, and symbolize good documentation practices in clinical research.	
Management Action Plans	
C.1	The study team will ensure that source documentation is filed for study #140173.
C.2	The study team will ensure that CRF's are completed or lack thereof is indicated for study #081041.
C.3	The study team will consider revising the adverse event log to capture PI sign-off for each event listed.

C. Subject Files Documentation – Detailed Discussion

Maintaining good clinical documentation in a clinical trial is key to support study results, confirm eligibility of a subject, document the participation of a subject from consenting to study completion, and forms a foundation for data transcribed on a CRF which is ultimately translated into a clinical study report.

Source Documentation and Case Report Forms

For study #140173, we noted that source documentation was not in subject files for some study procedures. There were six subjects for which fluorescein angiography documentation was missing from the study file. In addition, five subjects retina progress reports for their eye exams were missing for 11 study visits.

We also noted that the PI did not sign off on source documentation in subject files for study #140173, particularly for the fluorescein angiography and optical coherence tomography (OCT) tests. The sign-off evidences review by the PI of study test results.

Study #081041 had one sampled subject file (#16573001) that could not be located. Consequently, consent forms and enrollment forms for the study were not available for review.

We noted that CRFs were incomplete in several sampled subject files for study #081041. Per the research plan, the primary objective of the study was to collect blood samples and clinical data on subjects with heritable disease for genetic research on human tissue samples. It specified that all study subjects would have their ophthalmology records, medical history, and family history of disease reviewed, as well as blood draws.

The enrollment form (CRF developed for study) for study #081041 included sections for subject demographic, medical/family history, eye test results and disease information. However, we noted that in several cases the subject history, eye test and disease information was not captured in the enrollment form, even if this data was captured in the source document when located in subject file (i.e. retina progress report). The enrollment form was also not signed off to identify the study team member that completed it.

Per the Study Coordinator, data collection was focused on capturing subject demographic information and therefore other sections on the enrollment form were not consistently completed. The CRFs for this project were a means of recording relevant details as the subject discussed medical history and general demographics with study coordinators. CRF completion or lack thereof depended on the amount of detail available at the time of enrollment.

The Study Coordinator stated that most subjects were enrolled for study #081041 during their routine ophthalmology visit and performing an eye exam specifically for the study was rare. Only 25 of the 50 sampled subjects source documentation for their eye exam (retina progress report) was in file. The Study Coordinator indicated that the eye exam was standard of care and retina progress reports were only added as additional information.

Adverse Event Assessment

The adverse event logs for study #140173 had sections for capturing each event including its severity and causality assessment. There was only one sign off at the end of the log by the PI for all adverse events noted. As there are multiple events that occur over the course of study participation, better documentation practices would evidence PI assessment of each event by requiring PI sign off for each event noted on the adverse event log. We also noted that log was signed off by the PI in November

2016 in most cases, implying that the sign-off was triggered by the site visit. For four subjects, the sign-off by the PI was lacking in the log.

D.	Enrollment Log Accuracy
The study enrollment logs were inaccurate for two studies (#081041 and #140090).	
Risk Statement/Effect	
Inaccurate enrollment information impacts validity of information reported to the IRB.	
Management Action Plans	
D.1	The Study Coordinator has corrected the enrollment log for studies #081041 and #140090.
D.2	The study team will update the IRB with accurate enrollment information for studies #081041 and #140090.

D. Enrollment Log Accuracy – Detailed Discussion

The study enrollment log includes a list of subjects who were consented for the study and can be used to track subject status (enrolled, screen fail, withdrawn, complete etc.). Screening and enrollment logs are considered essential documents per GCP and is useful to track the number of subjects enrolled and the rate of enrollment for continuing renewal with the IRB.

We compared the subject withdrawals reported to the IRB in continuing reviews (from year 2014 onwards) and compared to the enrollment log for studies #081041 and #140090. Discrepancies were identified in the enrollment logs for both studies. Thirty-two (32) subjects for study #081041 and 18 subjects for study #140090, were identified as withdrawn on narrative summaries submitted to the IRB but could not be located on the study enrollment log.

In addition, one subject was identified as withdrawn in the narrative summary and listed on enrollment log but subject status needed to be updated to reflect withdrawal for study #081041. Similarly, we noted two subjects identified as withdrawn on the narrative summary submitted to the IRB for study #140090, but subject status indicated active status in the enrollment log. Further review by the Study Coordinator revealed that these two subjects were in fact in active status and IRB communication in the narrative summary was inaccurate.

Based on the above, it did not appear that the study logs were maintained consistently and accurately, raising question about the extent to which they can be relied on.

E.	Professional Fee Billing
Professional fee billing errors totaling \$746 were identified for one study (#140173).	
Risk Statement/Effect	
Inappropriate billing to subject accounts for study billable charges increase risk of fraudulent claims and double-charging which can incur substantial penalties for violations of federal and state billing requirements.	
Management Action Plans	
E.1	Professional fee charges have been corrected for the three subjects.
E.2	The study team has reviewed all study visits for any other missed study procedure costs that may have led to inappropriate billing. Identified charges have been submitted to Revenue Cycle for correction.
E.3	The study team will re-train staff to ensure that professional fee billing documents are obtained and retained for all study procedures performed at study visits.

E. Professional Fee Billing – Detailed Discussion

Our analysis of professional fee billing for a sample of eight subjects for study #140173 identified professional fee billing errors of \$746 for four study visits for three subjects (E014, E017 and E022). One subject's (E022) ophthalmic imaging charge had routed to collections. The Study Coordinator indicated that the initial (Day 0) study visit was generally standard of care billable to the subject/third party payor, as subjects were typically enrolled during their scheduled eye examination, unless referred from an outside medical group.

The study research plan and ICF specified that the subject would not incur any costs or expense for participation in the study. All study procedures were therefore not billable to the subjects, and the study team prevented charges from being billed by retaining all paper professional fee billing documentation when study procedures were performed. However, some procedures still routed inappropriately to the subject's account.

F.	Regulatory Documentation
Regulatory binders were incomplete in some cases.	
Risk Statement/Effect	
Regulatory binders provide an organizational framework for filing essential study documents, facilitate the effective and efficient management of studies, and symbolize good clinical documentation practices.	

Management Action Plan	
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F.1	The study team will ensure that regulatory binders are complete for their clinical trials. The checklist on the UCSD Research Compliance website can assist with ensuring future compliance.
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F. Regulatory Documentation – Detailed Discussion
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The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) Guidelines define Essential Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of Good Clinical Practice and with all applicable regulatory requirements. A regulatory binder or file contains all study-specific information and regulatory documentation. It organizes essential documents, provides easy access to essential documents by the trial monitor, auditor, IRB, or regulatory authorities for review/audit purposes, and allows research team members to reference information. The UCSD Research Compliance Program intranet has a checklist for regulatory binder documentation.

Regulatory binders were obtained and reviewed for the three studies with enrollment (#081041, #140090 and #140173). We noted that a complete set of required regulatory documents were not maintained. A summary of the regulatory documents not located for the three studies selected for detailed testing is presented in **Attachment B**.

G.	Research Training
The study team support staff had not completed the mandatory HRPP training.	
Risk Statement/Effect	
Training on the principles of conducting biomedical research is vital to ensuring that research studies are conducted in compliance with applicable regulations and guidelines. If the Principal Investigator and all key personnel have not completed required HRPP training, research projects may be delayed, as IRB may not grant approval for Initial and Continuing Reviews or amendments until training is complete.	
Management Action Plans	
G.1	All three support staff completed the mandatory HRPP training module in November 2016.
G.2	The PI completed Stem Cell Ethics training in November 2016.
G.3	The PI and study team will pursue one-on-one training sessions with the IRB to help achieve regulatory compliance.
G.4	The PI will ensure that he and the study team are compliant with mandatory HRPP and Stem Cell Ethics training going forward.

G. Research Training – Detailed Discussion

Biomedical Research Training

All Principal Investigators and "Key Personnel" who are engaged in research with living human beings, human tissue samples or identifiable private information, or conducting research under the review of UCSD IRBs are required to take the CITI Training Program. The required course is the Biomedical Course in Responsible Conduct of Research Protection of Human Research Subjects. Key personnel include faculty, staff or students who enroll individuals, obtain subject ICF, intervene or interact with subjects by performing invasive or non-invasive procedures, collect data directly or follow-up directly with participants, collect identifiable provide information from participants, have access to information that links participants names with their data, or act as authorized representatives for the investigators. The Principal Investigator and all key personnel must complete their CITI training before the HRPP review is completed at time of initial review, continuing review, and amendment requests. The PI certifies key personnel associated with the study have completed the appropriate CITI training by signing the current application Facesheets and/or Continuing Review Facepages.

Review of training records for the PI and his support staff revealed that although the PI completed the mandatory HRPP training, his three support staff had not. The support staff met the criteria for "key personnel" as described above and therefore were required to complete the training.

Stem Cell Ethics Training

Based on guidelines from the National Academy of Sciences, regulations from the California Institute of Regenerative Medicine, and guidelines of the participating institutions of the Sanford Consortium for Regenerative Medicine, the institutional Stem Cell Research Oversight Committees are charged with overseeing a requirement for ethics training. All PI and personnel who work with Human Embryonic Stem Cells (hESC), are required to complete initial and annual Stem Cell Ethics training.

We noted that study #140090 was approved by the Embryonic Stem Cell Research Oversight (ESCRO) Committee as it involves stem cell research. Consequently, the PI is subject to the Stem Cell Ethics training requirement. We followed up with the completion of training for Stem Cell Ethics for the PI with the Research Ethics Program but they were unable to locate any record confirming that training was completed. The PI indicated that the study ceased enrollment in September 2016 and he was working on final data input with the study sponsor for study closure.

ATTACHMENT A – Study Audit Template

General Information			
PI:		IRB #:	
Study Name:			
# of Subjects Enrolled / # Chosen for Review:		RCP Reviewer:	Date Review Initiated:
			Date On-site Review:
Review Type: Billing/Bulk <input type="checkbox"/> Device <input type="checkbox"/> Drug <input type="checkbox"/> Velos <input type="checkbox"/> Coverage Analysis <input type="checkbox"/> Regulatory Review <input type="checkbox"/> Consent Review <input type="checkbox"/> Other <input type="checkbox"/> (specify)			
Sponsor: Federal <input type="checkbox"/> Commercial <input type="checkbox"/> Departmental Funds <input type="checkbox"/> Investigator Initiated <input type="checkbox"/> Other <input type="checkbox"/> (specify)			
External Monitor?		Y <input type="checkbox"/> N <input type="checkbox"/>	Date of Last Visit:
Bulk #:		Index#:	
Investigational Drugs Used? Y <input type="checkbox"/> N <input type="checkbox"/> N/A <input type="checkbox"/> If yes, identify by name/IND:			
Investigational Device Used: IDE <input type="checkbox"/> HDE <input type="checkbox"/> NSR <input type="checkbox"/> N/A <input type="checkbox"/> Identification # (include Category/Class):			
Where did study procedures take place? Inpatient <input type="checkbox"/> Outpatient <input type="checkbox"/> (specify)			

Contact Information			
Name	Title	Phone	Email

Protection of Human Subjects <input type="checkbox"/> N/A				
	Yes	No	N/A	Comments/Exceptions
1. Is storage of study records adequate and secure? a. Describe the process for maintaining study records during the study and the plans for records retention once the study is complete.				
<i>For a sample of study subjects:</i>				
2. Are all applicable versions of the signed Consent Form present for each subject?				
3. Are all applicable versions of the signed assent form present for pediatric subjects age 7 years and older (when appropriate)?				Child Assent for subjects ages 7-12, Adolescent Assent for subjects 12-17
4. Was the consent form signed by the subject the most current version available?				
5. Is each Consent Form signed/dated prior to				

Adapted from Audit Templates available on the UCSD Research Compliance Program website.

ATTACHMENT A – Study Audit Template

Protection of Human Subjects <input type="checkbox"/> N/A				
	Yes	No	N/A	Comments/Exceptions
initial treatment? a. Is there documentation of the Informed Consent process in the source? b. Is there documentation that a copy of the Subject's Bill of Rights was provided to each subject?				
6. Is the HIPAA Authorization signed by each subject (when applicable)? a. Does the study require information listed in Section C? b. If so, is Section C completed appropriately or is there documentation re: participant declination? c. Has section G been completed?				Section G is only applicable for subjects consented after 9/23/2013
7. Is a copy of the signed Informed Consent Form and HIPAA uploaded in the subject's electronic medical record?				

Financial Administration & Billing <input type="checkbox"/> N/A				
	Yes	No	N/A	Comments/Exceptions
1. Was there a clinical trial agreement, contract or grant executed prior to initiation of the study?				
2. For a sample of subjects, verify that subjects (or their third party payer) were not charged for study procedures that were to be billed to the research study?				

Sample Collection and Storage <input type="checkbox"/> N/A				
	Yes	No	N/A	Comments/Exceptions
1. Does the study include sample collection? a. If using a central lab, are sampled de-identified in accordance with the consent form? b. Are sample temperature logs maintained?				
2. If other sub-sites are used are they: a. Approved by the IRB b. contract in place prior to sample collection c. transfers of samples is logged				
3. If sub-sites are used, understand the process for monitoring of sub-sites to ensure compliance with study protocol.				

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ATTACHMENT A – Study Audit Template

Investigational Drugs				<input type="checkbox"/> N/A
	Yes	No	N/A	Comments/Exceptions
1. Is the investigational drug identified on the IRB Face Sheet with IND number?				
2. Is the drug labeled for investigational use only?				
3. If investigational drugs are used in the study, is the UCSDMC Investigational Drug Service involved? NOTE: If yes, skip questions 4 -12.				
4. Is documentation of receipt of study drug present? Who supplies the drug?				
5. Is the lot # and expiration date for the study drug documented if applicable?				
6. Has the expiration date of the study drug passed?				
7. Is the investigational drug labeled in accordance w/ guidelines provided in the protocol? (Drug Fact Sheet?)				
8. Is the study drug stored in an appropriate location with restricted access?				
9. Describe the process for inventory control of the study drugs, i.e. is there adequate separation of duties in the receipt, dispensing, disposal or wastage of study drugs?				
10. Is documentation of distribution, return, and disposition of study drug present (i.e., drug accountability log) logs?				
11. Are study drugs stored in accordance with specified storage conditions? a. Is a temperature log maintained?				
12. Does the physical inventory match the Drug Accountability log?				

Unexpected Problems Involving Risks (UPRs) and Adverse Events				<input type="checkbox"/> N/A
<i>For a sample of study subjects:</i>	Yes	No	N/A	Comments/Exceptions
1. Were there any adverse events/UPRs?				
2. Is there documentation of adverse events/UPRs in the subjects research record?				
3. Does review of subject electronic medical record for study visit identify any adverse events?				

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ATTACHMENT A – Study Audit Template

Unexpected Problems Involving Risks (UPRs) and Adverse Events <input type="checkbox"/> N/A				
<i>For a sample of study subjects:</i>	Yes	No	N/A	Comments/Exceptions
a. If yes, were these events noted in the adverse event log?				
4. Were UPRs reported to the IRB within 10 working days of knowledge of the event?				
5. Were adverse events/non-UPRs reported to the IRB at the time of continuing review?				

Regulatory Binder/File <input type="checkbox"/> N/A				
	Yes	No	N/A	Comments/Exceptions
1. Master Protocol, including subsection for: a. protocol amendments b. protocol signature pages				
2. Investigator’s Brochure, Package Insert or Product Information (include all versions)				
3. FDA letter or other documentation of IND, IDE and other designation (as applicable)				
4. IND Safety Reports				
5. DSMB Reports				
6. IRB-approved Informed Consent and/or Assent Forms (include all versions)				
7. HIPAA Authorization form				
8. IRB-approved Advertisements/Flyers				
9. Protocol Deviation/Violation Reports (UPR Reports)				
10. IRB Correspondence, includes all submissions and correspondence to/from IRB such as: a. HRPP Application Facepages b. Research Plan c. IND Fact Sheet d. Continuing Review Facepages e. Continuing Review Narrative f. Study closure facepages g. Submission and response letters from research unit h. IRB letters				
11. Continuing Reviews/10-Year Resubmission a. Was there any lapse in IRB approval? b. Were participants enrolled during this lapsed period?				

Adapted from Audit Templates available on the UCSD Research Compliance Program website.

ATTACHMENT A – Study Audit Template

Regulatory Binder/File	<input type="checkbox"/> N/A			
	Yes	No	N/A	Comments/Exceptions
c. If yes, was the IRB notified?				
d. Were study activities conducted during lapse in IRB approval?				
e. If yes, is there documentation of IRB approval on file?				
12. Were amendments submitted to the IRB?				
13. Were participants required to be re-consented as a result of an amendment? - Specify amendment (e.g., protocol version, reason for amendment, consent version, IRB approval date).				
14. Correspondence, submission forms and/or approvals from other institutional committees (as applicable)				
15. Sponsor correspondence (study-related correspondence to/from site and sponsor/CRO)				
16. Federalwide Assurance Letter (FWA)				
17. Regulatory notes to file				
18. Monitoring Visit Reports				
19. FDA Form 1572 or device equivalent				
20. Curricula Vitae and Professional Licenses of investigators and staff				
21. Financial Disclosure Forms				
22. Screening and Enrollment Log				
23. Site Visit/Monitoring Log				
24. Delegation of Responsibilities Log				
25. Site Signature Log (as applicable)				
26. Training Certificates/Logs (as applicable, may include site initiation visit attendance log)				
27. Storage/Equipment Monitoring Logs (e.g. temperature log for freezer)				
28. Retained Tissue Log (as applicable)				
29. Laboratory Licenses and Certificates (e.g., CAP, CLIA)				
30. Lab Normals/Reference Ranges				
31. Curriculum Vitae of Laboratory Director (as required)				
32. Were any FDA or outside regulatory audits performed? a. If Yes were they reported to RCP?				

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ATTACHMENT A – Study Audit Template

ClinicalTrials.gov Requirements				<input type="checkbox"/> N/A
	Yes	No	N/A	Comments/Exceptions
1. Is the study required to be registered on ClinicalTrials.gov?				
2. Has the study been registered on ClinicalTrials.gov? a. If yes, list the ClinicalTrials.gov number				
<i>For PI initiated studies or studies where the PI holds the IND or IDE:</i>				
3. Was the study registered within the required timeframe?				FDAAA 801 requires registration within 21 days of enrollment of the first subject. ICMJE and CMS require registration prior to enrollment of the first subject.
4. Was the recruitment status and overall recruitment status updated within 30 days of a change?				
5. Have other changes or updates, such as protocol amendments, been made at least every 12 months?				Per ClinicalTrials.gov, it is recommended the Record Verification Date be updated at least every 6 months for studies that are not yet completed, even if there were no changes to the record.
6. If the study is closed, have results been submitted no later than 12 months after the date of final data collection?				

Source Documentation and CRF Review				<input type="checkbox"/> N/A
<i>For a sample of subjects:</i>				
	Yes	No	N/A	Comments/Exceptions
1. Is the source record complete and maintained with current source documentation?				
2. Is there documentation to support eligibility criteria? a. Does eligibility criteria appear to be met for subject inclusion (as per research plan inclusion/exclusion criteria)				
3. Have all procedures that are outlined in the protocol been completed? a. If no, were missed visits or procedures documented in the source?				
4. Have all AE's documented been entered on the AE log? a. Are all AE's entered appropriately on the CRF? b. Is there documentation that the PI has assessed causality of the AE's?				
5. Have all concomitant medications (CC meds) documented been entered on the CC med				

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ATTACHMENT A – Study Audit Template

Source Documentation and CRF Review <input type="checkbox"/> N/A				
<i>For a sample of subjects:</i>				
	Yes	No	N/A	Comments/Exceptions
log?				
a. Are all CC meds entered appropriately on the CRF?				
6. Are drug/device compliance rates documented at each visit?				
7. Has the PI signed and dated all required source documents including study labs, physical exams, etc?				
8. Is the source data recorded accurately in the CRF?				

Notes
<i>To be used for additional documentation of issues noted above</i>

Adapted from Audit Templates available on the UCSD Research Compliance Program website.

ATTACHMENT B - Summary of Findings by Study

IRB #	Study Type	No. of Subjects Enrolled	Informed Consent and HIPAA Foms	IRB Reporting - Protocol Deviations	IRB Reporting - Adverse events	Subject File Documentation	Enrollment Log	Professional Fee Billing	Regulatory Binder Documents
081041	Multiple internal funding	Over 16,000	- Two subjects had not signed most current version of ICF. - One subject assent form was filed but not signed by subject. - Section C (15 subjects) and Section G (25 subjects)of HIPAA Authorization was not complete.	N/A	N/A	- One subject file could not be located. - CRF (enrollment form) was incomplete with subject demographic, medical/family history, eye test and disease information in several cases. - Source document (retina progress report) was not in file for 25 of 50 subjects.	Thirty-two (32) subjects were identified as withdrawn on narrative summaries submitted to the IRB but could not be located on the study enrollment log. - One subject was identified as withdrawn on narrative summary submitted to IRB but subject status had not been updated on enrollment log.	N/A	Selected regulatory binder documentation was not maintained including: IRB Consent forms (all versions), HIPAA Authorization, Federal Wide Assurance Letter, Curriculum Vitae (CV) and Licenses of staff, Delegation of responsibility Log, Site Signature Log, Sample storage freezer logs. In addition, there were only partial documentation for the following: IRB correspondence, Protocol amendments, Training certificates (for PI).
140090	CIRM research grant	410	- Adoloscent ICF not signed for one minor. - One subject ICF was dated after study procedures were conducted. - Section C (19 subjects) and Section G (31 subjects)of HIPAA Authorization was not complete. - HIV testing of Section C not completed on HIPAA Form.	Seven subjects did not meet the enrollment criteria as specified in the research plan.	N/A	- There were six subjects for which fluorescein angiography documentation was missing from study file. In addition, five subjects retina progress reports for their eye exams were missing for 11 study visits. - PI had not signed off on source documentation for fluorescein angiography and OCT tests.	- Eighteen (18) subjects were identified as withdrawn on narrative summaries submitted to the IRB but could not be located on the study enrollment log. - Two subjects were identified as withdrawn on narrative summary submitted to IRB but subject status was active on enrollment log. Further review by the study coordinator revealed that these two subjects were in fact in active status and IRB communication in the narrative summary was inaccurate.	N/A	Selected regulatory binder documentation was not maintained including: Federal Wide Assurance Letter, CV and Licenses of staff, Sample storage freezer logs. In addition, there was partial documentation for the following: Training certificates (for PI).
140173	Regenron Pharmaceut icals (PI-initiated)	47	- Two subjects had not signed most current version of ICF. - Section C (1 subjects) and Section G (4 subjects)of HIPAA Authorization was not complete.	-Minor protocol deviations for missed/delayed study procedures. - Follow up contact timeline inconsistent in protocol, CRF, and ICF.	Five subjects with total of seven non-UPRs had not been reported to IRB	N/A	N/A	\$746 in professional fee billing errors were identified for three subjects	Sample storage freezer logs were not maintained.