Human Research Quality Improvement Program
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Routine Onsite Review Report

IND Sponsor / Co-Investigator:	Diego Pizzagalli, PhD
Location:	McLean - Psychiatry
HRC Protocol #:	2012p002593
Protocol Title:	*Early Life Stress and Depression: Molecular and Functional Imaging Approaches*
Date of Review:	08/18/2015
Date of Report:	09/21/2015
Reviewed By:	Emily Ouellette and Angela Savlidis

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CONFIDENTIAL INTERNAL REVIEW DOCUMENT

I. Introduction

The Partners Human Research Quality Improvement Program (QI Program) conducted an on-site review of the study *Early Life Stress and Depression: Molecular and Functional Imaging Approaches*, HRC protocol # 2012p002593. Diego Pizzagalli, PhD (McLean) is the IND Sponsor (Amisulpride, IND #107564), grant holder and co-investigator. Georges El Fakhri, PhD (MGH) is the Principal Investigator. The first three study visits take place at McLean Hospital. The fourth visit (PET scan) takes place at MGH.

This review is part of QI Program's Sponsor-Investigator mandatory educational audit program. The purpose of this program is to ensure that investigators holding IND or IDE applications are fulfilling the responsibilities set forth in the FDA regulations for drug/device research. As part of this service, QI provides education and feedback regarding Sponsor-Investigator FDA responsibilities as needed. There are two studies under this IND. The QI Program provided an IND certification visit to Dr. Pizzagalli on 2/7/13.

QI specialists, Emily Ouellette and Angela Savlidis met with Diego Pizzagalli, Ph.D, IND Sponsor, Co-I; Rachel Clegg, Research Assistant and David Crowley, Senior Research Project Manager on 08/18/2015. During the on-site review, specialists reviewed: IND documentation; a sample of regulatory documentation and HRC documentation; consent forms for 19 subjects and data for 2. Total number of enrolled subjects is 99. This report documents on-site observations and corrective actions for protocol # 2012p002593.

II. Observations and Corrective Actions

Observations of study documentation are made according to federal regulations, institutional policies, and Good Clinical Practices. Federal regulations include 45 CFR 46, Protection of Human Subjects http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm. Studies that involve a product regulated by the Food and Drug Administration (FDA) must also adhere to FDA regulations http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm.

Institutional polices include Partners Human Research Committee (PHRC) policies at http://healthcare.partners.org/phsirb/guidance.htm. Investigators must adhere to federal regulations and institutional policies.

Investigators are required to maintain records of their human-subjects research activities. Good records are essential for verifying the quality of study data produced and demonstrating investigator compliance with the IRB approved protocol. In order to achieve the highest standards of study documentation, observations are made in accordance with Good Clinical Practice (GCP) guidelines (http://www.ich.org/LOB/media/MEDIA482.pdf).

Corrective actions for observations made at the time of the onsite review that are not in compliance with federal regulations, institutional policies, or not meeting GCP guidelines have been provided in the table(s) below. To improve the overall quality of the research, and to promote the highest standard for human subject's research, these corrective actions should be implemented as soon as possible. The site is responsible for reporting observations of noncompliance to the IRB in accordance with institutional policy. The QI Program is responsible for reporting serious or continuing noncompliance to the IRB and/or institutional official if the site neglects to do so.

III. Conclusions

The QI Program onsite review revealed some deviations from federal regulations, Partners IRB policy and Good Clinical Practices including deficiencies in consent documentation, documentation of delegation and an outdated FDA 1572 form.

Observations not in compliance with federal regulations, Partners IRB policy and Good Clinical Practices are provided to the research team in Appendix 1 along with recommended corrective actions. The recommendations provided in Appendix 1 should be applied to all research studies being conducted in the department.

The QI program considers the following to be the site's priorities in achieving corrective action:

1. Clarify the responsibilities of Dr. Fakhri (PI) and Dr. Pizzagalli (Co-I; IND Sponsor). The QI Program suggests the PI and IND Sponsor review the Sponsor and Investigator Responsibilities as stated in 21 CFR 312.50 and 312.60. If an FDA inspection occurred, both PI and IND Sponsor would be held accountable for the respective responsibilities. For example, the PI would be responsible for study conduct at both MGH and McLean including but not limited to: monitoring, AE reporting, staff training and task delegation. The PHRC also has a policy on PI Responsibilities. If any PI tasks have been delegated to Dr. Pizzagalli, the PI should document in writing which responsibilities have been delegated.
2. The PI is responsible for conducting and supervising the study including proper delegation. Complete the delegation log to include all IRB approved study staff with signatures, start date, end date and all delegated tasks. See appendix for more details.
3. The FDA 1572 form found on site contained outdated information. The IND Sponsor is responsible for obtaining an updated FDA form 1572 "Statement of the Investigator" from PI and submitting to the FDA. Ensure PI, research facilities, IRB information and sub-investigators information accurately reflects the current status of the study. See appendix for more details.
4. The IND Sponsor must ensure that each site investigator is complying with the signed FDA form 1572 "Statement of the Investigator" and conducting all monitoring activities as outlined in the protocol (21CFR312.56). The PI should develop a plan for the systematic review of study documents to ensure completeness and accuracy of informed consents, REDCap database/ CRFs, and documentation of monitoring activity. See Appendix for more details.
5. Study team should ensure that all study procedures are properly documented in subject files, including but not limited to:
    a. Documentation of pregnancy test
    b. Filing questionnaires for each subject
    c. Documentation of eligibility and providing copy of the consent to subjects.

The QI program is committed to helping the study team implements the corrective actions for this study and is available to meet as needed in applying proper study management procedures. Please contact Emily Ouellette at eouellette@partners.org / 617-424-4136 or Angela Savlidis at asavlidis@partners.org / 617-424-4117 if you have questions.

Note: many of the online links to PHRC policies and QI tools in this report are now housed on the Partners Research Navigator website. To facilitate viewing of links, sign in to Research Navigator with your Partners user name and password. If you have problems viewing links after signing in, contact Michele Gomez at mgomez6@partners.org / 617-424-4138.

Appendix 1

HRC Documentation

Observation	Applicable Regulation/Policy/GCP	Corrective Action
Copies of all signed and dated IRB correspondences could not be easily found on file. Site provided QI to electronic access to numerous folders; QI found initial IRB submission saved in a folder, unable to find other submissions. *Note: During debriefing, study team said that they do have copies of all IRB document saved electronically.*	All study-related correspondence with the IRB should be maintained in a separate file for each study [PHRC Guidance: Record Keeping and Record Retention Requirements; GCP 8.3.3]	PI should ensure all IRB documents are easy to locate for an outside review (e.g. FDA). If saved electronically, add note to file in Regulatory binder with the location. Other tips to keep in mind: To ensure that the study file provides an accurate history of activity from start to completion, maintain all correspondence with the IRB. This includes submissions (including attached documents e.g. updated protocol etc.), required modifications letters, Responses to Required Modificiations, as well as Approval Letters. IRB is working out some glitches with the Insight application, until these are resolved, it is not recommended that the site rely on Insight as a repository.

Informed Consent Process

Observation	Applicable Regulation/Policy/GCP	Corrective Action
Copy of consent form instead of orginial was found on file for subjects enrolled in the study. • Copy of consent was seen on file for subject ELS 013.	The original signed and dated research consent form should be retained in the research record [PHRC Guidance: Informed Consent of Research Subjects; GCP 4.8.1]	PI should obtain the original consent form if possible. Write a signed and dated Note to File if the original consent form cannot be located to explain why a copy is found on file.

Observation	Applicable Regulation/Policy/GCP	Corrective Action
Data recorded on the informed consent document has been obscured. Language "McLean Research Pharmacy study #274" was written on the first and last page of consent for subjects ELS 001 and ELS 007.	Any change or correction to a subject documentation sheet should not obscure the original entry.[GCP 4.9.3]	Going forward, do not write notes or stray markings on informed consents. If necessary write a signed and dated note to file to explain the correction.
Fields on the IRB approval footer were cut off when the ICF was printed/photocopied. This was seen for the following subjects: • ELS 007 • ELS 085 • ELS 068 • ELS 090	Subjects must be given and sign the most recently approved version of the research consent form. The entire IRB approval footer should be visible in the consnet form the subject is signing.[PHRC Policy: Informed Consent of Research Subjects; GCP 4.8.2]	QI advises printing blank IRB-approved consent forms directly from Insight. If you notice any fields are being cut off in the footer when printing, immediately contact your protocol administrator.
Options section for future studies located within the text of the consent form are not consistently/accurately completed by the subject. This was seen for subjects ELS 023 and ELS 036	The informed consent of subjects must be obtained and documented in writing before the start of any study-related procedures.[PHRC Guidance: Informed Consent of Research Subjects in accordance with 45 CFR 46; GCP 4.8.8]	If the subject is active in the study, request he/she complete the option section with the current date. If the subject is no longer active in the study and/or can not be contacted, the study procedure cannot be performed as consent was not obtained from the subject.
Subject did not date informed consent form for themselves. • Subject ELS 068 did not date the consent.	The written informed consent form must be signed and dated by the subject or his/her legally authorized representative (or surrogate) and the investigator (or study staff if approved by the PHRC) who obtained the subject's consent.[21 CFR 50.27 (a); PHRC Policy: Informed Consent of Research Subjects; GCP 4.8.8]	Ensure that at the time of consent, the subject (or the subject's legally authorized representative), dates the consent form for themselves. If an individual other than the subject dated the consent form, write a signed and dated note to file explaining the circumstances.
The entire consent form is not on file for	A legally effective informed consent must	Locate the missing pages if possible. If

Observation	Applicable Regulation/Policy/GCP	Corrective Action
subjects. • Consent form pages 16 and 17 were missing for subject ELS 036	be on file.[PHRC Guidance: Informed Consent of Research Subjects in accordance with 45 CFR 46]	pages cannot be located report to the IRB according to PHRC policy. In the future, ensure that the original entire consent form is filed in the subject's folder.
There is no documentation of the informed consent process or that the subject's have been given a copy of the consent form. This was seen for all reviewed subjects.	A copy of the consent form must be given to the person signing the form.[21 CFR 50.27; PHRC Guidance: Informed Consent of Research Subjects in accordance with 45 CFR 46; GCP 4.8.11]	Report the instances in which a subject was not given a copy of the consent form to the IRB. To document the informed consent process, the investigator should consider including the following information in a clinic chart/progress note/other source document: that XX study was explained, questions were answered (if any), subject agreed to participate and signed the consent form, and a copy of the signed consent form was given to the subject. This note should be signed and dated by the person obtaining consent. The Documentation of Informed Consent Process template can be found at: https://partnershealthcare-public.sharepoint.com/_layouts/15/WopiFrame.aspx?sourcedoc={F1184466-CCD4-43EB-AD83-AC277DC22228}&file=documentation-informed-consent-process.dot&action=default&DefaultItemOpen=1

Regulatory Documentation

Observation	Applicable Regulation/Policy/GCP	Corrective Action
Current CVs and medical liscensures (if applicaable) for all study staff are not on file. Examples include but are not limited to: • NO CVs found for Alyssa Peechatka, BS; Anga Haile; Arthur Siegel, MD, Ashlee Victoria Vant-Veer, PhD; Blaise Frederick and David Olson, MD, PhD. • No medical licensure found for Arthur Siegel, MD.	A CV and/or other relevant documents evidencing qualifications and eligibility to conduct trial and/or provide medical supervision of subjects should be on file for investigator(s) and subinvestigators [PHRC Guidance: Record Keeping and Record Retention Requirements; GCP 4.1.1]	CVs and licensure (if applicable) should be maintained on file to document the qualifications of study staff. The QI program recommends that CVs be signed, dated, and updated every 2 years. If this information is filed collectively or electronically, write a signed and dated note-to-file indicating where the CVs are located.
Delegation of responsibility log is incomplete. • Some IRB approved staff members are not listed on the delegation log including but not limited to: Alyssa Peechatka, BS; Anja Haile; Arthur Siegel, MD, Ashlee Victoria Vant-Veer, PhD; David Crowley, Elyssa Marie Barrick. • Delegation log did not contain signatures for any study staff members. Due to this, QI and study coordinator were not able to determine who consented the subjects.	Document a list of the appropriately qualified persons to whom significant study-related tasks have been delegated [PHRC Guidance: Principal Investigators and Delegation of Study-Related Tasks to Co-Investigators and Study Staff; GCP 4.1.5]	Ensure all IRB approved study staff are listed on the delegation log. Document which study related procedures each study staff member has been delegated by the PI. Add study staff signatures. The PI should sign and date this log as appropriate. A template can be found at: https://partnershealthcare-public.sharepoint.com/_layouts/WopiFrame.aspx?sourcedoc=%7bB344D765-5E55-42F7-8492-DAB4DA7153F5%7d&file=site-signature-delegation-responsibility-log.doc&action=default Clear delegation log with signatures helps document appropriate delegation of tasks and assists outside reviewer (e.g. FDA)

Observation	Applicable Regulation/Policy/GCP	Corrective Action
		determining who signed the informed consent form.
PI is responsible for ensuring monitoring is occuring to ensure subject safety and data integrity. Documentation for these monitoring activities is incomplete. Protocol states that PI & Co-Is will hold regular meetings to review data integrity and safety concerns. Per discussion with IND Sponsor, meetings occur weekly and study team communicates frequently. No documentation of these meetings found in regulatory binder; however IND Sponsor explained that there are agendas for these meetings.	As IND Sponsor: Must monitor the progress of all clinical investigations conducted under the IND. [21CFR312.56, 21 CFR 312 50] As IND Clinical Investigator: Documentation of study-related activity performed to monitor the study progress and the accuracy and completeness of the study records should be on file.; [21CFR312.62(b); PHRC Guidance: Record Keeping and Record Retention Requirements; GCP 5.18.3]	Ensure that documentation includes all monitoring activities as specified in protocol. Add agendas to regulatory binder or store electronically in easily accessible location. Going forward, agendas should include list of topics and names of attendees. QI recommends implementing a more systematic way to review files for data integrity. Possible methods include study team member reviewing a sample of study documents on a pre-determined schedule (e.g. every month, 2 months) for completeness and accuracy. Also as discussed, another method that some departments use is to have study coordinators from different studies cross-cross-check/review a sample of documents from each others' protocols. Whichever method, document the monitoring activity using a monitoring log (customizable). Template can be found: https://partnershealthcare-public.sharepoint.com/_layouts/15/WopiFrame.aspx?sourcedoc=%7b0A381284-3CBF-471C-9DC6-B988F7A93007%7d&file=monitoring-

Observation	Applicable Regulation/Policy/GCP	Corrective Action
		log.dot&action=default
FDA Financial Disclosure statements for principal and co-investigators are not on file. Not necessary? *Note: The only exception to this FDA requirement is if the Sponsor-Investigator has no intention to take the investigational product for labeling change or marketing approval.*	The sponsor of the IND should obtain financial disclosure statements.[21 CFR 312.53 (c) (4)]	As IND Sponsor, Dr. Pizzagalli, please confirm whether you plan to submit a marketing application in the future or not. If yes, locate and file financial disclosure statements. A template for the FDA Form 3455 is located at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048310.pdf If no, maintaining FDA financial disclosure statements on site are not needed at this time.
FDA Form 1572 found onsite needs updating. The 1572 form that QI found on site appeared to be part of the orginal application and included as sub-investigators: Dan Iosifescu, Maurizo Fava, Nancy Brooks, Sunny Dutra. QI notes that as part of an IND amendment (9/28/10), the cover letter states that David Olson, Breanna Glaser & Andrew Cohen.	A signed investigator statement (Form FDA 1572) containing: the name and address of the investigator, name/code number of the protocol(s) conducted under the IND, names and addresses of research and clinical laboratory facilities, name and address of the reviewing IRB, a commitment by the investigator, and a list of names of the sub-investigators who will be assisting the investigator in the conduct of the investigation should be maintained.[21 CFR 312.53 (c)(1)]	Determine when the last 1572 form was submitted for the site to the FDA and if it does not accurately reflect the current sub-investigators and location in the study, update the form and the IND Sponsor should submit to the FDA as an informational amendment. See FDA guidance on the 1572 form for addtional guidance: http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm214282.pdf
Documentation of study staff training incomplete.	The investigator should ensure that all persons assisting with the trial are	Organize study staff training either by person or by topic to allow potential

Observation	Applicable Regulation/Policy/GCP	Corrective Action
QI found various training documents within the “liscensure” folder. However, given the organization, QI review found it difficult to determine if documentation was complete.	adequately informed about the protocol, the investigational products, and their trial related duties and functions.[PHRC Guidance: Principal Investigator's Responsiblities; GCP 4.2.4]	outside reviewer (e.g. FDA) to determine if all needed training has taken place.

Subject Documentation

Observation	Applicable Regulation/Policy/GCP	Corrective Action
Blank fields and incomplete data entries that do not affect study outcomes were observed throughout the subjects' files. • Subject ID was only on the first and last page of the consent for all reviewed subjects.	An investigator is responsible for maintaining adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62 (b); PHRC Guidance: Record Keeping and Record Retention Requirements; GCP 4.9.1]	Add study ID on every page of the consent form. Do not leave blanks. Study staff also can use pre-printed labels.
Data collection sheets/CRFs are not signed and dated by the person completing the form/procedures. Study staff initials were missing for the following: • Vital signs at MRI session which was done on 9/30/13 for subject ELS 001 • Pregnancy test form for subjects ELS 001 and ELS 007. • C-SSRS form for subject ELS 001	Data collection sheets/CRFs should be signed and dated by the person completing the form/procedures to document that the investigator or authorized member of the investigator's staff confirms the observations recorded.[GCP 8.3.14]	Ensure that all data collection sheets/CRFs are initialed/signed and dated by the person conducting the exam or interview. If current forms do not include a signature and date line, revise the documents to provide these sections.
Handwritten notes on the CRF/data collection sheets are not signed and dated.	The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data.[PHRC Guidance:	Notes on the data collection sheets should be legible, signed and dated. The person writing the note should initial and date it.

Observation	Applicable Regulation/Policy/GCP	Corrective Action
• Handwritten demographic note for subject ELS 007 was not signed and initialed by study staff.	Record Keeping and Record Retention Requirements; GCP 4.9.1]	
Source documentation is not consistently on file to verify study procedures and/or the information in CRFs. • Questionnaires at each study visit were not seen on file for all reviewed subjects. • SCATT task for subject ELS 003 was not seen on file. • There was no documentation of follow up calls. *Note: per study staff follow up phone calls were done, but they did not document this.*	An investigator is responsible for maintaining adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b); PHRC Guidance: Record Keeping and Record Retention Requirements; GCP 4.9.1]	Obtain and file source documentation for each subject. If questionaanires stored in different location write master Note to File indicating the location. If SCATT task was not completed, add this to Minor Deviation log and report to IRB at the next Continuing Review.
Source documentation to verify eligibility is not consistently on file. • Eligibility form was not seen on file for subject ELS 001	An investigator is responsible for maintaining adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b); PHRC Guidance: Record Keeping and Record Retention Requirements; GCP 4.9.1]	All subjects enrolled in a study must have adequate source documentation in their study file that they have been included or excluded appropriately. If source is available to verify this information, document the missing information into the subject's study binder. If not, write a signed and dated note to file to explaining how this eligibility criteria was assessed. The QI Program has developed an eligibility assessment checklist: https://partnershealthcare-public.sharepoint.com/_layouts/WopiFrame.aspx?sourcedoc=%7b3EF5711A-800A-47D7-ACC3-06AA345CB557%7d&file=subject-

Observation	Applicable Regulation/Policy/GCP	Corrective Action
		eligibility-checklist.doc&action=default