THE SECRETARY OF VETERANS AFFAIRS
WASHINGTON

The Honorable Henry Kerner
Special Counsel
U.S. Office of Special Counsel
1730 M Street, NW, Suite 300
Washington, DC 20036

RE: Office of Special Counsel File Nos. DI-16-1945/DI-17-1294

Dear Mr. Kerner:

I am responding to your office's January 14, 2019, request for a supplemental report to provide additional information related to the Department of Veterans Affairs' (VA) supplemental report of January 4, 2018, on the VA San Diego Healthcare System, located in San Diego, California. The purpose of Office of Special Counsel's latest request was to address a new concern communicated by whistleblowers regarding the InTeam study. Specifically, it was alleged that portions of patients' liver biopsy samples intended only for clinical diagnostic use by San Diego's Pathology and Laboratory Medicine Service were taken from patients enrolled in the study by San Diego InTeam personnel for research purposes.

The 2019 VA review also identified that: (1) liver tissue from at least eight participants was placed into the InTeam Consortium Study Project repository; and (2) San Diego interventional radiologists obtained additional liver biopsy samples from patients specifically for the study without effectively verifying whether this was approved by the Institutional Review Board. These issues are addressed in the enclosed supplemental report.

Thank you for the opportunity to respond.

Sincerely,

Robert L. Wilkie

Enclosure

DEPARTMENT OF VETERANS AFFAIRS
Washington, DC

Supplemental Report
to the
Office of Special Counsel

OSC File Numbers DI-16-1945 and DI-17-1294

VA San Diego Healthcare System
San Diego, California

Report Date: July 2, 2019

TRIM 2017-C-8

EXECUTIVE SUMMARY

In April 2017, the Office of the Medical Inspector (OMI), in partnership with the Office of Research Oversight (ORO), led a Department of Veterans Affairs (VA) investigation at the VA San Diego Healthcare System (San Diego) into three whistleblower allegations that were referred by the Office of Special Counsel (OSC) on March 8, 2017. Two of the allegations pertained to non-research clinical care concerns, and one of the allegations pertained to standard of care concerns associated with a San Diego Institutional Review Board (IRB)-approved research protocol titled, "Integrated Approaches for Identifying Molecular Targets in Alcoholic Hepatitis (InTeam)." The research allegation involved a concern that clinically unnecessary liver biopsies were being obtained under the guise of standard of care so that liver tissue could be obtained for the InTeam study. As corollary concerns, it was also alleged that liver biopsy tissue was obtained from subjects enrolled in the study (prospective collection) in violation of the protocol, which (according to the allegation) only permitted the use of tissue samples existing prior to the study, and that patients who enrolled in the study were not informed that their prospectively collected biopsies would be included in the study. These research concerns were not substantiated. However, other issues pertaining to the research were identified during the review and communicated to OSC in July 2017, including findings that: the IRB did not initially utilize qualified clinical consultants to determine if transjugular biopsies were standard of care for the patient cohort to be enrolled in the study; and the Principal Investigator had not adequately maintained research records or trained and supervised staff.

In April 2018, whistleblowers communicated a new specific concern regarding the InTeam study. Specifically, it was alleged that portions of patients' liver biopsy samples intended only for clinical diagnostic use by San Diego's Pathology and Laboratory Medicine Service (PLMS) were taken from patients enrolled in the study by San Diego InTeam study personnel for research purposes. It was alleged that such action constituted noncompliance with the approved study protocol and that the purported reduction in the size of the specimens intended for diagnostic analysis by PLMS could compromise the ability to conduct said analysis. San Diego leadership initiated an internal investigation that did not substantiate these allegations (i.e., no portions of biopsy samples obtained for clinical diagnostic purposes were diverted for research purposes). Instead, the San Diego investigation established (San Diego IRB Report, dated October 19, 2018) that additional (extra) biopsy samples were collected specifically for research purposes from nine patients enrolled in the San Diego InTeam study. The IRB determined that the collection of additional biopsy samples specifically for research constituted serious noncompliance with the approved protocol, which only allowed the study team to be provided with excess diagnostic tissue, i.e., leftover tissue obtained, but not needed, for diagnostic purposes. A second biopsy, which involved inserting a needle into the liver a second time, would be associated with an increased risk of bleeding or other complication.

The IRB further found that San Diego InTeam subjects had neither been informed that additional (extra) biopsy samples would be collected specifically for research purposes

nor informed of the additional risks associated with collecting an additional biopsy sample for research.

On November 2, 2018, OSC closed its case pertaining to the allegations referred to VA in March 2017, and issued a letter to the President indicating that OSC found aspects of VA's findings to be unreasonable. Specifically, OSC indicated that it continued to have concerns about whether transjugular biopsies were standard of care for patients enrolled in the InTeam protocol, and that liver specimens were prospectively collected from enrolled subjects for purposes of the study even though the approved protocol purportedly only allowed the use of liver tissue existing prior to the start of the research.

Based on OSC's residual concerns and the San Diego IRB's new noncompliance finding, OMI and ORO conducted an additional review of the research protocol. This review included: a site visit at San Diego on January 14–17, 2019; an analysis of documentary evidence; and interviews with San Diego personnel involved with the review, approval, and conduct of the research protocol, clinicians who conducted liver biopsy procedures or clinical diagnostic analysis of liver tissue from patients enrolled in the research protocol, and the whistleblowers. The review focused on assessing: (1) whether liver biopsies were clinically appropriate for the subset of patients who enrolled in the InTeam study at San Diego and received such biopsies; (2) whether the approved protocol allowed research use of excess liver tissue prospectively obtained from the enrolled subjects (versus tissue samples existing prior to the research study); and (3) newly identified evidence of extra liver biopsy samples having been obtained solely for purposes of research and in violation of the approved study protocol.

The 2019 OMI-ORO joint review (2019 VA review) reconfirmed the 2017 determination that the approved San Diego InTeam research protocol permitted excess liver tissue remaining after clinical diagnostic use to be provided for the study, even if the biopsy procedure to obtain said tissue had been performed after the research protocol approval date (prospective collection of tissue sample). The 2019 VA review also independently validated San Diego's internal investigation findings that additional (extra) liver tissue was obtained from enrolled subjects specifically and solely for research purposes; those subjects were not appropriately informed of the additional risks of taking an extra biopsy sample specifically and solely for research purposes; and that obtaining the additional tissue constituted a serious deviation from the approved research protocol. The 2019 VA review did not substantiate the allegation that the separate liver biopsy specimens designated specifically for clinical diagnostic analysis by PLMS were intercepted or compromised by San Diego InTeam study personnel.

In addition to substantiating noncompliance with the approved process for obtaining liver tissue for the research protocol, the 2019 VA review also identified that: (1) liver tissue from at least eight participants was placed into the InTeam Consortium Study Project repository; and (2) San Diego interventional radiologists obtained additional liver biopsy samples from patients specifically for the study without effectively verifying whether this was approved by the IRB.

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I. Introduction

The Office of the Medical Inspector (OMI), Veterans Health Administration (VHA), independently investigates issues related to quality of care, including those arising from evaluations of particular cases and programs. The Office of Research Oversight (ORO), VHA, oversees Department of Veterans Affairs (VA) research program compliance with respect to human subject protections, laboratory animal welfare, research safety and laboratory security, research information security, and research misconduct.

OMI and ORO conducted a joint on-site review at the VA San Diego Healthcare System (San Diego) on January 14–17, 2019, (2019 VA review). This review supplemented previous investigatory activities, including a previous site visit conducted at San Diego on April 10–13, 2017, led by OMI with ORO staff participation (2017 VA review). The 2017 VA review was prompted by an Office of Special Counsel (OSC) referral of allegations to VA on March 8, 2017. Two of the allegations pertained to non-research clinical care concerns, and one of the allegations pertained to standard of care concerns associated with a San Diego Institutional Review Board (IRB)-approved research protocol titled, "Integrated Approaches for Identifying Molecular Targets in Alcoholic Hepatitis (InTeam)." The research allegation involved a concern that clinically unnecessary liver biopsies were being obtained under the guise of standard of care so that liver tissue could be obtained for the study. It was further alleged that liver specimens were prospectively collected from enrolled subjects for purposes of the study even though the approved protocol purportedly only allowed the use of liver tissue samples existing prior to the start of the research, and that patients who enrolled in the study were not informed that their prospectively obtained biopsies would be used for the study. The research concerns were not substantiated. However, other issues pertaining to the research were identified during the review and communicated to OSC in July 2017, including findings that: the IRB did not initially utilize qualified clinical consultants to determine if transjugular biopsies to confirm alcoholic hepatitis was the standard of care; and the Principal Investigator (PI) had not adequately maintained research records or trained and supervised staff.

The 2019 VA review described here was precipitated, in part, by OSC's concerns about aspects of some findings from the 2017 VA review. Specifically, in a letter to the President, dated November 2, 2018, OSC expressed continuing concerns about whether transjugular biopsies were a standard of care procedure for the patient cohort enrolled in the San Diego InTeam study, and whether the approved study protocol allowed research use of excess liver tissue prospectively obtained from the enrolled subjects (versus tissue samples existing prior to the research study). The 2019 VA review was also precipitated by an October 11, 2018, IRB determination that a serious deviation from the approved San Diego InTeam study protocol had occurred; namely, that additional (extra) biopsy samples were collected from subjects specifically and solely for research purposes, instead of any excess tissue from samples obtained for clinical purposes, as required by the study protocol.

Based on the concerns raised by OSC with regard to the findings of the 2017 VA review, and the October 11, 2018, San Diego IRB serious noncompliance determination, OMI and ORO jointly conducted a follow-up review of the San Diego InTeam study. Specifically, the 2019 VA review focused on assessing:

- Whether biopsies were clinically appropriate for the subset of patients who enrolled in the study and received such biopsies;

- Whether the approved protocol allowed research use of excess liver tissue prospectively obtained from the enrolled subjects (versus tissue samples existing prior to the research study); and

- Newly identified evidence of extra liver biopsy samples having been obtained solely for purposes of research and in violation of the study protocol.

II. Method of Review

The VA team conducting the investigation consisted of the Medical Inspector and two Clinical Program Managers, all from OMI; and the Executive Director, and four staff members certified in Health Research Compliance, all from ORO.

VA's on-site review at San Diego included interviews of facility research leadership, the Research Compliance Officer (RCO), IRB Chair and Vice Chair, other IRB voting members, Research Service administrators, the Chief of Pathology and Laboratory Medicine Service (PLMS), staff pathologists, Interventional Radiology staff, and current and former members of the San Diego InTeam research team. The VA team examined documents associated with the review, approval, and conduct of the San Diego InTeam protocol including: San Diego IRB application materials, correspondence, and meeting minutes; investigators' protocol records; research participants' medical records, signed informed consents, and HIPAA authorizations; San Diego RCO audit records; VHA and San Diego policies regarding human subjects research and use of pathology services; clinical guidelines for the management of alcoholic liver disease; OMI reports; OSC communications; and the whistleblowers' allegations.

Entrance and exit briefings were held with San Diego leadership on January 14 and January 17, 2019, respectively. The whistleblowers were interviewed separately and in person on January 15 and January 16, 2019, at San Diego.

The following employees participated in the Entrance Briefing:

- Veterans Integrated Services Network (VISN) 22 Deputy Quality Management Officer (by phone)
- Medical Center Director (MCD)
- Chief of Staff (CoS)
- Associate Director, Patient Care Services/Nurse Executive
- Assistant Director
- Associate Director

- Chief of Performance Improvement Management Service (PIMS)
- Program Specialist, Peer Review Coordinator for PIMS

The following current and former San Diego employees were interviewed:

- Current PI for the San Diego InTeam study
- Former PI for the San Diego InTeam study (former San Diego employee) (by phone)
- IRB Chair
- IRB Vice Chair
- Two IRB Members
- CoS
- Associate Chief of Staff for Research and Development (ACOS/R&D)
- Director of the Research Projects Section
- RCO
- Chief of PLMS
- Pathologist
- Staff Pathologist
- Staff Physician, Interventional Radiology Section
- Two Interventional Radiologists (former San Diego employees)
- Two Registered Nurses (RN), Interventional Radiology Section
- Two Former San Diego InTeam Study Coordinators
- Clinical Research Associate
- Director of Liver and Transplantation Clinics
- Former Chair of the San Diego Subcommittee on Research Safety (SRS) (former San Diego employee)

The following employees participated in the Exit Briefing:

- VISN 22 Deputy Quality Management Officer (by phone)
- MCD
- CoS
- Associate Director, Patient Care Services/Nurse Executive
- Assistant Director
- Associate Director
- Chief of PIMS
- Program Specialist, Peer Review Coordinator for PIMS

III. Background

VA Facility

San Diego is a complexity level 1a care facility academically affiliated with University of California San Diego (UCSD). San Diego operates a research program involving human subjects, laboratory animals, and hazardous agents, with a research project (direct cost) budget of approximately $42.2 million in Fiscal Year (FY) 2018, of which approximately $20.3 million was provided by VHA's Office of Research and Development (ORD).[1] The Veterans Medical Research Foundation (VMRF) provides a flexible funding mechanism for non-VA sponsored research at San Diego.

At the time of VA's review, there were 563 active research protocols conducted by 205 PIs, including 424 studies involving human subjects. The research portfolio included studies on spinal cord injury; traumatic brain injury; chronic and neuropathic pain; cardiovascular, pancreatic, kidney, lung, and liver disease; substance abuse; mental health; and oncology.

San Diego maintains its own Research and Development Committee, IRB, Institutional Animal Care and Use Committee (IACUC), SRS, and Institutional Biosafety Committee (IBC). San Diego has also executed a memorandum of understanding to utilize the VA Central IRB (CIRB) as an IRB of record for participation in multi-site studies.

San Diego has a Federal-wide Assurance (FWA) for the Protection of Human Subjects (Assurance #FWA00001893 expiring January 15, 2024,) on file with the Department of Health and Human Services (HHS), Office for Human Research Protections (OHRP).

Integrated Approaches for Identifying Molecular Targets in Alcoholic Hepatitis (InTeam) Study

The InTeam Consortium Study Project was funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), a division within the National Institutes of Health (NIH).[2] The InTeam Consortium Study Project Leader was a physician who was affiliated with the University of North Carolina at Chapel Hill (UNC) at the time of initial funding for the project.[3] The consortium of participating sites involved 12 locations, including seven locations in the U.S.[4] San Diego was one of those participating sites. The former PI, who was the Chief of Gastroenterology at San Diego, served as the PI for the San Diego InTeam study until he retired from San Diego in mid-2018. A Co-Investigator on the San Diego InTeam study subsequently assumed PI responsibilities for the

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[1] Data from the facility's filed Research and Development Information System (RDIS) report.
[2] Project #1U01AA021908, Molecular Subtypes for Targeted Therapies in Alcoholic Hepatitis.
[3] At the time of initial funding for the project, the Project Leader was affiliated with, and the coordinating site for the consortium was located at, the University of North Carolina at Chapel Hill. At the time of the 2019 VA review, the Project Leader was affiliated with, and the coordinating site for the consortium was located at, the University of Pittsburgh.
[4] Per an electronic message from the InTeam Project Leader to a member of the 2019 VA review team, dated February 18, 2019, and additional information available at ClinicalTrials.gov (see https://clinicaltrials.gov/ct2/show/NCT02075918).

study.[5, 6] VMRF functioned as the subaward subrecipient (Subaward #0059011 (130258-11)) on behalf of San Diego for funding associated with those research activities of the project that were conducted at San Diego.

The objective of the InTeam Consortium Study Project was "the creation of an extensive Human Biorepository Core that contains biospecimens from patients with alcoholic hepatitis, together with a comprehensive database."[7] The InTeam Consortium Study Project sought to prospectively include patients between the ages of 18 and 70 years of age with active alcohol abuse and clinical indications of alcoholic hepatitis.[8, 9]

San Diego IRB Review and Approval of the InTeam Protocol

The San Diego InTeam protocol, covering those aspects of the InTeam consortium project to be performed at San Diego pertaining to data and biospecimen collection, was initially submitted for Research and Development Committee review on December 4, 2012.[10] After an initial pre-review, the protocol was routed for review by several Research and Development Committee subcommittees, including the San Diego IRB. The IRB discussed the proposed protocol during four convened meetings. On February 14, February 21, and February 28, 2013, the IRB deferred additional review pending "major revisions" and clarifications concerning several aspects of the proposed study, including whether transjugular biopsies were standard of care for the patients to be enrolled in the study.[11] On March 6, 2013, the convened IRB reviewed a resubmission of the protocol, and based on the revisions and PI clarifications, determined that the research represented minimal risk to human subjects, and approved the protocol with a required, "minor correction to documentation" (modification).[12] The IRB approved the required modification on March 12, 2013.[13] The Research and Development Committee reviewed and approved the protocol on

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[5] Documented in the San Diego IRB meeting minutes, dated June 14, 2018.

[6] The new San Diego InTeam PI was also the lead PI for the InTeam Consortium Study-associated project, "Microbiota as Therapeutic Targets in Alcoholic Hepatitis."

[7] Per the "Background and Rationale" section of the "UNC (master) Protocol (Version 1.0)," dated September 26, 2012, included by the San Diego InTeam PI in a March 4, 2013, resubmission to the San Diego IRB.

[8] Prospective research involves collection of materials (data, documents, records, or specimens) from subjects during the study period.

[9] Per the "Inclusion/exclusion criteria" section of the "UNC (master) Protocol (Version 1.0)," dated September 26, 2012, InTeam Master Protocol [200.0B 7/21/2014], InTeam Master Protocol [300.1B, 11/7/2016], and InTeam Master Protocol [300.1C 9/5/2017].

[10] Documented in San Diego Protocol Application 1.7.

[11] Documented in the San Diego IRB meeting minutes, dated February 14, February 21, and February 28, 2013.

[12] Based on a clarification from the PI that liver biopsies would be performed if and as warranted for clinical care (e.g., to guide treatment decisions and/or when confirmatory histological diagnosis is clinically necessary), the "IRB determined that the research presents minimal risk to human subjects in that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests." San Diego IRB meeting minutes dated March 6, 2013.

[13] Subsequently, documented in the San Diego IRB meeting minutes, dated March 21, 2013.

March 20, 2013, on which date the San Diego InTeam protocol became approved VA research.[14, 15]

2017 OSC Referral of Allegations to VA

On March 8, 2017, OSC referred three allegations to VA.[16] The allegations were:

- "[The San Diego Chief of Gastroenterology] is performing unapproved human liver research, without informed consent, that places patients at serious risk;
- "[The San Diego Chief of Gastroenterology] is not properly advising patients of their options, thereby delaying proper care; and
- "[The San Diego Chief of Gastroenterology] directed San Diego staff to delete pending consults without proper medical review or follow-up, in violation of VHA clinical policy and, in some cases, information security policy."

2017 VA Review of Allegations Referred by OSC

The Acting Under Secretary for Health requested that OMI assemble and lead a VA team to investigate the allegations referred by OSC. The VA team conducted a site visit at San Diego on April 10-13, 2017, and issued a report of its findings on July 10, 2017. This report was subsequently transmitted by the VA Chief of Staff to OSC on July 20, 2017.

The research allegation involved a concern that a clinically unnecessary liver biopsy procedure was being performed on patients under the guise of standard of care (for clinical diagnostic purposes) so that excess liver tissue remaining after clinical analysis could be obtained for the study. It was further alleged that liver specimens were prospectively collected from enrolled subjects for purposes of the study even though the approved protocol purportedly only allowed the use of liver tissue existing prior to the start of the research, and that patients who enrolled in the study were not informed that their prospectively obtained biopsies would be used for the study. Through interviews with the named whistleblowers in OSC's March 8, 2017, referral letter to VA, and a review of San Diego's research portfolio, the 2017 VA review determined that the research allegation pertained to the San Diego InTeam study.

The 2017 VA review did not substantiate the research concerns as alleged.[17] VA established that: (1) the San Diego InTeam protocol was approved by required

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[14] Documented in the San Diego Research and Development Committee meeting minutes, dated March 20, 2013, and in a memorandum from the ACOS/R&D to the PI dated March 21, 2013.

[15] Per VHA Handbook 1200.01, Research and Development Committee (version dated June 16, 2009) §4.d, "[o]nce R&D Committee approval has been given, the research becomes VA approved research."

[16] OSC letter, dated March 8, 2017, to the Secretary of VA with subject line of "OSC File Nos. DI-16-1945 and DI-17-1294."

[17] Documented in the July 10, 2017, VA Report to OSC, OSC File Numbers DI-16-1945 and DI-17-1294 (report transmitted July 20, 2017).

review committees prior to the conduct of research procedures at San Diego; (2) the IRB-approved San Diego InTeam protocol allowed the research use of excess liver biopsy tissue remaining from biopsies conducted prospectively (i.e., after the research was initiated) for clinical diagnostic purposes in the course of participants' clinical care; (3) research participants or their legally authorized representative (LAR) had provided signed informed consent for participation in the study; (4) the IRB-approved research informed consent document (ICD) informed participants that a portion of their liver specimens obtained in the course of their clinical care could be made available for the San Diego InTeam study; and (5) transjugular biopsies performed on a subset of participants enrolled in the study at San Diego were clinically indicated, as determined by a review of the participants' medical records. However, other issues pertaining to the study were identified by the VA team, including findings that: The San Diego IRB did not initially utilize qualified clinical consultants to determine if transjugular biopsies were standard of care for the patient cohort to be enrolled by the San Diego InTeam protocol and the San Diego InTeam study PI had not adequately maintained research records or trained and supervised staff. These concerns were documented in VA's report transmitted to OSC on July 20, 2017.

2018 VA Supplemental Report to OSC

On October 16, 2017, OSC requested that VA provide clarifications regarding the 2017 VA report. Specifically, OSC requested additional information pertaining to VA's review of the research-related allegation, including aspects related to transjugular biopsies being clinically warranted, and whether the approved protocol permitted only "on the shelf" liver biopsy specimens (i.e., those obtained prior to IRB approval and initiation of the research) to be provided for San Diego InTeam use.

On January 4, 2018, VA transmitted a supplemental report to OSC.[18] With regard to transjugular biopsies, VA's response indicated that "in the [InTeam protocol] patient population, the transjugular [liver biopsy] approach is considered safe and well-tolerated, and is generally the first-line option for patients in whom the percutaneous [liver biopsy] approach is suboptimal, contraindicated, or has failed." VA also reaffirmed its concern regarding the San Diego IRB's initial approval of the InTeam protocol in the absence of the IRB having appropriate expertise about whether transjugular biopsies constituted standard of care in patients with alcoholic hepatitis, and, in the absence of such expertise, failure of the IRB to consult with an appropriate qualified consultant. Regarding the clarification on the liver biopsy samples that could be provided for the study under the approved protocol, VA reaffirmed in its response that "the [San Diego] IRB record reflects approval of surplus [liver] tissue obtained prospectively for clinical purposes."

OSC Letter to the President

In a November 2, 2018, letter to the President, OSC concluded that VA's findings —

[18] VA Supplemental Report to the Office of Special Counsel (OSC), San Diego VA Medical Center, San Diego, California, OSC File Nos DI-16-1945, DI-17-1294, dated December 26, 2017.

that transjugular biopsies are standard of care for the InTeam patient cohort, and that the approved protocol permitted the use of liver tissue obtained prospectively during the course of enrolled subjects' clinical care — were unreasonable.

New Allegation and San Diego IRB Findings

Independent of the issuance of OSC's letter to the President in the fall of 2018, ORO received a notification from San Diego personnel on October 25, 2018, indicating that the San Diego IRB had made a serious noncompliance determination regarding the San Diego InTeam protocol.[19] This determination was based on the results of a San Diego investigation into a new allegation, the aspects of which are described below.

In April 2018, one of the whistleblowers who was a source of the allegations referred by OSC to VA in 2017, communicated a new research concern to the San Diego ACOS/R&D.[20] Specifically, the whistleblower alleged that liver biopsy samples were "being acquired [under the guise of excess standard of care] BEFORE they have been used and fully accessed by Pathology for standard of care." The whistleblower asserted the following:

> "For a liver biopsy this is malpractice as well as a violation of the IRB as it does change the size of the sample that is available to Pathology and size is one of the limitations of being able to achieve a diagnosis and hence standard of care. If the sample that [is received by] Pathology is too small, then a diagnosis can't be made. The Radiologist cannot make this decision. The PI has made the decision in this case, reducing the size of the biopsy being made available to Pathology and so compromising the patient care."

On May 14, 2018, the San Diego CoS tasked the San Diego IRB with investigating the new allegation.[21]

The IRB did not substantiate the overarching concern, as alleged, that San Diego InTeam study personnel compromised liver biopsy specimens intended for clinical diagnostic purposes through reduction of the diagnostic specimen size.[22] However, of even greater concern, the IRB did identify (apart from the allegation) that additional (extra) liver biopsy samples were obtained from nine San Diego InTeam participants specifically for research purposes. The IRB re-affirmed that the approved protocol only

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[19] VHA Handbook 1058.01 §4.s. Serious Noncompliance. Serious noncompliance is any failure to adhere to requirements for conducting human research that may reasonably be regarded as: (1) Presenting a genuine risk of substantive harm to the safety, rights, or welfare of human research subjects, research personnel, or others, including their rights to privacy and confidentiality of identifiable private information; or (2) Substantively compromising a facility's [Human Research Protection Program (HRPP)]."

[20] Per an electronic message from the whistleblower to the San Diego Director, Associate Director, COS, ACOS/R&D, and RCO, the OSC, and UCSD staff, dated April 26, 2018.

[21] A voting member of the IRB, the Director of the Research Projects Section, and an IRB coordinator conducted the review on behalf of the IRB. The review findings were communicated to the IRB in a draft report dated October 11, 2018.

[22] San Diego IRB report dated October 19, 2018, "Inquiry of Concerns Human Subject Research Protocol H120108."

permitted use of leftover (excess) clinical diagnostic liver tissue. The IRB further determined that the research ICD for the study neither informed subjects that additional liver tissue would be obtained for research purposes nor informed subjects of any additional risks related to obtaining additional liver tissue for research purposes.[23]

Based on its findings, the convened IRB determined that serious noncompliance had occurred.[24] The IRB's findings, determinations, and recommendations were summarized in a report dated October 19, 2018. Although not an original recommendation of the IRB, the Director of San Diego subsequently concluded that "direct communication with the study participants was warranted."[25] On February 13, 2019, in accordance with VHA Directive 1004.08, Disclosure of Adverse Events to Patients, San Diego leadership sent notifications regarding the protocol violation to the living San Diego InTeam participants that underwent liver biopsies.[26]

Through information gathered during its review, VA established this chronology of events:

December 4, 2012: An initial version of the San Diego InTeam protocol was submitted for review by relevant San Diego Research and Development Committees.

January 9, 2013: The ACOS/R&D forwarded the San Diego SRS Chair's concerns regarding the San Diego InTeam protocol to the administrator tasked with scheduling pending reviews and requested that the Chair be added as an "Ad Hoc Reviewer" to the IRB, or that her comments alternatively be incorporated "at the scientific review stage."[27, 28]

February 14, 2013: "The [convened San Diego] IRB discussed the biopsy procedures at length and debated whether or not this may be considered standard of care. The issue remained unresolved after discussion. The IRB could not make a final determination concerning this protocol…" The IRB required "major revisions" and clarifications regarding characterization of transjugular biopsies as standard of care and references to use of "archival" samples.[29]

February 21, 2013: The convened San Diego IRB was informed that the SRS had shared review comments from its initial review on February 13, 2013. The IRB minutes

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[23] Per the San Diego IRB meeting minutes, dated October 19, 2018: "Specifically, the committee found that archival samples were not being obtained for use in research as indicated in the approved protocol. Instead, a sample, independent of the clinical sample, was being provided for research purposes without being processed through the [San Diego] Pathology laboratory. The nine affected subjects completed the study between September 2014 through December 2016. The consent form signed by the subjects informed that if a liver biopsy specimen would be obtained for their routine clinical care, a portion of that biopsy may be collected for research. The consent form did not identify if additional cores would be taken or if additional risks would be present."

[24] Documented in the San Diego IRB meeting minutes, dated October 11, 2018.

[25] Per an electronic message from the San Diego Director to a member of the 2019 VA review team, dated November 29, 2018.

[26] Per an electronic message from the San Diego Chief of PIMS to a member of the 2019 VA review team, dated February 25, 2019. VHA Directive 1004.08, *Disclosure of Adverse Events to Patients*, dated October 2, 2012.

[27] Documented in an electronic message from the ACOS/R&D dated January 9, 2013.

[28] The San Diego SRS Chair subsequently became a whistleblower who referred allegations to OSC.

[29] Documented in the San Diego IRB meeting minutes, dated February 14, 2013.

documented a decision to "review the protocol, and consider the SRS comments, when a response to the prior deferral is submitted."[30]

February 28, 2013: The convened San Diego IRB requested additional clarifications regarding use of "archival liver biopsy samples" and characterization of liver biopsies as standard of care.[31]

March 1, 2013: The San Diego SRS approved the protocol.[32]

March 6, 2013: The convened San Diego IRB reviewed the San Diego InTeam protocol PI's response to the IRB's requested clarifications of February 28.[33] "The IRB concurred with [the PI's] response" and approved the protocol pending minor corrections.

March 12, 2013: Through an expedited review, a revised version of the San Diego InTeam protocol, which incorporated IRB-requested corrections, was approved.[34]

March 20, 2013: The San Diego Research and Development Committee reviewed and approved the San Diego InTeam protocol, resulting in the study becoming approved San Diego research.[35]

March 21, 2013: The San Diego ACOS/R&D communicated Research and Development Committee and subcommittee approvals to the PI.[36]

February 3, 2014: Informed consent was obtained from the first human research participant (#P001) who agreed to enroll in the San Diego InTeam study.[37]

September 23, 2014: Informed consent was obtained from San Diego InTeam participant #P004 who was the first subject from whom a prospectively obtained liver specimen was sent to the InTeam Consortium Study Project repository.[38]

December 1, 2016: Informed consent was obtained from San Diego InTeam participant #P020 who was the last subject from whom a prospectively obtained liver

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[30] Documented in the San Diego IRB meeting minutes, dated February 21, 2013.
[31] Documented in the San Diego IRB meeting minutes, dated February 28, 2013.
[32] Documented in the San Diego Research and Development Committee meeting minutes, dated March 20, 2013.
[33] The San Diego InTeam PI's response, as documented in the San Diego IRB meeting minutes dated March 6, 2013, was as follows: "The protocol application was clarified to reflect that liver biopsies are not part of this specific protocol. If liver biopsies are done it is with the expectation that they are done by the clinicians only according to the standard clinical judgment of the clinicians and is done when treatments are considered, and establishment of the proper histologic diagnosis is required. Clinicians are encouraged to follow standard practice guidelines in terms of making decisions regarding liver biopsies. This applies to cases related to severe alcoholic hepatitis as per the guidelines (American Academy for the Study of Liver Diseases 2010 and European Association for the Study of the Liver 2012)."
[34] Documented in the San Diego IRB meeting minutes, dated March 21, 2013.
[35] Documented in the San Diego Research and Development Committee meeting minutes, dated March 20, 2013.
[36] Documented in a San Diego ACOS/R&D memorandum to the San Diego InTeam PI, dated March 21, 2013.
[37] Per multiple San Diego InTeam study records, including ICDs and the "InTeam Updated Patient Log 2018," last saved on April 12, 2018. Also, documented in a San Diego RCO Informed Consent Audit Checklist, dated June 12, 2014.
[38] Per multiple San Diego InTeam study records, including ICDs and the "InTeam Updated Patient Log 2018," last saved on April 12, 2018. Also, documented in a San Diego RCO Informed Consent Audit Checklist, dated April 13, 2015.

specimen was sent to the InTeam Project Consortium Study Project repository.[39]

March 8, 2017: OSC referred to VA a whistleblower disclosure containing three allegations made against the San Diego Chief of Gastroenterology. One of the allegations was primarily focused on the clinical appropriateness of transjugular biopsies that were the source of liver specimens for the San Diego InTeam study, and two of the allegations pertained to other clinical care concerns that did not involve research.[40]

April 10-13, 2017: The 2017 VA review team conducted a site visit to San Diego.

July 20, 2017: The 2017 VA review team's report, dated July 10, 2017, was transmitted by the VA Chief of Staff to OSC.[41]

October 16, 2017: OSC requested that VA submit a supplemental report providing additional clarifications on the July 10, 2017, report and a status update on recommendations contained in the report.

January 4, 2018: The Executive in Charge, VHA Office of the Under Secretary for Health transmitted VA's supplemental report, dated December 26, 2017, to OSC.[42]

February 28, 2018: Informed consent was obtained from the last human research participant (P022) enrolled in the San Diego InTeam protocol.[43]

April 26, 2018: One of the original whistleblowers submitted a new allegation that portions of liver biopsy specimens obtained from patients enrolled in the study were taken by San Diego InTeam study personnel for research purposes prior to the biopsy specimens being delivered to Pathology for clinical diagnostic use as intended. It was alleged that such action constituted noncompliance with the approved study protocol and that the purported reduction in the size of the specimens intended for diagnostic analysis could compromise the ability to conduct said analysis.[44]

May 14, 2018: The San Diego CoS requested that the IRB investigate the whistleblower's concern.[45]

May 23, 2018: The San Diego IRB requested that the PI "refrain from enrolling new

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[39] Per multiple San Diego InTeam study records, including ICDs and the "InTeam Updated Patient Log 2018," last saved on April 12, 2018. Also, documented in a San Diego RCO Informed Consent Audit Checklist, dated June 15, 2017.

[40] OSC letter, dated March 8, 2017, to the Secretary of VA with subject line of "OSC File Nos. DI-16-1945 and DI-17-1294."

[41] VA Report to the Office of Special Counsel, OSC File Numbers DI-16-1945 and DI-17-1294, dated July 10, 2017. Transmittal cover letter dated July 20, 2017.

[42] VA Supplemental Report to the Office of Special Counsel (OSC), San Diego VA Medical Center, San Diego, California, OSC File Nos DI-16-1945, DI-17-1294, dated December 26, 2017. Transmittal cover letter dated January 4, 2018.

[43] Per multiple San Diego InTeam study records, including ICDs and "InTeam Updated Patient Log 2018," last saved on April 12, 2018.

[44] Per an electronic message from the whistleblower to the San Diego Director, Associate Director, COS, ACOS/R&D, and RCO, the OSC, and UCSD staff, dated April 26, 2018.

[45] Documented in a letter from the San Diego COS, who on that date was also Acting San Diego Director, to the Chair, IRB, dated May 14, 2018.

subjects or obtaining new biological specimens for this research study."[46]

June 14, 2018: The IRB approved a change in PI for the San Diego InTeam study, from the former PI to the current PI.[47]

October 11, 2018: The convened San Diego IRB reviewed the IRB investigative team's finding that additional (extra) liver biopsy samples were obtained specifically for research purposes. The IRB determined that this represented serious noncompliance as the approved study protocol only allowed for any leftover (excess) clinical diagnostic liver tissue to be provided for the study.[48]

October 19, 2018: The San Diego IRB finalized its report, "Inquiry of Concerns, Human Subject Research Protocol H120108."

October 25, 2018: For the first time, San Diego notified ORO of the new allegations received by San Diego personnel in April 2018, the findings from San Diego's investigation into the allegations, and the San Diego IRB's serious noncompliance determination.[49]

October 31, 2018: San Diego notified HHS-OHRP of the IRB serious noncompliance determination.[50]

November 2, 2018: Temporally coincident with the San Diego IRB's issuance of its report, OSC issued a letter to the President outlining lingering concerns with the 2017 VA review and supplemental information provided by VA.[51]

November 26, 2018: The San Diego Director expanded the IRB hold on San Diego InTeam protocol activities to include "recruitment and other non-clinically necessary activities" pending completion of ongoing compliance reviews.[52]

November 29, 2018: The San Diego Director informed ORO that affected San Diego InTeam participants would be notified of the protocol deviations.[53]

November 30, 2018: San Diego InTeam protocol funding ended.[54]

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[46] Documented in a San Diego IRB memorandum to the San Diego InTeam PI and co-Investigator, dated May 23, 2018.

[47] Documented in San Diego InTeam Human Protocol Amendment (Version 11.0), dated March 29, 2018, and San Diego IRB meeting minutes, dated June 14, 2018.

[48] Documented in the San Diego IRB meeting minutes, dated October 11, 2018.

[49] Per an electronic message with attachment from the San Diego Director of the Research Projects Section to ORO, dated October 25, 2018.

[50] Per an electronic message with attachment from the San Diego Director of the Research Projects Section to OHRP, dated October 31, 2018.

[51] OSC letter, dated November 2, 2018, to the President with subject line of "OSC File Nos. DI-16-1945 and DI-17-1294." Letter indicated that OSC found aspects of VA's response to the original allegations to be unreasonable.

[52] Per an electronic message from the San Diego Director to a member of the 2019 VA review team, dated November 26, 2018.

[53] Per an electronic message from the San Diego Director to a member of the 2019 VA review team, dated November 29, 2018.

[54] Per the San Diego InTeam PI's "IRB Protocol Closure" request dated March 6, 2019: "Funding for this study ended on November 30, 2018. All sites were closed to enrollment and are undergoing closeout procedures." It is further noted that November 30, 2018, date was also indicated in Amendment 2, FDP Research Subaward Agreement (0059011 (130258-11)), dated July 16, 2018, as the projected date for funding to end.

December 6, 2018: The San Diego IRB notified the study sponsor that the San Diego IRB had made a human research related noncompliance finding.[55]

January 14-17, 2019: The 2019 VA review team, comprised of representatives from OMI and ORO, conducted a follow-up site visit to San Diego.

February 2019: Letters, dated February 13, 2019, were sent to four living San Diego InTeam participants (#P004, P007, P018, and P019) notifying them of study noncompliance pertaining to the unconsented collection of an additional liver biopsy sample for research purposes.[56]

March 5, 2019: The San Diego IRB approval for the San Diego InTeam protocol expired.[57]

April 11, 2019: The San Diego IRB approved the closure of the San Diego InTeam protocol.[58]

IV. Concerns, Findings, Conclusions, and Recommendations

A. U.S. Office of Special Counsel Concern Regarding VA's Assertion That Transjugular Biopsies Are Standard of Care for the Patient Cohort Enrolled in the San Diego InTeam Study.

As indicated in its letter to the President, dated November 2, 2018, OSC found VA's previous assertion that transjugular biopsies are the standard of care for the patients eligible for enrollment in the InTeam study to be "unreasonable." Specifically, OSC stated in its letter that "the VA asserted that transjugular biopsies are the standard of care for these patients but failed to adequately reconcile this finding with the fact that, prior to the research protocol, no transjugular biopsies were performed at San Diego." OSC further indicated that "[i]f, as the VA states, transjugular biopsies are the standard of care, this leaves open the important question of how the standard of care was met prior to the initiation of the research project."

Findings

In 2010, the American Academy for the Study of Liver Diseases published guidelines stating that liver biopsy was not necessary in alcoholic liver disease, but was useful in establishing a diagnosis. More recently, in January 2018, the American College of Gastroenterology published a clinical guideline on alcoholic liver disease describing the need for a liver biopsy to confirm the diagnosis of alcoholic hepatitis as an "area of controversy." However, as alcoholic liver disease progresses, liver biopsies may become more important in the staging of cirrhosis.

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[55] Per an electronic message with attachments from the San Diego Director of the Research Projects Section to NIAAA, dated December 6, 2018.

[56] Per an electronic message from the San Diego Chief of PIMS to a member of the 2019 VA review team, dated February 25, 2019, notifications were sent to "all living study participants who had a liver biopsy that contributed to the study."

[57] Documented in a San Diego IRB memorandum to the San Diego InTeam PI, dated March 7, 2019.

[58] Per an electronic communication from the San Diego Director of the Research Projects Section to a member of the 2019 VA review team, on April 12, 2019.

As such, the standard of care for alcoholic liver disease may include getting a liver biopsy; therefore, performing a transjugular biopsy would not violate the standard of care. VA's assertion that performing a transjugular biopsy on these patients met standard of care is not the same as stating that only a transjugular biopsy would meet the standard of care.

Liver biopsies are conducted to diagnose liver disease, and to assist with determining the most appropriate treatment for a patient. Physicians perform different types of liver biopsies depending on the needs of the patient. The most common type of liver biopsy is a percutaneous liver biopsy, which involves inserting a needle through the abdomen into the liver. Other types include a transjugular biopsy (inserting a tube into the jugular vein and passing it down through the vein into the liver) and a laparoscopic biopsy, where a small abdominal incision is made into the abdomen. Whether or not to perform any liver biopsy on a specific patient is a clinical decision, made based on the patient's condition, co-morbidities, and wishes regarding his or her health care.

Liver biopsies are generally safe procedures, but may be associated with a number of risks, such as bleeding, infection, or accidental injury to another organ, regardless of the type of biopsy used. The choice of one technique over another may be based on availability, personal preference, and the clinical situation. Transjugular biopsies also have additional risks such as development of a hematoma (collection of blood) in the neck, injuries to facial nerves, voice problems, or a lung puncture.

In addition, specific limitations associated with the type of biopsy may govern which biopsy technique is considered best for a specific patient. For example, a patient with a focal liver lesion would not usually be a candidate for transjugular biopsy because the physician would not necessarily be able to reach the focal liver lesion through the jugular vein. Finally, the experience of the physician with a certain biopsy technique may also play a role in the selection of a specific procedure.

Variations in physician experience and patient need for a certain biopsy technique likely explain disagreements among the San Diego clinical staff regarding what constitutes "standard of care." The former PI maintained that transjugular biopsies were the best practice – or "standard of care" – in diagnosing alcoholic liver disease, even though San Diego had never performed this procedure before on this group. Our review of several patients' electronic medical records includes documentation that following the initial use of transjugular biopsies, one of the whistleblowers also ordered this type of biopsy for patients with alcoholic or other types of liver disease. This contradicts his claims that these types of liver biopsies are never indicated. Further review of the former PI's recommendations for transjugular biopsies indicated that, on at least seven occasions, he overruled colleagues who did not recommend this procedure. The medical literature does not definitively establish a preferred biopsy technique for diagnosing alcoholic liver disease because, as previously stated, the preferred technique varies depending on other health conditions of the patient. The VA investigative team made arrangements for each of the cases to be objectively reviewed through an external peer review. These reviews are ongoing and were not able to be completed during this investigative period. Actions to be taken, if any, will be

determined in accordance with the Management Review section of VHA Directive 1190, Peer Review for Quality Management, and VHA Notice 2018-05, Amendment to VHA Handbook 1100.18, Reporting and Responding to State Licensing Boards.[59]

Conclusion

- Transjugular liver biopsies are the standard of care for the types of patients enrolled in the San Diego InTeam Study; however, the specific clinical case needs to be reviewed in order to determine if and what type of biopsy should be pursued. The term standard of care does not equate to the provision of the medical treatment for all patients Actions to be taken, if any, will be determined in accordance with the Management Review section of VHA Directive 1190, Peer Review for Quality Management, and VHA Notice 2018-05, Amendment to VHA Handbook 1100.18, Reporting and Responding to State Licensing Boards.

Recommendation to San Diego

None.

B. U.S. Office of Special Counsel Concern Regarding VA's Assertion That the Approved Study Protocol Allowed Research Use of Excess Liver Tissue Prospectively Obtained from the Enrolled Subjects (Versus Tissue Samples Existing Prior to the Research Study).

As indicated in its letter, dated November 2, 2018, OSC raised concern about VA's assertion that the IRB-approved San Diego InTeam protocol allowed the research use of excess liver tissue from clinical biopsies obtained prospectively (i.e., after the study was initiated). As indicated in OSC's letter, the basis for this concern was that the protocol indicated the study team would be provided with "archival" liver biopsy tissue, and that one of the whistleblowers asserted that "VA's own definition of archival [is] obtained prior to the approval and initiation of any research..."

Findings

Based on both the documentary and testimonial evidence presented below, the 2019 VA review reaffirms the 2017 VA review conclusion that the whistleblower's assertion is misplaced.

The convened San Diego IRB approved the San Diego InTeam protocol on March 6, 2013.[60] At the time of approval, the IRB requested minor corrections to the protocol, and a revised version of the protocol incorporating the requested corrections was approved via expedited review on March 12, 2013.[61] The approved protocol

[59] VHA Directive 1190, Peer Review for Quality Management, November 21, 2018. VHA Notice 2018-05, Amendment to VHA Handbook 1100.18, Reporting and Responding to State Licensing Boards, February 5, 2018.
[60] Documented in the San Diego IRB meeting minutes, dated March 6, 2013.
[61] Documented in the San Diego IRB meeting minutes, dated March 21, 2013.

stated that "[i]f the patients have a liver biopsy in the course of their routine care, we request that we have access to archival tissue samples for further studies only" (emphasis added).[62] The accompanying approved research ICD stated: "If you agree to be in the study, the following will happen to you:...If a liver biopsy is done this will be part of your routine care to make sure of the diagnosis and not part of the research process. However, if available, a portion of this sample may be collected for research purposes" (emphases added).[63] The research ICD further stated that "[i]f liver biopsy specimen are obtained as part of routine clinical care, a portion of this biopsy may be collected for research."[64] Notably, these statements in the protocol and the ICD did not use the past tense in referring to the biopsy procedure from which the liver tissue would be obtained for the study. It is further noted that obtaining patients' informed consent to participate in the study and enrolling patients into the study occurred after the study protocol was approved. Thus, at the time when subjects provided consent to participate in the study, they were being notified (via the research informed consent process) that the study allowed excess liver tissue to be obtained for the study if a liver biopsy procedure is going to be performed as part of the clinical care that they would receive after their enrollment in the study.

OSC's concern was based on the use of the term "archival" to qualify the liver biopsy samples that would be provided for the study. The 2019 VA review specifically assessed for the local San Diego understanding and use of the term "archival." Interviews with San Diego staff revealed that the term was used colloquially at San Diego to refer to tissue that was leftover (in excess) and/or no longer needed by San Diego PLMS for clinical diagnostic purposes. For example, during questioning by the 2019 VA review team about the San Diego staff's understanding of the meaning of "archival" tissue:

- The San Diego IRB Chair, a physician, stated: "So basically 'archival' would mean that it is tissue that is obtained for a clinical purpose. [The tissue is taken] to pathology. Pathology makes their determinations and their studies. And once it's 'left over,' quote-unquote, that's what the archival tissue would be defined as. And so, the understanding would be that the investigator would obtain it from pathology after pathology was done with it."[65]

- The San Diego IRB Vice Chair, a physician, stated: "So archival samples by its very nature is that it is taken from pathology...[Sample] goes through the pathology lab...After they are done with whatever diagnoses they make, there's always spare, or there's other things which you can use for research purposes."[66]

- A member of the San Diego IRB, a pharmacist, stated: "[A]rchived biopsies [meant that] after pathology looked at the samples, and [they] decided that they didn't need

[62] Documented in a revised version of the San Diego InTeam protocol, approved March 12, 2013. This statement appears in protocol sections 5, 9, 9.6, and 9.7.
[63] This statement appears in Section 3 of San Diego InTeam ICD, approved March 12, 2013.
[64] This statement appears in Section 4 of San Diego InTeam ICD, approved March 12, 2013.
[65] Transcript from January 15, 2019, interview with the San Diego IRB Chair (W.P.) (page 19).
[66] Transcript from January 15, 2019, interview with the San Diego IRB Vice-Chair (S.M.) (pages 6 and 7).

all of it, the rest is saved. That was our definition of archived samples."[67]

- The San Diego RCO, a scientist, stated: "I thought we kind of understood that [archival samples are] samples that were processed through laboratory medicine and are no longer required. That's my understanding. There was some discussion I think at the IRB meeting of making sure we both have an agreement that's what we meant. I think that everyone pretty much understands archival means submitted to the lab and then made available afterwards."[68]

- The San Diego Chief of PLMS, a physician who heads the clinical service line responsible for processing and analyzing clinical diagnostic samples at San Diego, stated: "Once [a sample] comes into pathology, any tissue that's processed into a block, a paraffin block, that gets archived as part of the pathology...So generally, [a sample] comes to the clinical lab. We review it. There's enough tissue. If it's wet tissue, we usually look at real time, and then [researchers] take a portion of it if we find out we have enough diagnostic material. But if there isn't, then we're going to take the whole thing for diagnosis first. And then anything left over is stored in the paraffin blocks after processing, [researchers] can have some of that."[69]

Thus, as indicated by interviews with a broad array of San Diego staff involved in clinical and research activities, the term "archival" was used colloquially, and commonly understood and used at San Diego to refer to processed clinical diagnostic samples that are left over or no longer needed by San Diego PLMS, rather than to tissues harvested and stored prior to the start of any given research study.

OSC's November 2, 2018, letter also referenced an assertion made by one of the whistleblowers that VA's own definition of archival means: obtained prior to the approval and initiation of any research.[70] The VA review team was unable to identify a specific San Diego policy that defines archival samples in terms of when clinical diagnostic samples are obtained in relation to the start of a research study. A review of San Diego Memorandum 113-03, "Specimen Collection and Processing,"[71] which established policies and procedures for collecting and processing laboratory specimens at San Diego, did not identify a definition for, or any other reference to, the term "archival." Further, individuals interviewed during the review were unable to identify a specific local policy or training document that defined "archival" with regard to clinical diagnostic samples. A review of VHA Handbook 1106.01, "Pathology and Laboratory Medicine Service (PLMS) Procedures," which sets forth VHA nationwide procedures for pathology services, similarly did not identify a definition for, or any other reference to,

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[67] Transcript from January 14, 2019, interview with San Diego IRB member (S.F.) (page 8).
[68] Transcript from January 15, 2019, interview with San Diego RCO (H.K.) (page 19).
[69] Transcript from January 15, 2019, interview with the San Diego Chief of PLMS (J.W.R.) (pages 14-16).
[70] OSC's reference to such an assertion appears to be based, at least in part, on a February 27, 2018, letter to OSC, in which one of the whistleblowers stated: "The definition of archival is also very clear from all the human research training that all researchers are responsible to know. Archival means already obtained for either clinical or previous research purposes ('on the shelf') prior to any initiation of research on this protocol."
[71] Versions of the memorandum that were in effect at various times during the course of the study and reviewed by the 2019 VA review team included versions issued on August 13, 2012, July 9, 2014, May 4, 2016, and April 19, 2017.

the term "archival" in the context of clinical diagnostic samples.[72, 73] It is further noted that during an interview with the whistleblower who previously indicated to OSC that "archival" meant samples already obtained prior to the initiation of research, the whistleblower stated that: "[W]hen you get samples from pathology, you have to sign them out…[a]nd that ensures that they are archival…Of all samples that make it to pathology...[an individual in the San Diego PLMS who acts as a 'gatekeeper'] only gets them after the diagnosis is made and they are archived, meaning the clinicians are finished with them for now."[74] Thus, the whistleblower expressed a similar understanding to that of San Diego staff interviewed – that the term "archival" was used to refer to clinical diagnostic samples that are no longer needed by the San Diego PLMS.

Regardless of how the meaning of "archival" samples may be construed beyond the common understanding that was held by IRB members and the Chief of PLMS, documentary evidence establishes that the San Diego IRB approved the San Diego InTeam protocol with a clear understanding that the protocol allowed for the research use of any excess liver tissue prospectively obtained from enrolled subjects who underwent the liver biopsy procedure in the course of their clinical care. This evidence includes the following documents related to the IRB's review of the San Diego InTeam protocol:

- The San Diego IRB meeting minutes, dated February 14, 2013, indicated: "The IRB could not make a final determination concerning [the InTeam] protocol and requests correction, revision, and additional information as follows: clarify if 'archival' samples are those in existence prior to this protocol application or those that may be obtained on enrolled subjects."

- In response to the IRB request for clarification, the PI submitted a response to the IRB, dated February 25, 2013,[75] informing the committee that: "'[A]rchival specimens' are those that are obtained on subjects as part of routine care and are stored in pathology laboratory. These can consist of specimens that have been obtained previously as well as specimens that are obtained as part of routine care after the patient is enrolled."

- The San Diego IRB meeting minutes, dated February 28, 2013, documented that "the investigator [has] indicated that 'archival samples' could theoretically be

[72] VHA Handbook 1106.01, dated October 6, 2008, did reference the term "archived" and "archiving," respectively, in the contexts of computer software and records management. A subsequent version of the Handbook, dated January 29, 2016, referenced the term "archived" and "archive," respectively, in the contexts of computer software and diagnostic electron microscopy digital images.

[73] A member of the 2019 VA review team also spoke on March 14, 2019, with the VHA National Director of PLMS (M.I.), the individual who has responsibility for VHA Handbook 1106.01. In that conversation, the Director indicated that he was unaware of a formal definition in VHA policy for "archival" in the context of clinical diagnostic samples and further indicated that his familiarity with the use of the term within VHA was in the context of records management.

[74] Transcript from January 15, 2019, interview with whistleblower (M.B.) (pages 24-25).

[75] "San Diego HRPP Program – Response to IRB," dated February 25, 2013.

collected as part of standard of care for a patient while they [sic] are consented in the study, and that the biopsy would be used for research."

Thus, during its review of the San Diego InTeam protocol, the San Diego IRB requested and received unambiguous clarification that the study team was proposing to obtain excess liver tissue from patients who underwent a liver biopsy procedure as part of their standard of care after enrollment in the study. With the knowledge of this clarification, which was documented in the IRB's meeting minutes, the IRB subsequently approved the study at a convened meeting on March 6, 2013.

Conclusion

- As approved by the San Diego IRB, the San Diego InTeam protocol allowed for excess liver tissue – designated as "archival" tissue – to be provided for the study even if said tissue was obtained from liver biopsies performed after the study was approved. Correspondingly, the 2019 VA review reaffirms the 2017 VA review conclusion on this issue.

Recommendation to San Diego

None.

C. New Whistleblower Allegation of Research Noncompliance Involving Acquisition of Extra Liver Biopsy Tissue Specifically for the San Diego InTeam Study.

In late April 2018, a new allegation regarding the process for obtaining liver biopsy tissue for the San Diego InTeam study was communicated to San Diego leadership.[76] In that communication, one of the original whistleblowers alleged that portions of liver biopsy specimens designated for clinical diagnostic analysis were taken from the specimens prior to analysis by PLMS and provided to San Diego InTeam study personnel for research use. The whistleblower expressed concern that reducing the size of biopsies before use by PLMS could compromise the clinical diagnostic analysis, and hence, patient care. In May 2018, the San Diego CoS tasked the IRB with investigating the new concerns.[77]

Findings

The San Diego IRB review did not substantiate the whistleblower's assertion that the study team had reduced the size of those liver biopsy specimens collected for

[76] Per an electronic message from the whistleblower to the San Diego Director, Associate Director, COS, ACOS/R&D, and RCO, the OSC, and UCSD staff, dated April 26, 2018.

[77] The IRB investigation involved review of applicable VHA and San Diego policy documents, protocol documents, IRB records, and electronic medical records. The IRB investigative team interviewed the San Diego InTeam PI and study coordinator, a San Diego interventional radiologist that had performed some of the liver biopsies for patients enrolled in the San Diego InTeam study, and the Chief of PLMS.

diagnostic purposes.[78] Correspondingly, the IRB also did not substantiate the related concern that San Diego InTeam study practices had compromised PLMS' ability to make a clinical diagnosis. Nevertheless, the IRB's review established (unrelated to the whistleblower's allegation) that the San Diego InTeam study was not conducted as approved. Specifically, the IRB found that the San Diego InTeam study team had not obtained excess (left over) liver tissue for the study from PLMS following PLMS' analysis of the tissue (as required by the approved study protocol). Instead, the IRB found that San Diego interventional radiologists obtained additional (extra) liver biopsy samples specifically for the San Diego InTeam study, and that the samples obtained for research purposes were in addition to specimens obtained for clinical diagnostic purposes.[79] The IRB further established that patients were not appropriately informed via the research ICD that extra biopsy samples would be obtained specifically for research purposes and of the added risk associated with taking an additional biopsy sample for research purposes.[80]

On October 11, 2018, the convened IRB determined that "collecting non-archival samples constituted serious noncompliance."[81] The IRB required that the PI amend the San Diego InTeam protocol and ICD to accurately describe collection of a research specimen separate from the clinical specimen, and describe the risks associated with collection of the additional research specimen. The IRB concurrently determined that "additional risks [from the collection of the additional research samples] were not substantial, and there were no documented complications for any of the participants."

As part of the scope of the 2019 VA review, the OMI-ORO review team conducted a de novo independent examination of the aforementioned concern investigated by the San Diego IRB in 2018.

2019 VA Review

Identification of San Diego InTeam Study Participants

The 2017 VA review established that research records for the San Diego InTeam study were poorly maintained and incomplete.[82] This was reaffirmed by, and also hampered, the 2019 VA review. For example, San Diego InTeam study personnel maintained individual binders for participants; however, San Diego personnel were unable to locate study binders requested by the 2019 VA review team for three participants (study

[78] San Diego IRB report dated October 19, 2018, "Inquiry of Concerns Human Subject Research Protocol H120108." "The [IRB] review did not substantiate the [whistleblower] concern that a portion of the clinical sample was provided for research purposes prior to use by Pathology [PLMS] for standard of care diagnostic purposes."

[79] San Diego IRB report dated October 19, 2018, "Inquiry of Concerns Human Subject Research Protocol H120108." "Instead, the IRB found that a research specimen was obtained independent of the clinical sample after the [interventional radiology (IR)] surgeon determined that a sufficient specimen was obtained for clinical purpose."

[80] San Diego IRB report dated October 19, 2018, "Inquiry of Concerns Human Subject Research Protocol H120108." "Nevertheless, the IRB found that the neither [sic] protocol nor ICD adequately described the collection of the research specimen independent of the clinical specimen."

[81] Documented in the San Diego IRB meeting minutes, dated October 11, 2018.

[82] Documented in the July 10, 2017, VA Report to OSC, OSC File Numbers DI-16-1945 and DI-17-1294.

participants #P001, P002, and P003).[83] Further, although required by local policy, the PI had not maintained a master list of all participants that provided consent to participate in the San Diego InTeam study.[84] Specifically, it was identified during the 2019 VA review of study documents provided by San Diego that the PI had omitted non-alcoholic healthy controls ("H" subjects) from the master list of study participants. The PI had instead only retained a listing of suspected alcoholic hepatitis patients ("P" subjects), alcohol use disorder controls ("C" subjects), and screen failures.[85]

In the absence of a complete PI-maintained master list of participants, the 2019 VA review included the development of an investigative master listing of San Diego InTeam participants. The investigative listing of study participants was amalgamated from several PI versions of the San Diego InTeam subject log, signed ICDs, RCO audit records, and biospecimen logs provided by the InTeam Consortium Study Project Leader.[86] Based on the synthesis of information from various source documents, the 2019 VA review team identified that the San Diego InTeam study enrolled: (i) 22 suspected alcoholic hepatitis patients ("P" participants) referenced in San Diego InTeam records as participants P001 through P022, and an additional two suspected alcoholic hepatitis patients who provided consent to participate in the study but were identified in study records as screen failures; (ii) 19 alcohol use disorder control patients ("C" participants) referenced in study records as participants C001 through C019; and (iii) 18 non-alcoholic healthy controls ("H" participants) referenced in study records as participants H001 through H0018. The 2019 VA review also identified 54 patients who were screened but did not consent to study participation, and who were referenced in San Diego InTeam study records as screen failures.[87]

Identification of San Diego InTeam Study Participants from Whom Study Personnel Received Liver Biopsy Samples

The San Diego IRB's 2018 noncompliance report concluded that additional (extra) liver biopsy samples were obtained from nine (9) "P" subjects for research purposes without their consent.[88] However, neither the IRB's report, the minutes of the meeting in which

the report was reviewed by the IRB, nor San Diego's noncompliance report to ORO identified the nine specific subjects from whom the extra biopsy samples were obtained specifically for research purposes. During the course of its review, the 2019 VA review

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[83] It was suggested in an electronic message from the current San Diego InTeam protocol PI to the San Diego Peer Review Coordinator, dated January 23, 2019, that adequate records were not retained for participants #P001, P002, and P003 because, after obtaining their informed consent, it was established that these patients were screen failures as they did not meet inclusion/exclusion criteria (i.e., steroid use, and biopsies did not confirm clinically suspected alcoholic hepatitis).

[84] Specifically, the "Standard Operating Policies and Procedures for the San Diego Institutional Review Board and Human Research Protection Program," dated March 4, 2015, and amended September 28, 2017 stated: "The investigator must maintain a master list of all subjects for whom informed consent has been obtained."

[85] Per the "InTeam Updated Patient Log 2018," last saved on April 12, 2018.

[86] The 2019 VA review team identified several discrepancies in information across these documents.

[87] The San Diego InTeam PI's "screen fail" listing included patients that "refused to participate."

[88] San Diego IRB report dated October 19, 2018, "Inquiry of Concerns Human Subject Research Protocol H120108." "Research Records documented that the PI had obtained liver biopsy specimens from 9 of the 22 subjects with alcoholic hepatitis between September 2014 and December 2016."

team requested, and San Diego personnel subsequently provided, the study participant identification numbers for the nine subjects (study participants P004, P005, P006, P010, P012, P016, P018, P019, and P020).[89]

The 2019 VA review independently identified that 13 of the 22 patients identified as "P" participants in the San Diego InTeam alcoholic hepatitis study underwent liver biopsies within close temporal proximity to providing consent to participate in the study (including, but not limited to, the nine subjects whose extra sample was determined by the San Diego IRB investigation to have been obtained for research purposes).[90, 91] The study participant identification numbers of these 13 patients were as follows: P001, P002, P003, **P004, P005, P006**, P007, **P010, P012**, P016, **P018, P019**, and **P020**. The 2019 VA review further identified that of the 13 "P" participants that underwent a liver biopsy, liver tissue from eight participants (**bolded and underlined in the preceding sentence**) was reported as received by the InTeam Consortium Study Project repository.[92]

Although the 2019 VA review team identified eight subjects from whom a liver biopsy sample was provided for the San Diego InTeam study, the review team could not make a definitive conclusion as to whether a research biopsy sample had been obtained from a ninth subject (P016) and provided for the San Diego InTeam study. Participant P016 was one of the nine participants from whom the San Diego IRB originally concluded a

liver biopsy sample had been obtained and provided for the San Diego InTeam study. However, the InTeam Consortium Project repository did not have a record of receiving

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[89] Per an electronic message from the San Diego Director of the Research Projects Section to the San Diego Chief of PIMS, dated January 14, 2019.

[90] Methodology used to establish liver biopsy status: San Diego InTeam study records were reviewed and information obtained from the InTeam Consortium Study Project repository regarding liver biopsy samples received from San Diego. Further, an electronic medical record review was conducted for the 22 "P" participants identified as having been included as a "suspected alcoholic hepatitis patient" in the San Diego InTeam protocol. For each "P" patient, the date of InTeam consent was cross referenced with any report of liver biopsy listed in the "Imaging" (local only) field under the "Health Summary" heading on the "Reports" tab. This report incorporates any liver biopsy documented in the medical record to have occurred 7 days prior and up to 90 days after the date of InTeam consent. NOTE: All 13 biopsy procedures identified as part of this review occurred within a range of 7 days before to 7 days after the date of San Diego InTeam study consent. Additional detail and confirmation of the biopsy procedures was obtained by reviewing: Reports tab, under the Anatomic Pathology heading, liver biopsy specimen reports. Consults tab, Interventional Radiology Consults and any associated Pathology Surgical Consults. Notes tab, provider notes were reviewed for content related to liver biopsy procedures. Liver biopsy Informed Consent Discussion Progress Notes were reviewed, with additional detail sought via Vista Imaging Display for review of scanned documents, as necessary. Orders tab, liver biopsy associated orders were reviewed using the Custom Order View, ALL Orders, All Services, with the "Only list orders placed during time period" option. Specifically, Imaging, Nursing and Consult orders were reviewed.

[91] Table 1 provides additional detail.

[92] Methodology used to establish receipt of specimens by the InTeam Consortium Study Project repository: The InTeam Consortium Project Leader provided an inventory of specimens received from San Diego. The inventory, last updated by the InTeam Consortium Project Leader on December 11, 2018, included subject identification and subject biospecimen codes. The 2019 VA review team compared the InTeam Consortium Study Project repository codes against the San Diego InTeam subject logs to identify the individual subjects associated with the liver specimens documented as received by the repository. Through this process the 2019 VA review team established that the liver specimens reported by the InTeam Consortium Project Leader as having been received by the consortium repository corresponded to San Diego InTeam participants P004, P005, P006, P010, P012, P018, P019, and P020.

a liver biopsy sample from this participant.[93] It is further noted that the medical record for this patient indicated that three biopsy passes were performed and three samples ("fragments") provided to PLMS. Although this evidence suggests that a research-specific biopsy sample may not have been obtained from this participant, the review team notes that a "Liver Tissue" collection date, which for other participants reflected acquisition of liver tissue for the InTeam Consortium Study Project repository, was recorded for this subject in the "InTeam Updated Patient Log 2018," and a "yes" response was also entered in this same log in the column for "Liver Tissue: Frozen."[94] (Subsequent to the 2019 VA review team's site visit to San Diego, the review team was provided with an internal San Diego correspondence indicating that San Diego personnel no longer believe that an extra biopsy sample was obtained specifically for research purposes from this participant).[95]

Inconsistent medical record documentation and incomplete San Diego InTeam protocol records confounded the 2019 VA review team's efforts to conclusively rule in or rule out whether the other four enrolled "P" participants who received a liver biopsy (P001, P002, P003, and P007)[96] had their biopsy tissue provided to the San Diego InTeam study. For example, by cross-referencing confirmed instances of samples being provided for the study (based on tissue being received by the repository) against interventional radiology procedure notes, the 2019 VA review team established that obtaining liver tissue for research use was inconsistently documented in the medical record. This inconsistency limited the ability to draw firm conclusions on whether a sample had been provided to the San Diego InTeam study.

As noted previously, the San Diego InTeam staff had either failed to establish or had not retained adequate study records for three participants (P001, P002, and P003). The former San Diego InTeam PI had assured the San Diego IRB that liver samples were not collected for the San Diego InTeam study from these patients.[97] However, a research coordinator note in the "InTeam Updated Patient Log 2018" stated

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[93] It is the 2019 VA review team's understanding that at the time of the San Diego IRB investigation, the IRB was unaware of the discordance between the information in the San Diego study team documentation and that maintained by the InTeam Project Consortium repository.

[94] Per the "InTeam Updated Patient Log 2018," last saved on April 12, 2018. Entries in the "Liver Tissue: Frozen" column could not be used to conclusively establish that a sample was obtained for research as the column also included a "Yes" entry for subject P011, a patient that did not have liver biopsy (liver biopsy was planned but canceled).

[95] Per an electronic message from the San Diego Director of the Research Projects Section to the San Diego Chief of PIMS, dated March 21, 2019, "One subject (P016) had a clinical biopsy, but no research sample was obtained. This was confirmed by review of medical records that document three samples were taken by IR and pathology records that confirm three samples were received. Noted that the IRB's report included this subject as one of nine originally thought to have had a research biopsy taken."

[96] In a letter dated February 13, 2019, San Diego notified participant P007 that, "[A]t the time of your liver biopsy, an additional liver sample was collected primarily for research purposes and was given directly to the research team." However, per an electronic message from the San Diego Director of the Research Projects Section to the San Diego Chief of PIMS, dated January 14, 2019, this individual was not one of the nine participants referenced in the IRB's noncompliance report. The 2019 VA review team alerted San Diego of the apparent discrepancy in the communication to participant P007.

[97] A March 26, 2014, progress report from the PI to the IRB included the statement, "We have submitted the continuing review for this project, and from January through February 2014 we recruited our first 3 patients for this study [P001, P002 and P003]. Each subject was evaluated for alcoholic hepatitis and had liver biopsies as part of routine hospital evaluation. The only samples collected from these patients were stool samples."

ambiguously that a "Biopsy [was] done for regular care [of participant P003], sample not retained for InTeam use."[98]

The 2019 VA review also considered the whistleblowers' assertion that liver biopsies were required from all participants because the "parent protocol of the InTeam described the liver biopsy as indispensable for any other collections (blood and stool) for the biorepository."[99, 100, 101] The 2017 and 2019 VA reviews did not substantiate the whistleblower allegations that liver biopsies were required from all participants. Furthermore, there were nine "P" participants (P008, P009, P011, P013, P014, P015, P017, P021, P022) enrolled in the San Diego InTeam study for whom the review team did not identify any evidence of a liver biopsy being performed around the time of research recruitment.[102] The 2019 VA review also established from a review of study records that if a liver biopsy was not obtained for any particular subject, the study team continued with collection of other research specimens from that subject.

Conclusion

- Liver tissue from biopsies performed on at least eight "P" participants was obtained for the San Diego InTeam study.

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[98] This notation was included in the "InTeam Updated Patient Log 2018," last saved on April 12, 2018.

[99] The whistleblowers provided VA a letter dated December 4, 2018, that they sent to OHRP in which the whistleblowers asserted that, "The liver biopsy was REQUIRED for all the materials obtained from the subjects (liver, blood, and stool) to be acceptable into the Biorepository." During a January 16, 2019, interview whistleblower M.C. also stated that "The situation, the protocol states unequivocally that the biopsy is not required. This is a big lie." During a January 16, 2019, interview whistleblower WB1 clarified that he learned of the "requirement" after the 2017 VA review from his examination of documents on the Web site clinicaltrials.gov. ClinicalTrials.gov Identifier: NCT02075918; 1U01AA021908-01 [U.S. NIH Grant/Contract].

[100] It is acknowledged that the InTeam Consortium Study Project master protocol section concerning the care of patients suspected of having alcoholic hepatitis could have led to a mistaken impression that study participation required liver biopsies of all such subjects. Specifically, the master protocol included a statement that, "Although the existence of [alcoholic hepatitis (AH)] can be highly suspected based on clinical and analytical criteria, a definitive diagnosis requires histological confirmation. A liver biopsy is particularly indicated in patients with other potential causes (eg. concomitant cocaine consumption, positive [antinuclear antibody (ANA) titer], suspicion of [drug induced liver injury (DILI)], etc) and when there are some atypical clinical or analytical features." However, the 2019 VA review established, from review of global InTeam biopsy participation rates, that biopsies were not required of all such subjects. The InTeam Consortium Study Project also did not describe liver biopsies as indispensable for any other biorepository collections.

[101] During a January 16, 2019, interview with the VA review team, one of the whistleblowers WB2 described concerns about "28 subjects that had liver biopsies." This report acknowledges that two lines in VA's Supplemental Report included errors that may have contributed to the presumption that 28 San Diego InTeam participants had undergone liver biopsies. Specifically, the Supplemental report included the statements, "At the time of our report, the Medical Center had enrolled 84 Veterans in the InTeam study since 2013. Of the 84, only 28 had transjugular biopsies." The statement concerning total enrollment was incorrect. As of the time of the report, the San Diego InTeam PI had represented that 83 (not 84 as stated in the report) patients had been either enrolled or screened for enrollment into the San Diego InTeam protocol. Additionally, the statement concerning the total number of San Diego InTeam participant transjugular biopsies was incorrect. The referenced "28 [that] had transjugular biopsies" represented the total number of transjugular biopsies conducted by the facility (between October 1, 2012, and April 1, 2017,) irrespective of the InTeam study.

[102] A medical record review also confirmed that the two San Diego InTeam "screen failures" who consented to study participation but were subsequently found to have not met inclusion criteria and/or met exclusion criteria, did not undergo liver biopsies.

Recommendation to San Diego

None.

Process by Which Liver Biopsy Samples Were Obtained for the San Diego InTeam Study

The 2019 VA review investigated the process by which the San Diego InTeam study team obtained liver biopsy samples. The 2019 VA review also investigated the Interventional Radiology Section's role in the conduct of unapproved research procedures.[103] In addition, the 2019 VA review investigated whistleblower allegations that San Diego InTeam study team practices had compromised PLMS's ability to make diagnoses.

The San Diego IRB's 2018 investigation established from interviews with the former San Diego InTeam PI and study coordinator that fresh, unfixed liver tissue specimens were obtained for the study directly from the San Diego Interventional Radiology Section rather than from PLMS.[104] The 2019 VA review team also confirmed this based on interviews it conducted with a San Diego interventional radiologist,[105] Interventional Radiology Section nurses,[106, 107] and the former San Diego InTeam PI. Notably, when the former San Diego InTeam PI was asked, "Specifically with respect to the biopsies [provided to the San Diego InTeam study team], do you recall where the biopsies would have been collected?," he responded that these "Biopsies are collected by the interventional radiology physicians."[108] However, this practice conflicted with information that the PI provided to the San Diego IRB in 2013. Specifically, the San Diego protocol submitted by the PI to the San Diego IRB for review and approval indicated in protocol Sections 5 and 9 that "[i]f the patients have a liver biopsy in the course of their routine care, [the San Diego study team] request[s] that [the study team has] access to archival tissue samples for further studies only." Protocol Section 10 indicated "[t]he protocol assures that archival liver biopsy tissue from patients is only used..."[109] As established by the 2019 VA review team (and described previously in this report), the term "archival" was commonly understood and used colloquially at

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[103] Methodology used to review communication gaps between Interventional Radiology Section and research: The 2019 VA review received testimonial evidence from: both the current and prior San Diego InTeam PIs; the COS; the ACOS/R&D; the Chief of PLMS; two pathologists that conducted clinical diagnostic assessments of liver samples obtained from San Diego InTeam participants; three of the four interventional radiologists that performed liver biopsies on the 13 San Diego InTeam participants identified as having undergone a liver biopsy; two Interventional Radiology nurses; two prior San Diego InTeam study coordinators; the IRB Chair; and members of the IRB's investigative team.

[104] San Diego IRB report dated October 19, 2018, "Inquiry of Concerns Human Subject Research Protocol H120108." "The PI and study coordinator confirmed that for the nine specimens obtained for this study, all were obtained directly from IR [Interventional Radiology Section]. Therefore, these were not archival samples as indicated in the IRB approved protocol since clinical testing had not been completed."

[105] Transcript from January 14, 2019, interview with San Diego interventional radiologist Employee 1 (page 19).

[106] Transcript from January 16, 2019, interview with a San Diego Interventional Radiology Section nurse Employee 2 (pages 7-8).

[107] Transcript from January 16, 2019, interview with a San Diego Interventional Radiology Section nurse Employee 3 (page 11).

[108] Transcript from January 16, 2019, interview with the former San Diego InTeam PI Employee 4 (page 10).

[109] Documented in San Diego InTeam Human Protocol (Version 1.8), dated March 11, 2013, approved by expedited IRB review on March 12, 2013.

San Diego to refer to processed clinical diagnostic samples that are left over or no longer needed by San Diego PLMS. It is further noted that documentary evidence indicated that the PI had a similar understanding of the meaning of the term "archival." Specifically, in response to the IRB's pre-approval request for a clarification about the nature of the archival biopsy samples that were proposed to be obtained for the study, the PI submitted a response informing the IRB that: "'[A]rchival specimens' are those that are obtained on subjects as part of routine care and are stored in pathology laboratory."[110] Thus, in contrast to the information the PI provided to the IRB and that formed the understanding of what the IRB subsequently approved, the PI did not obtain excess (archival) tissue samples from PLMS. Instead, the San Diego InTeam study personnel obtained fresh (unfixed) liver samples directly from Interventional Radiology. The San Diego IRB's 2018 investigation also established that the San Diego Interventional Radiology Section obtained liver samples specifically for research purposes and that samples were obtained above and beyond those needed for clinical diagnostic purposes by PLMS. The 2019 VA review team also confirmed this based on interviews it conducted with a San Diego interventional radiologist[111] and an Interventional Radiology Section nurse.[112] This practice of obtaining additional samples specifically for research purposes conflicted with information the former San Diego InTeam PI provided to the San Diego IRB when the study protocol was under review by the IRB in 2013. Specifically, in correspondence included with a March 4, 2013, revised protocol submission to the IRB, the PI indicated that "we will access archival liver biopsy tissue only if the biopsy was obtained as part of routine clinical care...[n]o tissue specimens are obtained for research purposes only."[113] Thus, in contrast to the information the PI provided to the IRB and that formed the understanding of what the IRB subsequently approved, additional biopsy samples were obtained solely for research purposes from patients enrolled in the study and who underwent the biopsy procedure as part of their care.

During an interview with the 2019 VA review team, the former PI explained that he unilaterally implemented a process for directly retrieving specimens from the San Diego interventional radiologists to resolve "integrity of the research" "RNA analysis" concerns.[114] However, the PI acknowledged never having discussed the "integrity of

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[110] "San Diego HRPP Program – Response to IRB," dated February 25, 2013.

[111] Transcript from January 14, 2019, interview with San Diego interventional radiologist Employee 1 (page 18). "[W]e take the amount that's for diagnostic purposes and we'll get an extra core for research...."

[112] Transcript from January 16, 2019, interview with a San Diego Interventional Radiology Section nurse Employee 2 (page 20). "[W]e always did the extra [liver biopsy] pass on his research people."

[113] The PI's statement was included in "Additional remarks from investigator 2/13/2013 (Version 1.0)," an attachment to "IRB Review Response Form (Version 2.0)," dated March 4, 2013. The PI's correspondence to the IRB acknowledged the IRB's questions regarding Human Protocol (Version 1.6) and summarized the corresponding modifications incorporated in Human Protocol (Version 1.7).

[114] Transcript from January 16, 2019, interview with the former San Diego InTeam PI Employee 4 (pages 17-18). "It's just that I'm very concerned about the integrity of the research. These small samples -- again, 1 millimeter is what was required. It's needed for RNA analysis, and we could possibly get them after pathology processing. I was concerned that would be degraded and not representative of the other sites in the nation...So, I reviewed the risks and benefits on both sides. The risks of going through all this trouble and not getting an adequate specimen so you can't make research decisions sort of goes against the purpose of what the patient had signed up for and what the -- you know, investigators and ultimately what I believe society is interested in. So, those are sort of, you know, the balances that were under consideration."

research" concern with PLMS.[115] The PI further acknowledged having made the San Diego InTeam liver tissue collection arrangements directly with Interventional Radiology Section staff.[116] Interventional Radiology Section staff also recalled having directly transferred liver biopsy tissue to San Diego InTeam staff.[117, 118] Regardless of the PI's motivations, the San Diego InTeam study personnel's failure to conduct the research as approved represented a deviation from the protocol and noncompliance with VA policy.[119]

The 2019 VA review also found that the Interventional Radiology Section had not used an effective process to verify that the collection of an additional biopsy sample specifically for research purposes was described in the San Diego InTeam protocol and approved by the San Diego IRB. Specifically, none of the Interventional Radiology Section staff interviewed recalled having received or reviewed the San Diego InTeam protocol.[120, 121, 122, 123] During interviews with the 2019 VA review team, two of the interventional radiologists that took additional liver samples for research indicated that they assumed or may have assumed, incorrectly and without verification, that the

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[115] "*Q. Was there ever any consideration about asking Pathology to slightly alter that process so that you could get excess directly from Pathology? Was there ever consideration of having them treat a portion of it slightly different so that they could potentially use it but you as well?* A. That is -- actually, that could actually have been done. Yes, I believe that could have worked. Again, if Pathology would be cooperative to -- that would be one way to -- of proceeding with this. As we have, you know, indicated in the protocol, that would be -- that example would totally be consistent with what my thinking is. *Q. Did you ever pursue that alternative?* A. No, I did not."

[116] "*Q. [F]or coordination with your study, do you recall having any conversations with Interventional Radiology about coordinating that [tissue collection] aspect of the study?* A. Yeah, going back to when the protocol first started, I discussed it with the interventional radiologists, and I understand that there were -- there's turnover and changes in the staff, but the original discussions were with the original radiologists."

[117] Transcript from January 16, 2019, interview with a San Diego Interventional Radiology Section nurse Employee 2 (pages 7-8). "When we were taking our sample for Cytology, [the PI] would bring us a little vial in a specimen bag labeled with whatever the patient's ID number was for the research. And [the PI] asked us to put a fresh -- to get an additional sample...And they [the PI and his coordinator] would always say, 'As soon as you get the sample,...call us immediately, and we'll come pick it up.'"

[118] Transcript from January 16, 2019, interview with a San Diego Interventional Radiology Section nurse Employee 3 (page 11). "My recollection is to call one of them [PI or study coordinator] and they would come and get the sample, you know, in the vial, in the bag."

[119] VHA Handbook 1200.05 §29.c(1) (November 12, 2014). "Once approved by the IRB, the protocol must be implemented as approved. All modifications to the approved research protocol or consent form must be approved by the IRB prior to initiating the changes except when necessary to eliminate apparent immediate hazards to the subject."

[120] Transcript from January 14, 2019, interview with San Diego interventional radiologist Employee 1 (pages 8-9). "A. I don't ask for them to send me the protocol or any protocol changes or anything like that. At some point I have to trust the system. And if, you, it's got an IRB approval and my colleague is, you know, bringing me the same study, then I trust that they are presenting me with what they are." "*Q. "[D]o you recall the interactions concerning that particular [InTeam] study?* A. I do remember the initiation of that study because we were getting these requests. I called [the PI] and asked him some questions. *Q. Did he provide any materials during that interaction?* A. No, nothing written."

[121] Transcript from January 15, 2019, interview with former San Diego interventional radiologist Employee 5 (page 6). "*Q. Do you remember how you became aware of the study?* A. You know, as I remember, I think [the PI] came down and said he was going to do a study. He said, 'Would you guys be willing to do transjugular liver biopsies?' And I said yes. You know, we were willing to do that. *Q. As part of that conversation, did he provide the protocol, the informed consent document, or any other reference materials to guide the expectations for you?* A. No. I never saw any of that stuff. No."

[122] Transcript from January 16, 2019, interview with a San Diego Interventional Radiology Section nurse Employee 2 (page 7). "I don't recall seeing any research documents, no."

[123] Transcript from January 16, 2019, interview with a San Diego Interventional Radiology Section nurse Employee 3 (page 10). "I think in past studies we have had a copy. I think we've been presented with a copy of the IRB, and I don't recall reading anything for [the PI]. [The PI] could have had it. I don't remember."

San Diego InTeam PI had obtained IRB approval to take additional (extra) liver biopsy specimens for research purposes.[124, 125]

In contrast, PLMS leadership described an expectation that PIs provide an approved IRB protocol describing the specimens being requested for research. The Chief of PLMS also articulated the expectation that PLMS would review and retain the research documents in its files.[126] The San Diego CoS likewise expressed discomfort in clinical staff relying on verbal information to indicate the scope and extent of clinical procedures that may be performed in conjunction with an IRB-approved study, and instead articulated a preference that written documentation be provided.[127] Thus, there were differing expectations between San Diego Interventional Radiologists and other clinical staff as to the level of verification that should be performed to confirm that research-specific procedures conducted in the course of performing clinical duties were consistent with those approved by the IRB (and, correspondingly, the IRB-approved protocol).

The 2019 VA review team did not identify evidence that the acquisition of additional liver tissue by the Interventional Radiology Section for the San Diego InTeam study compromised the ability of PLMS to conduct its analysis of the separate samples collected specifically for PLMS for clinical diagnostic purposes.[128] The 2019 VA review instead independently confirmed the San Diego IRB finding that interventional

radiologists took an additional (extra) biopsy specimens from patients specifically for research use after separate clinical specimens had been obtained. Specifically, the

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[124] Transcript from January 14, 2019, interview with San Diego interventional radiologist [redacted] (page 32). "*Q. So to your recollection, did [the PI] specifically represent to you that his IRB protocol allowed for an extra sample to be collected for research purposes?* A. That, I don't know. I don't know if I assumed it...or if [the PI] specifically asked for [extra biopsy samples to be obtained]."

[125] Transcript from January 15, 2019, interview with former San Diego interventional radiologist [redacted] (page 17). "I just assumed it [the extra biopsy for research] was approved."

[126] Transcript from January 15, 2019, interview with San Diego Chief of PLMS [redacted] (page 18). "We have to review the IRB protocol to make sure that we have on file -- we have one copy on file that this particular researcher can get this particular type of sample to have it."

[127] Transcript from January 14, 2019, interview with San Diego COS [redacted] pages 19-20). "I would like to think that everyone participating in a research protocol is aware of what the informed consent document says and that there is a written protocol on how to obtain the samples. I would -- it would make me uncomfortable to just rely on something verbal...I think we have to have an expectation that if -- particularly if you're doing a procedure or have an active role in a protocol, that you are aware, and you have a written -- a written standard operating procedure so that you know what you're supposed to be doing and what has been approved by the IRB or not."

[128] A specific whistleblower allegation involved the concern that clinical diagnostic samples were cut to allocate a piece for research. However, during interviews with the 2019 VA review team, one of the whistleblowers indicated that he *assumed* this to be the case. "*Q...[Y]ou indicated that a research coordinator had mentioned that they got a fresh sample [from Interventional Radiology]. One of the specific allegations that were made was that the sample that was supposedly intended for Pathology was specifically cut. Now, there could be other ways you could get a fresh sample. You could do an extra pass of the biopsy specifically for research. Were you specifically told by the research coordinator that the sample intended for Pathology was cut or whether or not there was an additional sample taken independent of what Pathology needed?* A. I make that assumption...*Q. So, I understand you're indicating you made an assumption that a piece was cut. So, basically then if, in fact, it's always -- we allow that it's possible that an extra sample was taken beyond what was needed for path, if you're assuming that it was cut, then you're also making the assumption that the -- that the specimen provided to path was compromised. But we could allow for the fact that possibly an extra sample beyond what path needed was taken and therefore the pathology sample was not compromised. Is that a possibility?* A. It's a possibility. *Q. Okay.* A. It's a possibility that makes sense, yeah." Transcript from January 16, 2019, interview with whistleblower [redacted] (pages 39-41).

lead San Diego interventional radiologist stated, "We [Interventional Radiology Section] don't short-change pathology in order to…allow the research to happen," and that the section's process involved first securing sufficient "quality" liver tissue cores for diagnostic purposes, and then making an assessment to proceed with taking an extra core for research.[129] Nursing staff corroborated that "our doctors would take their [diagnostic] samples and then they would – for the very last sample get one additional, and they would put it into the [study-provided] vial."[130] The Chief of PLMS also stated that she was unaware of clinical samples being diverted for research or a portion removed therefrom that compromised diagnostic analysis.[131]

Conclusions

- The 2019 VA review **substantiated** that the manner in which liver biopsy tissue was obtained for the San Diego InTeam study was noncompliant with the IRB-approved study protocol. Specifically, in contrast to obtaining excess ("archival") clinical diagnostic liver tissue from PLMS as allowed by the protocol, additional (extra) tissue was obtained for research purposes by interventional radiology directly from patients undergoing a liver biopsy procedure. The 2019 VA review also found that interventional radiologists took the additional liver samples specifically for research purposes without effectively verifying this had been approved by the IRB.

- The 2019 VA review **did not substantiate** the whistleblower's allegation that clinical diagnostic samples intended for PLMS had been compromised for purposes of the research.

Recommendation to San Diego

1. San Diego personnel should establish uniform expectations and processes for clinical service lines to verify that procedures performed specifically for research purposes (i.e., not necessary for clinical care) have received appropriate approvals prior to performing such procedures. Non-compliance should be addressed through education, training, and/or disciplinary actions, as indicated.

Adequacy of the San Diego InTeam Informed Consent Process with Regard to How Liver Samples Were Actually Obtained for the Study

The San Diego IRB 2018 noncompliance investigation established that the approved San Diego InTeam ICD neither informed subjects that additional liver tissue would be obtained for research purposes nor informed subjects of any additional risks related to

[129] Transcript from January 14, 2019, interview with San Diego interventional radiologist Employee 1 (pages 18-19).
[130] Transcript from January 16, 2019, interview with a San Diego Interventional Radiology Section nurse Employee 2 (page 10).
[131] Transcript from January 15, 2019, interview with San Diego Chief of PLMS Employee 6 (pages 16-17).

obtaining additional liver tissue for research purposes.[132, 133] The 2019 VA review similarly established this as described below.

The IRB-approved ICD included several statements that collections of liver biopsies were to be conducted for clinical care and were not to be done solely for research purposes.[134, 135] However, as described previously in this report, additional liver biopsy tissue was obtained from San Diego InTeam participants specifically for research purposes, in violation of the protocol and ICD. Thus, participants were not appropriately informed of the actual procedures that they might be subject to as part of their participation in the study. This failure to appropriately inform participants of the actual procedures that they might undergo represented noncompliance with then existing Federal regulation and VA policy.[136]

The 2019 VA review team further identified that obtaining additional liver tissue for research purposes, beyond that needed for clinical diagnostic purposes, was associated with increased risk for subjects. Specifically, during interviews with three interventional radiologists, each of them informed the review team that the process of obtaining the additional research sample would introduce an increased risk of bleeding,[137, 138] and increased risk of pain.[139] However, these increased risks associated with obtaining an additional liver sample for research purposes were not described in the ICD. Correspondingly, San Diego InTeam participants were not appropriately informed of the actual risks of participation in the study. This failure to notify participants of the actual

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[132] San Diego IRB report dated October 19, 2018, "Inquiry of Concerns Human Subject Research Protocol H120108." "The ICD did not inform that additional tissue may be taken or address whether there were any additional risks related to the biopsy procedure (i.e., in addition to risks identified within the clinical consent for this procedure)."

[133] Transcript from January 14, 2019, interview with San Diego interventional radiologist Employee 1 (page 23). The interventional radiologist described that the procedural risks delineated in the clinical consent would have been slightly higher for patients from whom additional tissue was removed for research. In its report to ORO, the facility asserted that clinical records did not document any liver biopsy procedural complications.

[134] San Diego InTeam ICD, approved June 2, 2014.

[135] "If a liver biopsy is done this will be part of your routine care to make sure of the diagnosis and not part of the research process. However, if available, a portion of this sample may be collected for research purposes."

[136] VHA Handbook 1200.05 §31.a(4) (May 2, 2012). Elements of Informed Consent Required by the Common Rule. Except as provided in paragraphs 34, 35, and 36 of this Handbook, 38 CFR 16.116(a) requires the following elements of informed consent be provided to each subject: "A Description of the Procedures to be Followed." VHA Handbook 1200.05 §15.b(1) (November 12, 2014). "Except as provided in paragraph 15.e. [Waiver or Alteration of Informed Consent], in seeking informed consent the following information must be provided to each subject: A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental."

[137] Transcript from January 14, 2019, interview with San Diego interventional radiologist Employee 7 (page 23). "[T]he bleeding risk of a transjugular liver biopsy is going to be probably on the order of 5 percent or less and, you know, each additional pass would potentially set you up for bleeding more."

[138] Transcript from January 17, 2019, interview with former San Diego interventional radiologist Employee 8 (page 12-13). "[P]ercutaneous unless you put a guide needle and then through that guide needle get multiple samples, if you insert the needle multiple times, instead of putting a guide, just put the needle multiple times, that increases, obviously, the risk of bleeding..."

[139] Transcript from January 15, 2019, interview with former San Diego interventional radiologist Employee 5 (page 14-15). "I think with each pass, there's a risk. So, more passes, more risk. So yes. The more you do, the more -- you know, the more you do, a higher yield, but there's -- it comes with a price, sometimes, the complications...[T]he most common complication is actually pain after a biopsy."

risks of participation in the study constituted noncompliance with Federal regulation and VA policy.[140]

The 2019 VA review further identified that in the case of participant P005, an extra liver biopsy was obtained for research purposes before San Diego InTeam study personnel secured documentation of informed consent from the participant. The electronic medical record documented that this participant underwent a liver biopsy on October 21, 2014.[141] It was also established that a liver biopsy sample obtained from this participant was provided to the InTeam Consortium Project repository. However, the ICD to participate in the San Diego InTeam study was signed by the participant's LAR on behalf of the participant on October 22, 2014, one day after the biopsy procedure.[142] Despite the electronic medical record's documentation that the procedure occurred on October 21, 2014, a biospecimen log provided by the InTeam Consortium Study Project Leader, and research data entry forms retained by San Diego indicated that San Diego InTeam personnel reported that the liver tissue "collection date" occurred on October 22, 2014, in line with the date the participant's LAR signed the research ICD. The 2019 VA review concluded that a liver biopsy specimen was in fact obtained from participant P005 before research informed consent was obtained.

The 2019 VA review also examined whistleblower concerns that patients were coerced into providing consent for research participation.[143] The whistleblowers did not provide evidence to support the allegation, and the 2017 and 2019 VA reviews did not discover any information that would substantiate the allegation. Additionally, ICDs signed by participants or their LAR all contained a statement that participation in the research is voluntary, and that refusal to participate or withdrawing later will not result in penalties or loss of VA benefits.[144] The allegation that participants were coerced into research participation was not substantiated.

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[140] VHA Handbook 1200.05 §31.a(6) (May 2, 2012). Elements of Informed Consent Required by the Common Rule. Except as provided in paragraphs 34, 35, and 36 of this Handbook, 38 CFR 16.116(a) requires the following elements of informed consent be provided to each subject: A description of any reasonably foreseeable risks or discomforts to the subject (38 CFR 16.116(a)(2)). (a) This description is to include, but not be limited to, physical, social, legal, economic, and psychological risks. (b) Risks that do not result from the research, but that result solely from treatments or services that have been designated in the IRB-approved protocol to be the responsibility of the health care provider, should not be described in the consent form. The informed consent process is to include language advising subjects to review the risks of such clinical treatments or services with their health care provider(s)." VHA Handbook 1200.05 §15.b(2) (November 12, 2014). "[I]n seeking informed consent the following information must be provided to each subject: A description of any reasonably foreseeable risks or discomforts to the subject."

[141] Electronically time and date stamped Radiology Nursing entries in the electronic medical record documented that the patient had a liver biopsy on October 21, 2014, including a "Pre-Procedure Nurses Note" electronically signed at 2:42 pm and a post procedure note electronically signed at 4:03 pm.

[142] Per Participant P005's San Diego InTeam ICD, signed by the LAR at 1:25 pm on October 22, 2014.

[143] A whistleblower letter to OSC dated February 27, 2018, asserted that, "[The PI] also lied to [the potential subjects] and coerced them to get their consent. These patients were told by [the PI] that they required these procedures to receive medical care. It was implied that without these procedures they would not get quality medical care."

[144] Research Informed Consent—Integrated Approaches for Identifying Molecular Targets in Alcoholic Hepatitis (InTeam) (Approved March 12, 2013) §15. "You have been informed that you do not have to take part in this study, and your refusal to participate will involve no penalty or loss of rights to which you are entitled. You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled."

Conclusion

- The San Diego InTeam participants were neither appropriately informed that an additional biopsy sample would be obtained specifically for research purposes nor appropriately informed of the increased risks of obtaining the additional biopsy sample.

Recommendation to San Diego

2. San Diego should consult with the VA National Center for Ethics in Healthcare concerning the research use of liver tissue samples obtained without appropriate consent.

Additional Issues

Use of Cognitive Assessments to Determine Capacity to Consent

The 2017 VA report to OSC noted, "One of the whistleblowers expressed concern that the InTeam protocol included subjects who, due to disease progression, lacked the ability to give effective informed consent." The 2017 VA review determined that the approved research protocol included provisions for assessing decisional capacity. Specifically, the San Diego InTeam protocol acknowledged that some patients could have decisional impairment and the PI's submission to the IRB included a decisional capacity assessment form "Evaluation to Sign a Consent Form for Research."[145]

The 2019 VA review confirmed that an assessment to determine a patient's ability to provide informed consent for research participation was documented for each "P" participant. Specifically, "Progress Notes" contained within the electronic medical record documented that San Diego InTeam personnel incorporated a cognitive assessment during the informed consent process.[146] The Progress Notes included templated statements requiring specific responses to an assessment regarding whether the "Subject was alert, oriented, and attentive while the study was explained." The Progress Note template also included the option to document, "Subject was not capable of making a decision to participate in study" and a corresponding field, "Surrogate approval was provided by _____." During previous interviews with the 2017 VA review team, the former San Diego InTeam PI stated that he participated in the screening and informed consent process for each of the inpatient ("P") participants.[147] The PI's

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[145] Documented in San Diego InTeam Human Protocol (Version 1. 8), dated March 11, 2013, §10.5: "Many patients suffering from acute alcoholic hepatitis have very poor health, and the research team does not wish for these subjects to feel forced to participate because of their failing health. Because some patients with alcoholic hepatitis may have encephalopathy, we will use a decisional capacity assessment to determine ability to obtain informed consent. If it appears that this capacity is impaired, we will obtain surrogate consent. This is added to the consent form and Protocol Application." The PI provided the IRB an associated InTeam form, "Evaluation to Sign a Consent Form for Research."

[146] Electronic medical record, "Progress Notes, Research Consent," and "Progress Notes, Gastroenterology Attending Note."

[147] Transcript from April 10, 2017, interview with the San Diego InTeam PI (S.H.) (pages 25-26). "[Q.] [O]nce you've been alerted by one of the medical team, whether it's a fellow or somebody else that knows about your study, who

statement concerning the screening and consenting process was corroborated by the San Diego InTeam research coordinator.[148] During the 2019 VA review, the former San Diego InTeam PI further articulated his process for conducing decisional assessments.[149] Research records also reflected an assessment of potential cognitive impairment at follow-up San Diego InTeam protocol visits.[150]

Although the 2019 VA review team was able to identify evidence that decisional assessments were conducted, the team was unable to identify evidence that the San Diego InTeam PI had documented the cognitive assessments with the "Evaluation to Sign a Consent Form for Research" form, the specific form submitted by the study team to the San Diego IRB indicating how the decisional assessment would be conducted.[151] Although there was no evidence identified that the specific form and exact questions on that form were used to conduct the assessments, the assessment questions documented in medical record "Progress Notes" as having been asked of potential participants were of a similar nature to those in the form provided to the IRB.

Conclusion

- Assessments to evaluate decisional capacity to provide informed consent to participate in the study were conducted. Although the 2019 VA review team did not identify evidence that a form provided to the IRB by the study team was used for conducting the assessments, a comparable assessment was documented as having been completed. Specifically, the electronic medical record for each "P" participant included documentation that the informed consent process included a decisional assessment component.

Recommendation to San Diego

3. The IRB and research investigators should ensure that any forms proposed to be used in a protocol to determine cognitive capacity to consent are used.

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completes the screening process? And then who consents the subject, the inpatient? A. Then it's [study coordinator] and myself who do that. Q. Both of you together? A. Yes…I personally consent every patient."

[148] Transcript from April 12, 2017, interview with the San Diego InTeam Research Coordinator Employee 3 (pages 5-6). "[The PI] talks to the patient. He does a physical examination and introduces the study to the patient. And we go over the consent form...And then they sign the consent form. But there have been times when we decide not to do that because the patient is in a state that he doesn't seem to be understanding what he's signing. So, we just screen fail them, or we don't choose to enroll them that day."

[149] Transcript from January 16, 2019, interview with the former San Diego InTeam PI Employee 4 (page 8). "Q. Do you recall how the decisional assessments were conducted? A. Yeah. I mean, you have to make sure that the patient is oriented to person, place and time and make sure they repeat -- are able to repeat the protocol. And to the best of your knowledge, you have to be assured that they understand it and fully know all the risks and benefits. And then you can -- if you are convinced of that, then you can move forward. But it is a matter of, you know, making sure that patients demonstrate understanding."

[150] San Diego InTeam data collection tools and records documented that research participants were also monitored for cognitive function during scheduled study visits.

[151] Transcript from January 16, 2019, interview with the former San Diego InTeam PI Employee 4 (pages 8-9). The former San Diego InTeam PI readily articulated the process for conducing decisional assessments but could not recall having implemented use of a specific San Diego InTeam form. Further, documentary evidence of the use of the form was not found in records reviewed by the 2019 VA review team.

Pregnant Women

During the 2019 VA review, one of the whistleblowers reasserted a concern that an initial version of a San Diego InTeam protocol submission indicated that pregnant women could be included in the study.[152] The 2019 VA review team notes the following: (1) the review team did not identify any evidence that the San Diego IRB had approved any version of the San Diego InTeam protocol that would have allowed pregnant women to have been included in the study; (2) the version of the San Diego InTeam protocol that was initially approved by the IRB specifically referenced pregnancy as an exclusion criterion;[153] and (3) no women identified as pregnant were enrolled in the San Diego InTeam study.[154]

Conclusion

- The San Diego InTeam study was never approved by the IRB to include pregnant women, and no women identified as pregnant were enrolled in the San Diego study.

Recommendation to San Diego

None.

External Case Reviews

The medical literature does not definitively establish a preferred biopsy technique for diagnosing alcoholic liver disease because, as previously stated, the preferred technique varies depending on other health conditions of the patient. The VA investigative team made arrangements for each of the cases to be objectively reviewed through an external peer review. These external peer reviews are ongoing. A subsequent report will be issued addressing clinical care concerns pertaining to the transjugular biopsy procedure performed on subjects enrolled in the research protocol.

V. Summary Statement

The approved research protocol only permitted the research use of liver tissue remaining after clinical diagnostic use (excess tissue), even if the biopsy occurred after the research protocol approval date (prospectively obtained tissues). However, the 2019 VA review independently confirmed the San Diego IRB's 2018 finding that additional (extra) liver tissue was obtained specifically for research purposes, and that obtaining the additional tissue constituted a serious deviation from the approved research protocol. The 2019 VA review further confirmed that participants were not appropriately informed that an extra liver biopsy sample would be obtained from them solely for research purposes and were not appropriately informed of the increased risks

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[152] Documented in a San Diego InTeam "Response to IRB," dated February 8, 2013.

[153] Documented in San Diego InTeam Human Protocol (Version 1.8), dated March 11, 2013. §2.1 "For each of the subject categories listed below, indicate whether or not these subjects will be enrolled (consented) in the study: (exclude cases of data or specimens only) Pregnant women [No] §10. Exclusion Criteria: 5.) Pregnancy."

[154] Per review of medical records and multiple San Diego InTeam study records, including data collection tools and "InTeam Updated Patient Log 2018," last saved on April 12, 2018.

of obtaining an additional sample for research purposes. The 2019 VA review did not substantiate the concern that other specimens intended for clinical diagnostic use had been compromised by any diversion of portions of those specimens for research purposes. Further, the 2019 VA review team concluded that the Interventional Radiology Section lacked an effective process to verify that the collection of additional biopsy samples for research purposes was appropriately approved.

Attachment A

Table 1: InTeam "P" Participants Liver Biopsy History[1]

Subject ID#	Research Consent Date	Liver Biopsy	Biopsy Type	Biopsy Date	InTeam Consortium Repository Received Liver Biopsy Tissue
2014					
P001	February 3	Yes	Transcutaneous	January 27	No
P002	February 19	Yes	Transjugular	February 19	No
P003	February 19	Yes	Transjugular	February 19	No
P004	September 23	Yes	Transjugular	September 30	**Yes**
P005	October 22	Yes	Transjugular	October 21	**Yes**
P006	October 22	Yes	Transjugular	October 22	**Yes**
P007	October 31	Yes	Transjugular	October 31	No
P008	November 19	No			
P009	December 3	No			
2015					
P010	March 4	Yes	Transjugular	March 4	**Yes**
P011	July 15	No			
P012	August 25	Yes	Transjugular	August 25	**Yes**
P013	August 5	No			
2016					
P014	January 12	No			
P015	January 15	No			
P016	January 29	Yes	Transjugular	February 2	No[2]
P017	March 3	No			
P018	August 8	Yes	Transjugular	August 9	**Yes**
P019	October 13	Yes	Transcutaneous	October 14	**Yes**
P020	December 1	Yes	Transjugular	December 5	**Yes**
2018					
P021	January 8	No			
P022	February 28	No			

[1] "P" participants were patients suspected of having alcoholic hepatitis.

[2] The San Diego IRB's report concluded that this participant was one of the nine participants from whom an extra liver biopsy sample had been obtained and provided for the San Diego InTeam study. However, the InTeam Consortium Project repository did not have a record of receiving a liver biopsy sample from this participant.

Attachment B

Data from the facility's filed Research and Development Information System (RDIS) report.

Project #1U01AA021908, Molecular Subtypes for Targeted Therapies in Alcoholic Hepatitis.

Electronic messages.

San Diego IRB meeting minutes.

Master Protocol (Version 1.0), dated September 26, 2012.

InTeam Master Protocol [300.1C September 7, 2017.

San Diego Protocol Application 1.7.

Memorandum from the ACOS/R&D to the PI dated March 21, 2013.

VHA Handbook 1200.01, Research and Development Committee, dated June 16, 2009.

OSC letter, dated March 8, 2017, to the Secretary of VA with subject line of "OSC File Nos. DI-16-1945 and DI-17-1294."

VA Report to OSC, OSC File Numbers DI-16-1945 and DI-17-1294 (report transmitted July 20, 2017).

VA Supplemental Report to the Office of Special Counsel (OSC), San Diego VA Medical Center, San Diego, California, OSC File Nos. DI-16-1945, DI-17-1294, dated December 26, 2017.

VHA Handbook 1058.01 §4.s. Serious Noncompliance.

InTeam study records.

OSC letter, dated November 2, 2018, to the President with subject line of "OSC File Nos. DI-16-1945 and DI-17-1294." Letter indicated that OSC found aspects of VA's response to the original allegations to be unreasonable.

Per an electronic message from the San Diego Director to a member of the 2019 VA review team, dated November 26, 2018.

San Diego InTeam PI's "IRB Protocol Closure" request dated March 6, 2019.

San Diego IRB memorandum to the San Diego InTeam PI, dated March 7, 2019.

American Association for the Study of Liver Diseases (AASLD) Position Paper - Liver Biopsy, Hepatology, March 2009.

"San Diego HRPP Program – Response to IRB," dated February 25, 2013.

Standard Operating Policies and Procedures for the San Diego Institutional Review Board and Human Research Protection Program, dated March 4, 2015, and amended September 28, 2017.

Per the "InTeam Updated Patient Log 2018," last saved on April 12, 2018.

VHA Handbook 1200.05 §31.a(6), May 2, 2012. Elements of Informed Consent Required by the Common Rule.

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