VA San Diego Health Care System
Institutional Review Board

INQUIRY of CONCERNS
HUMAN SUBJECT RESEARCH PROTOCOL H120108

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I. Introduction and Review Method

The VASDHS Institutional Review Board (IRB) serves as the primary IRB of record for human subject research conducted under VASDHS Federalwide Assurance (FWA00001893).

The VASDHS IRB was charged with investigating concerns related to research conducted under VASDHS IRB approved protocol H120108 titled, "Integrated Approaches for Identifying Molecular Targets in Alcoholic Hepatitis" (InTEAM). The apparent concerns were submitted to the VASDHS Chief of Staff, who forwarded the allegations to the IRB with a request for review.

The purpose of this review was to evaluate each concern and if a concern was substantiated, in part or in full, to determine whether protocol or policy violations occurred, whether there was any risk posed to subjects or others, and to provide recommendations to VASDHS Leadership regarding each of the concerns.

To facilitate the fact-finding portion of this inquiry, the IRB established a review team consisting of an IRB voting member, an Human Research Protection Program Analyst, and the Director of the Research Projects Section. The findings were presented to the convened IRB on October 11, 2018, for review and determination.

The IRB's review included individual interviews with the Principal Investigator (PI), primary Study Coordinator, Chief, Pathology and Laboratory Medicine Service (PALMS), Interventional Radiology, and review of the referenced protocol, research records, and medical records pertaining to research activities of subjects enrolled in this study.

II. Protocol Overview

InTEAM is a 10-site multicenter National Institutes of Health funded research program to study alcoholic hepatitis.

VASDHS patients who have suspected alcoholic hepatitis and who meet study related inclusion/exclusion criteria are eligible to participate in the study. The purpose of this study is to collect and preserve samples of blood, urine, stool, and liver tissue from patients with alcoholic hepatitis to be used in future research studies. The purpose of future studies using

these samples will be to develop new methods for diagnosing alcoholic hepatitis and its complications, to develop new markers for disease severity, and to identify new targets for improved therapy. The Liver Center of the Division of Digestive Diseases at the University of North Carolina is the program lead for this project and is responsible for management of the biorepository.

The local study, identified as Protocol H120108 titled, "Integrated Approaches for Identifying Molecular Targets in Alcoholic Hepatitis" (InTEAM) was initially approved by the VASDHS IRB on March 6, 2013.

At the time of this review, 41 VASDHS patients had been enrolled in the study including 19 control subjects and 22 subjects with diagnosis or suspected diagnosis, of alcoholic hepatitis. 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. It is noted that the PI of record during this period retired from the VA in June 2018, and the former Co-Investigator has assumed the role of PI.

III. Concerns, Findings, and Conclusions

The VASDHS IRB was requested to review and evaluate four specific concerns.

A. Concern #1: Acquisition of Samples Prior to Clinical Use

Concern that research (liver) samples were being acquired under the guise of excess samples from clinical standard of care before they were provided to and used by Pathology for standard of care diagnostic purposes.

Findings

1. VHA Handbook 1106.01 §3.a(2)j stipulates that the Chief, PALMS "provides oversight for all laboratory testing performed under the medical center/health care system." The Chief, PALMS confirmed that PALMS is responsible for management, oversight, and distribution of *archival* samples remaining after clinical testing is completed.

2. The IRB's understanding of the definition of an archival sample is tissues remaining after clinical use and diagnosis has been completed, i.e., excess sample. Archival samples would not include additional tissue collected specifically for research purpose. PALMS concurred with the IRB's understanding of archival samples and further informed that if a portion of a clinical sample is needed for research that sample may only be provided by PALMS after clinical processing is complete.

3. The IRB confirmed with PALMS that archival samples were not requested by or provided

to the PI for use in this study.

4. Versions 1.16 and 1.17 of Protocol H120108[1] document in §5, 9, 9.1, 9.6, 9.7b, and 10 that if a liver biopsy was done as part of standard of care, the PI would request access to the archival samples for research purposes. [See Appendix A.]

5. VASDHS Medical Center Memorandum (MCM) 113-03 further establishes local policy and procedures for collecting and processing laboratory specimens for diagnostic purposes. MCM 113-03 defines research specimens as any "specimen collected for the purpose of internal or external research approved through the appropriate committees and IRB."

6. The IRB established the following regarding local collection and processing of liver biopsies for clinical diagnosis of alcoholic hepatitis: (a) liver biopsies are generally performed by Interventional Radiology (IR); (b) IR places the clinical sample in a prepared and labeled vessel containing formalin fixative; (c) the specimen is transported to PALMS by a designated escort, who is responsible to sign upon delivery; and (d) PALMS takes custody and is responsible for clinical testing, any requests for archival tissue for research purposes are processed after clinical testing is complete.

7. Medical records documented that IR performed the liver biopsies for the nine subjects associated with this study and that all procedures were ordered as clinically indicated procedures.

8. The PI and study coordinator confirmed that for the nine specimens obtained for this study, all were obtained directly from IR. Therefore, these were not *archival* samples as indicated in the IRB approved protocol since clinical testing had not been completed.

9. IR reported that the study coordinator notified when patients enrolled in this study were scheduled for a liver biopsy. Prior to the patient's procedure, the study coordinator provided a prelabeled specimen tube to IR for the sample. IR further reported that if in the judgement of the surgeon, sufficient tissue was obtained for clinical purposes and it was deemed safe for the patient, an additional sample was obtained for research. The clinical specimen was processed in accord with standard clinical procedures and the research specimen was placed in the vial provided by the study coordinator and retrieved by the PI.

Conclusion

This review substantiated that the IRB approved protocol described acquisition of excess clinical samples for this research study. Specifically, the protocol consistently documented that archival samples would be obtained.

[1] Versions 1.16 and 1.17 were the IRB approved protocol versions between September 2014 and December 2016 when liver biopsy samples were obtained for this study.

The review did not substantiate the concern that a portion of the clinical specimen was provided for research purposes prior to use by Pathology for standard of care diagnostic purposes. Instead, the IRB found that a research specimen was obtained independent of the clinical sample after the IR surgeon determined that a sufficient specimen was obtained for clinical purpose.

Nevertheless, the IRB found that the neither protocol nor ICD adequately described the collection of the research specimen independent of the clinical specimen. Potential risks associated with this finding are discussed in Concern #3.

B. Concern #2: PI Altered Clinical Sample Compromising Diagnosis

Concern that the PI changed the size of the liver biopsy available to Pathology. Included in this concern was implication that this was a violation of the IRB, and may have limited Pathology's ability to make a diagnosis thus compromising patient care.

Findings

1. As established in Concern #1, IR performed the liver biopsies for the nine subjects associated with this study. IR reported that the PI was not present during any of the associated procedures and did not have access to the clinical sample. IR and Pathology records documented the collection and transfer of custody of the specimens between these Services.

2. Regarding the size of a clinical specimen, PALMS and IR reported that there is not an established minimum/maximum volume of liver tissue required for clinical testing. IR informed that the sample size and number of cores obtained is variable and depends on the professional judgement of the surgeon to assess a "good sample." The IRB confirmed through review of IR and Pathology reports for the nine subjects, up to five cores were collected and specimen samples sent to pathology were comprised of one to four cores per patient.

3. IR reported recalling at least one occurrence when a research sample was requested, but was not provided because the surgeon did not obtain what was considered more than sufficient for clinical purposes. The IRB confirmed through review of CPRS and research records that subjects P002 and P003 were enrolled in the study at the time of a clinically indicated biopsy but a sample was not provided to the PI for research purpose. The records did not document why a research sample was not obtained.

4. MCM 113-03 requires and the Chief, PALMS confirmed that if an insufficient or otherwise inadequate sample was received that would impair or limit the unit's ability to make a diagnosis, this must be documented and would be included in the pathology report. The

IRB reviewed pathology records for the nine subjects. Records for all nine subjects contained a clear testing outcome and none documented any concern regarding the specimen quality or difficulty in establishing a diagnosis.

Conclusion

This review did not substantiate that the PI changed the size of the liver biopsy available to Pathology. Instead, the review confirmed that the PI did not have access to the clinical sample after it was obtained by IR and transported to PALMS for processing. The review found that the IR surgeon was responsible for ensuring that a sufficient clinical specimen was obtained prior to provision of tissue for research purpose. The IRB did not substantiate that PALM's ability to make a diagnosis was compromised.

It is noted that if the PI had altered the clinical sample, this would have represented a violation of clinical practices, not a violation of the IRB. The IRB does not have review or oversight responsibility for clinical practices or procedures.

C. Concern #3: Research Staff Altered the Clinical Sample Compromising Standard of Care

Concern that the PI had his clinical coordinators go to Radiology and cut a piece from the liver biopsy during the procurement procedure BEFORE the biopsy was fixed and sent to Pathology. This was done because a frozen biopsy is optimal for the research, and is alleged to be a serious IRB violation. As a result, the realistic turn-around time for the diagnosis using these samples could not be standard of care.

Findings

1. As previously established, IR performed the liver biopsies for the nine subjects associated with this study. IR reported that neither the PI nor the study coordinator was present during any of the associated procedures and these individuals did not have access to the clinical sample. IR and Pathology records documented the collection and transfer of custody of the specimens between these Services.

2. IR and PALMS confirmed that liver specimens for clinical diagnosis of alcoholic hepatitis are deposited into prelabeled specimen containers containing a fixative solution.

3. IR and the study coordinator informed that when patients enrolled in this study were scheduled for a clinically indicated liver biopsy, the study coordinator was responsible to bring a prelabeled specimen tube to IR. The PI and study coordinator confirmed that the collection container for research did not contain fixative solution and this was in accord with the master protocol's collection guidelines.

4. A review of the IRB protocol file found the following:

a. H120108 Versions 1.16 and 1.17 were silent regarding whether the research sample would be obtained as fixed or unfixed tissue. Nevertheless, as previously established, both versions of the protocol described receipt of archival samples for research purposes. It is understood through this review that clinical (liver) biopsy specimens are fixed and, therefore, the archival samples would consist of fixed tissue. However, it is not apparent whether this was known by the IRB at the time of review/approval.

b. A February 24, 2014, dated version of the "Master Protocol,"[2] which was submitted as a component of an April 10, 2014, IRB approved study amendment adding a control group, documented that the biopsies would be placed in formalin containers and unfixed tissue would not be obtained. Specifically, the document noted that the "local protocol does not call for freezing a portion [of the specimen]. If this were done it would be immediately frozen in liquid nitrogen and stored at -80C and later sent to the Human Biorepository Core…"

c. The June 2, 2014 approved Informed Consent Document (ICD), which was signed by the nine subjects from whom liver biopsy tissue was obtained, informed that a portion of the patient's clinical biopsy may be collected for research purposes. [See Appendix A.] 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).

d. A July 21, 2014, dated version of the Master Protocol, which was submitted as a component of a September 30, 2014, IRB approved study amendment altering eligibility requirements, documented that the biopsies would be unfixed and placed in either sterile saline or RNALater® solution.[3] [See Appendix B]

Conclusion

This review did not substantiate that the PI's research staff altered the clinical biopsy. Instead, the review confirmed that research staff did not have access to the clinical sample. The review found that the IR surgeon was responsible for ensuring that a sufficient clinical specimen was obtained prior to provision of tissue for research purpose and that the clinical sample was appropriately transported to PALMS for processing.

The review substantiated that the research specimens were obtained as unfixed samples. Since the master protocol describes preparation of unfixed frozen samples, the IRB concluded that frozen biopsy specimens were likely optimal for the research project. However, since the

[2] Multisite studies frequently utilize a Master Protocol that describes study expectations at all performance sites and serves as a basis for the local site investigator to request local approval. The VASDHS IRB does not approve "Master Protocols", rather the PI is responsible to disclose in the local IRB application all work that will be conducted at this site.

[3] The amendment request did not mention a change in handling or processing of the research sample.

local IRB approved protocol described use of "archival samples" without specifying that these were unfixed samples, the IRB concluded that a protocol omission had occurred. The IRB further concluded that the consent form omitted information related to potential risks associated with taking more tissue than would have been taken for clinical diagnosis.

In consultation with IR, the IRB understands that the procedural risks delineated in the clinical consent would have been slightly higher for patients from whom additional tissue was removed for research. However, IR explained to the IRB reviewers that a transjugular biopsy, which was the method used for the nine subjects, uses a smaller core to obtain the specimen than a percutaneous liver biopsy. The smaller core requires more cores be obtained to secure a sufficient sample for pathology, but also carries less risk of bleeding and other complications. The method of collection was not determined based on the patient's participation in the study, but rather what was clinically indicated for the patient's care. Nevertheless, the research consent form should have informed patients of the elevated risk of procedural complications associated with the tissue obtained for research purpose. IR records did not document that any procedural complications had occurred in association with the procedures for the nine subjects.

The review did not substantiate that the ability to make a diagnosis was compromised. Instead, the review found that the clinical sample was obtained and handled in accord with standard of care practice. Therefore, the turn-around time for diagnosis was not affected by the subjects' participation in the research study.

D. Concern #4: Research Study Compromised Clinical Care

Concern that this protocol compromises the care of the patient by obtaining the research sample.

Findings

1. As established throughout this review, this inquiry found that the clinical specimen was obtained, managed, and processed in accord with standard of care procedures and patient records document these practices. Patient records and Interviews with IR further confirmed that all biopsies were clinically indicated.

Conclusion

This review did not find evidence to support the concern that patient care was compromised by obtaining the research sample.

IV. Remedial Actions and Recommendations

Based on the above findings, the IRB made the following recommendations:

1. On October 11, 2018, the VASDHS IRB determined that serious noncompliance occurred by the collection of an independent research specimen instead of use of archival tissue as described in IRB approved protocol H120108. This finding will be reported in accord with VHA Handbook 1058.01.

2. The current PI must amend the local protocol and informed consent document to accurately describe collection of a research specimen in addition to the clinical specimen. This includes correcting all references to collection of archival samples; ensuring that §9, 9.6, and 25 accurately describe involvement of IR; and ensuring the risks associated with collection of the research specimen are described in the protocol and in the informed consent document.

3. The current PI must respond to the IRB acknowledging the serious protocol violation and describing how protocol compliance will be ensured going forward.

4. The former PI should be notified of the outcome of this review.

5. The Human Research Protection Program (HRPP) will review with the VASHDS Office of Research Agreements Management (ORAM) to determine whether development of protocol based inter-service agreements could help assign responsibility and provide transparency related to research vs. clinical procedures.

Certification on behalf of the VASDHS IRB:

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William Penny, MD
Chair, VASHDS IRB

APPENDIX A

EXCERPTS FROM IRB APPROVED PROTOCOL H120108 AND CONSENT FORM

Protocol H120108 Versions 1.16 and 1.17:

- §5 Lay Summary – "If 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." trouble

- §9 Design and Methods – "If 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."

- §9.1 Clinical Procedures – "If a liver biopsy is done as part of standard of care, we will request access to the archival samples."

- §9.6 Specimens – "If 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."

- §9.7b Biorepository detail – "If 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."

- §10 Human Subjects – "Liver biopsy is not required for this protocol. (The protocol assures that archival liver biopsy tissue from patients is only used if published guidelines are followed as specified in AASLD Practice Guideline Hepatology 2010;51:307 and EASL Practice guideline. J Hepatology 2012;57:399. Specifically, these guidelines state that the liver biopsy is done to help in clinical decision making for severe alcoholic hepatitis, that liver biopsies are not done for investigational purposes only, and liver biopsies are not considered clinically indicated if no treatment for ALD or AH is contemplated.)

Informed Consent Document (ICD) v.2014-06-02:

- §3 What 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."

- §4 Research Procedures – "If liver biopsy specimens are obtained as part of routine clinical care, a portion of this biopsy may be collected for research."

APPENDIX B

InTeam Master Protocol [200.0B 7/21/2014]
Liver Biopsy Processing Procedures

LIVER BIOPSY.

Kit Components: One (1) 5 mL white tope tube, Two (2) prelabeled 2 mL blue top (Liver B/RNA) tubes
Also needed: sterile gloves, saline, sterile tweezers/needle, RNALater® and/or dry ice.

General Instructions:

☐ 1. The transjugular liver biopsy (we advise the use of tru-cut instead of aspirative biopsies) is for both clinical and research purposes. A fragment of the liver tissue (approx. 50% of the cylinder) should be processed for diagnostic purposes using the local protocol.
☐ 2. The remaining liver tissue (0.1-0.2 cm is the minimum) should be processed for the InTeam Human Biorepository. The liver tissue can be processed in two ways:

Method 1: Frozen

☐ 1. Liver tissue should be rinsed in saline solution and kept as sterile as possible throughout the entire process.
☐ 2. Using sterile tweezers/needle, transfer the liver tissue to one of the prelabled 2 mL blue toped cryovials.
☐ 3. Liver tissue should be immediately frozen in dry ice.
☐ 4. Match the 4 digit code on the blue cap vials (LB01-LB02) and check the appropriate **Collected** box on each vial label on the Specimen Collection Log Record patient ID.
☐ 5. Immediately after dispensing liver tissue into vials, blue cap vials should be stored at -80°C or in liquid nitrogen until shipping.
☐ 6. Write comments in the space labeled **Notes** (e.g. problems with blood draw, insufficient volume, spills, and identify the specific aliquot by the three character code).
☐ 7. The (1-2) frozen liver biopsy vials are to be placed into a plastic bag with a sheet of absorbent DriMop and shipped on dry ice.

Method 2: RNALater®

☐ 1. Liver tissue should be rinsed in saline solution and kept as sterile as possible throughout the entire process.
☐ 2. Fill blue cap liver biopsy vial with 1 mL of RNALater®.
☐ 3. Using sterile tweezers/needle, transfer the liver tissue to one of the prelabled 2 mL blue toped cryovials. The cryovial can be kept overnight at room temperature or a few days at 4C if necessary.
☐ 4. Match the four digit code on the blue cap vials (LB00-LB02) and check the appropriate **Collected** box on each vial label on the Specimen Collection Log, record patient ID.
☐ 5. Store blue cap vials at -20°C or -80°C until shipping.
☐ 6. Write comments in the space labeled **Notes** (e.g. problems with blood draw, insufficient volume, spills, and identify the specific aliquot by the three character code).
☐ 7. The (1-2) frozen liver biopsy vials are to be placed into a plastic bag with a sheet of absorbent DriMop and shipped on dry ice.

Which method to use:

☐ 1. If there is only enough liver tissue for 1 cryovial, preferably utilize method 1. If this is not possible, method 2 is permissible.
☐ 2. If dry ice is not available for immediate freezing of the cryovial, utilize Method 2. We recommend that the VIR personnel have some vials and RNALater® ready for use.
☐ 3. If there is enough liver tissue for more than 1 cryovial, preferably utilize both Method 1 and 2 if possible. This will allow the most use from our specimens.