INDIANA UNIVERSITY

OFFICE OF THE VICE PRESIDENT FOR RESEARCH

Office of Research Compliance

To: Samer Gawrieh
GASTROENTEROLOGY

From:

Chair - IRB-05
Human Subjects Office
Office of Research Compliance – Indiana University

Date: October 04, 2016

RE: **NOTICE OF EXPEDITED APPROVAL - RENEWAL**

Protocol Title: Hepatocellular carcinoma in patients with non-alcoholic fatty liver disease.

Study #: 1410516848R002 | N

Funding Agency/Sponsor: None

Review Level: Expedited

Status: Approved | Submitted to IRB

Study Approval Date: October 04, 2016

Study Expiration Date: October 03, 2018

The Indiana University Institutional Review Board (IRB) IRB00004961 | IRB-05 recently reviewed the renewal associated with the above-referenced protocol. In compliance with (as applicable) 21 C.F.R. § 56.109 (e) and 46 C.F.R. § 46.109 (d), this letter serves as written notification of the IRB's determination.

The study is approved under Expedited Category (5) Category 5: Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)**, with the following determinations, as applicable:**

Approval of this study is based on your agreement to abide by the policies and procedures of the Indiana University Human Research Protection Program and does not replace any other approvals that may be required. Relevant policies and procedures governing Human Subject Research can be found at: http://researchadmin.iu.edu/HumanSubjects/hs_policies.html.

As a reminder, IRB approval is required prior to implementing any changes or amendments in the protocol, regardless of how minor, except to eliminate immediate hazards to subjects. No changes to the informed consent document may be made without prior IRB approval.

If you submitted and/or are required to provide participants with an informed consent document, please ensure you are using the most recent version of the document to consent subjects.

The approval period is noted above. Failure to receive notification from the Human Subjects Office will not relieve you of your responsibility to ensure compliance with Federal Regulations regarding annual review [as applicable, 21 C.F.R. § 56.109(f) and 45 C.F.R. § 46.109(e)].

You should retain a copy of this letter and all associated approved study documents for your records. Please refer to the assigned study number and exact study title in future correspondence with our office. Additional information is available on our website at http://researchadmin.iu.edu/HumanSubjects/.

If your source of funding changes, you must submit an amendment to update your study documents immediately.

If you have any questions or require further information, please contact the Human Subjects Office via email at irb@iu.edu or via phone at (317)274-8289 (Indianapolis) or (812) 856-4242 (Bloomington).

You are invited, as part of ORA's ongoing program of quality improvement, to **participate in a short survey** to assess your experience and satisfaction with the IRB related to this approval. We estimate it will take you approximately **5 minutes to complete the survey.** The survey is housed on a Microsoft SharePoint secure site which requires CAS authentication. This survey is being administered by REEP; please contact us at reep@iu.edu if you have any questions or require additional information. Simply click on the link below, or cut and paste the entire URL into your browser to access the survey: https://www.sharepoint.iu.edu/sites/iu-ora/survey/Lists/Compliance/IRB_Survey/NewForm.aspx.

/enclosures

Columbia University Human Subjects Protocol Data Sheet

General Information

Protocol:	AAAO0410(M00Y03)	**Protocol Status:**	Approved
Effective Date:	08/17/2016	**Expiration Date:**	08/16/2017
Originating Department Code:		SRG Abd Liver (7551402)	
Principal Investigator:		Wattacheril, Julia (jjw2151)	
From what Columbia campus does this research originate:		Medical Center	
Title:	Hepatocellular Carcinoma (HCC) in Patients with Underlying Nonalcoholic Fatty Liver Disease (NAFLD)		
Protocol Version #:		**Abbreviated Title:**	HCC in Patients with Underlying NAFLD
Was this protocol previously assigned a number by an IRB:		No	

Is the purpose of this submission to obtain a "Not Human Subjects Research" determination?

No

IRB Expedited Determination

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnoses).

Renewal Information

Enrollment status:

Closed to further enrollment: remaining research activities are limited to data analysis only

Provide any additional information necessary to explain the study status:

n/a

Since the last renewal:

Have there been any changes in the relevant literature that would affect the study design or procedures?

No

Have there been any interim findings associated with this study?

No

Have there been any publications resulting from this study?

No

Have any participants been enrolled using the Short Form process?

No

Is there a Data Monitoring Committee (DMC), Data Safety Monitoring Board (DSMB), or other monitoring entity for this study?

No

Is an annual Progress Report required by the funding organization or coordinating center for this study?

No

Does this submission include a modification?

No

Columbia University IRB
Approved for use until: 08/16/2017

Does this submission include a report of a protocol violation?

No

Attributes

Special review type: Check all that apply or check "None of the Above" box.

[ ]Review for 45 CFR 46.118 Determination (involvement of human subjects is anticipated but is not yet defined)

[ ]Funding review for Administrative IRB approval (such as for Center or Training Grants)

[x]None of the above

IRB of record information: Will a Columbia IRB be the IRB that is responsible for providing review, approval, and oversight for this study?

Yes

Select the most appropriate response:

Columbia will be the IRB of record for the study procedures conducted by Columbia researchers (Note: this response will apply to most submissions).

Is this research part of a multicenter study?

Yes

Indicate Columbia's involvement by checking all applicable roles below

[x] Columbia is a study site

Does this submission describe and seek approval for the study procedures at Columbia?

Yes

[x] Columbia is the Lead Institution

Is the purpose of this submission to obtain approval for the Lead Institution responsibilities?

Yes

[ ] Columbia is serving as the Clinical Coordinating Center

[ ] Columbia is serving as the Data Coordinating Center

[ ] Columbia is serving as the site for a repository of biological specimens related to this study

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Please indicate if any of the following University resources are utilized:

[x] Cancer Center Clinical Protocol Data Management Compliance Core (CPDM)

[ ] CTSA-Irving Institute Clinical Research Resource (CRR)

[ ] CTSA- Irving Institute Columbia Community Partnership for Health (CCPH)

[ ] None of the above

Lead Institution/Coordinating Center

It was indicated on the Attributes Page that this submission includes details related to Columbia serving as a Coordinating Center or Lead Institution. If this is incorrect, please make the necessary revisions on the Attributes Page. Otherwise, provide the following information or indicate that it is included in an attached stand-alone protocol. If a particular section does not apply to your protocol, it is appropriate to enter 'N/A' in the text field.

Provide an outline of the organizational structure of the multicenter protocol, including all sites where enrollment

Columbia University IRB
Approved for use until: 08/16/2017

is expected and any committees responsible for administrative duties, subject/data/site monitoring, facilitation of communications, data analysis, etc.:

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol.

Columbia will serve as lead institution as Julia Wattacheril, MD has been appointed lead PI. IRB approval will be obtained at each site by the local PI (total 5 sites). Consents will not be needed as aforementioned (waivers to be applied for/obtained at each site). Data and safety monitoring is in accordance with each institutions' IRB with no intervention planned/retrospective review only.

Provide a description of the responsibilities of the coordinating center / lead institution with regard to communication and training of research personnel across sites:

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol.

Columbia will serve as lead institution as Julia Wattacheril, MD has been appointed lead PI. IRB approval will be obtained at each site by the local PI (total 5 sites). Consents will not be needed as aforementioned (waivers to be applied for/obtained at each site). Data and safety monitoring is in accordance with each institutions' IRB with no intervention planned/retrospective review only.

Provide a plan to ensure that collaborating sites do not begin any research-related activity until IRB approval has been granted for the conduct of research at that site:

(If Columbia is not the lead institution, enter "N/A" in the text box)

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol.

Columbia will serve as lead institution as Julia Wattacheril, MD has been appointed lead PI. IRB approval will be obtained at each site by the local PI (total 5 sites). Consents will not be needed as aforementioned (waivers to be applied for/obtained at each site). Data and safety monitoring is in accordance with each institutions' IRB with no intervention planned/retrospective review only.

Provide a description of the transmission of data to the data coordinating center:

(If there is not a designated data coordinating center, enter "N/A" in the text box)

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol.

N/A

Specify how and where the data will be analyzed and who is responsible for the analysis(es):

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol.

Data analysis will be performed using SAS and STATA statistical packages including Kaplan Meier survival plots, multivariate and univariate analysis at Massachusetts General Hospital/Harvard Medical School.

Background

Abbreviated Submission:

The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the

Columbia University IRB
Approved for use until: 08/16/2017

overall objectives.

If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone protocol, you will need to go back and provide this information in your submission.

Study Purpose and Rationale:

Provide pertinent background description with references that are related to the need to conduct this study. If this is a clinical trial, the background should include both preclinical and clinical data. Be brief and to the point.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Nonalcoholic fatty liver disease (NAFLD) affects approximately 30% of the U.S. population. Up to 10% of patients with NAFLD have nonalcoholic steatohepatitis (NASH). Patients with NASH can develop cirrhosis of the liver with all the inherent complications of end stage liver disease (ESLD) including HCC. In fact, it is projected that NAFLD will be the leading indication for liver transplantation in the next decade. The yearly risk of HCC in NASH cirrhosis has been estimated to be approximately 1%, with a five year cumulative incidence of up to 8%. The incidence of HCC has increased dramatically over the last decade, and early identification of HCC is critical so that different modalities of treatment, including transplant, can be offered in a timely fashion.

Unfortunately, many patients with NAFLD do not develop symptoms early in the disease process and often present at the time of hepatic decompensation or with a new diagnosis of HCC. Identifying risk factors that predispose NAFLD patients to develop HCC may be beneficial in order to help stratify at risk patients for more intensive surveillance

Aim: To retrospectively review the patients with HCC associated with nonalcoholic fatty liver disease (NAFLD) and compare them to patients with NAFLD without HCC to identify risk factors that may contribute to the development of HCC.

Study Design:

Describe the methodology that will be used in this study, covering such factors as retrospective vs. prospective data collection, interventional vs. non-interventional, randomized vs. non-randomized, observational, experimental, ethnography, etc.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

The proposed study is a retrospective, case-control study. Cases will be defined as either biopsy proven HCC and/or cross-sectional imaging by MRI/CT diagnostic of an OPTN Class 5B (or greater) HCC. Biopsy proven HCC cases will have arisen in a background of non-tumor tissue with histologic features of NASH cirrhosis. Radiologic defined HCCs must occur in patients with a clinical history supportive of NAFLD (presence of metabolic syndrome OR diabetes OR cardiovascular risk factors OR obesity; and without risk factors for other etiologies of chronic liver disease. The control population will have the same clinical history of NAFLD as cases, but will have negative imaging for HCC. Approximately 2000 patient records will be reviewed for demographic data (i.e., DOB, ethnicity, gender) and clinical data pre- and post-surgery. Clinical data will include date of liver biopsy, date of HCC diagnosis, method of HCC diagnosis, BMI, weight, height, postmenopausal status, histologic characteristics of HCC, comorbidities, medications, labs at biopsy (CBC, CMP, viral serologies, autoimmune markers, fasting insulin,

Columbia University IRB
Approved for use until: 08/16/2017

AFP, imaging data, decompensation events, tumor characteristics, date of death or last follow-up). The date range of the CUMC/NYPH patient charts to be reviewed will be from 1/1/2003 through 6/30/2014. It will be obtained from WebCIS, iNYP, and Eclipsys.

Statistical Procedures:

Provide sufficient details so that the adequacy of the statistical procedures can be evaluated including power calculations to justify the number of participants to be enrolled into the study. Definitions of subject terms such as enrolled and accrued as used for Rascal submissions can be found in the Subjects section.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

We are planning a study of matched sets of cases and controls with 3 matched control(s) per case. Prior data indicate that the probability of exposure among controls is 0.4 and the correlation coefficient for exposure between matched cases and controls is 0.2. If the true odds ratio for disease in exposed subjects relative to unexposed subjects is 2, we will need to study 64 case patients with 3 matched control(s) per case to be able to reject the null hypothesis that this odds ratio equals 1 with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. Data analysis will be performed using SAS and STATA statistical packages including Kaplan Meier survival plots, multivariate and univariate analysis at Massachusetts General Hospital/Harvard Medical School.

Exempt and Expedited

Is the purpose of this submission to obtain an exemption determination, in accordance with 45CFR46.101(b):

No

Is the purpose of this submission to seek expedited review , as per the federal categories referenced in 45CFR46.110?

Yes

Is the risk of harm to which subjects will be exposed as a result of this research no more than minimal?

No

NOTE: Based on this response, this project is not eligible for expedited review.

Funding

Is there any external funding or support that is applied for or awarded, or are you the recipient of a gift, for this project?

No

Locations

Location Type	Facility Name	Domestic or International	Geographic Location	Local IRB Ethics Approval	Local Site Approval
Offsite	Carolinas Medical	Domestic	Charlotte, NC	Yes	Yes

Columbia University IRB
Approved for use until: 08/16/2017

Location Type	Facility Name	Domestic or International	Geographic Location	Local IRB Ethics Approval	Local Site Approval
	Center				
Offsite	Vanderbilt University School of Medicine	Domestic	Nashville, TN	Yes	Yes
Offsite	Indiana University School of Medicine	Domestic	Indianapolis, IN	Yes	Yes
Offsite	Massachusetts General Hospital	Domestic	Boston, MA	Yes	Yes
Columbia/CUMC	Cancer Center				
Columbia/CUMC	New York Presbyterian Hospital - Columbia				

Personnel

UNI	Name	Role	Department	Edit/View	Obtaining Informed Consent
jjw2151	Wattacheril, Julia	Principal Investigator	MED Digestive & Liver Diseases (751870X)	Edit	N
ae2144	Emond, Anne	Coordinator	SRG Abd Dept (755140X)	Edit	N
	Roles and Experience: Regulatory Coordinator				
cm2065	Musat, Claudia	Coordinator	SRG Abd Dept (755140X)	Edit	N
geb2122	Bayona, Grace	Coordinator	SRG Abd Dept (755140X)	Edit	N
	Roles and Experience: Regulatory Coordinator				
sm3417	Munir, Samina	Coordinator	SRG Abd Dept (755140X)	Edit	N
tt2103	Lukose, Thresiamma	Investigator	SRG TI (755160X)	Edit	N
	Roles and Experience: Research Director				

Training and COI

The PI must ensure that each individual that is added as personnel has met the training requirements for this study (http://www.cumc.columbia.edu/dept/irb/education/index.html). For help identifying which research compliance trainings you may be required to take, visit the Research Compliance Training Finder.

UNI	Name	COI	HIPAA	HSP (CITI)	Research with Minors (CITI)	FDA-Regulated Research (CITI)	S-I	CRC
jjw2151	Wattacheril, Julia	09/06/2015	08/05/2011	03/29/2016	03/29/2016	03/29/2016		
ae2144	Emond, Anne	07/29/2016	07/13/2004	12/02/2014	12/02/2014	12/02/2014		12/13/2010
cm2065	Musat, Claudia	03/02/2016	06/28/2004	02/07/2014	02/07/2014	02/07/2014		12/22/2010
geb2122	Bayona, Grace	08/05/2016	10/16/2007	03/06/2014	03/06/2014	03/06/2014	08/20/2013	12/23/2010
sm3417	Munir, Samina	10/16/2015	12/20/2010	04/13/2015	04/13/2015	04/13/2015		12/28/2010

Columbia University IRB
Approved for use until: 08/16/2017

tt2103	Lukose, Thresiamma	08/15/2016	11/16/2005	02/07/2014	02/07/2014	02/07/2014	10/17/2011	12/30/2010

Departmental Approvers

Electronic Signature: Julia Wattacheril (751870X) - Principal Investigator Date: 08/15/2016

Electronic Signature: Tasha Smith (7571416) - Date: 08/16/2016

Privacy & Data Security

Indicate the methods by which data/research records will be maintained or stored (select all that apply):

[ ]Hardcopy (i.e., paper)

[x]Electronic

Where will the data be stored?

Y

[ ]On a System

[x]On an Endpoint

Identify what type of endpoint will be used (select all that apply):

[x]Desktop Computer

[ ]Laptop Computer

[ ]Mobile Device

[ ]Other

Does this study involve the receipt or collection of Sensitive Data?

Yes

If any Sensitive Data is lost or stolen as part of your research protocol, you must inform both the IRB and the appropriate IT Security Office (CUMC IT Security if at CUMC; CUIT if at any other University campus).

What type of Sensitive Data will be obtained or collected? Select all that apply:

[x]Personally Identifiable Information (PII), including Social Security Numbers (SSN)

Will Social Security Numbers (SSNs) be collected for any purpose?

No

[x]Protected Health Information (PHI), including a Limited Data Set (LDS)

If any PHI is lost or stolen, you must inform both the IRB and the Office of HIPAA Compliance.

Indicate plans for secure storage of electronic sensitive data: check all that apply

[ ]Sensitive data will not be stored in electronic format

[x]Sensitive data will be stored on a multi-user system

Provide the System ID number for the certified environment in which the Sensitive Data will be stored

4750

[x]Sensitive data will be stored on an encrypted endpoint

Columbia University IRB
Approved for use until: 08/16/2017

By Selecting an Endpoint Device and approving this protocol for submission to the IRB, the PI is attesting that the device and any removable media that may be used have been or will be registered and/or will be maintained in compliance with the University's Information Security Charter and all related policies. It is important that this information is updated, during the course of the study, as new devices are added.

Provide a description of how the confidentiality of study data will be ensured, addressing concerns or protections that specifically relate to the data storage elements identified above (e.g. hard copy, electronic, system, and/or endpoint):

Data will be collected from paper and electronic medical records, which are protected by standard privacy mechanisms adopted by NYPH. Information and data will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study or other research for which the use or disclosure has been approved. Electronic data containing PHI will be stored in secure CUMC IT certified systems and encrypted/ password protected endpoint devices.

Is there or will there be a Certificate of Confidentiality (CoC) for this research?

No

Provide a description of the protections in place to safeguard participants' privacy while information is being collected:

Participant privacy will be protected by storing all data collected on a password protected computer in a locked research office (for coordinator) and the PI's locked office.

Procedures

Is this project a clinical trial?

No

Is this project associated with, or an extension of, an existing Rascal protocol?

No

Do study procedures involve any of the following?

Analysis of existing data and/or prospective record review

Yes

Audio and/or video recording of research subjects

No

Biological specimens (collection or use of)

No

Cancer-related research

Yes

Note: If any of the first five options are checked, this submission will be routed to the Herbert Irving Comprehensive Cancer Center's Protocol Review and Monitoring Committee (PRMC).

[ ]Involves an intervention designed to diagnose, treat, prevent, or provide supportive care to subjects with or at risk of developing a form of cancer.

[ ]Uses specimens or patient information to assess cancer risk, clinical outcomes or response to therapies.

[x]Utilizes observation or surveillance (no intervention or alteration of patient status).

Columbia University IRB
Approved for use until: 08/16/2017

[x]Examines outcomes of healthy populations and cancer patients.

[ ]Evaluates the delivery, processes, management, organization or financing of cancer care.

[ ]None of the above

Drugs or Biologics

No

Future use of data and/or specimens

No

Genetic research

No

Human embryos or human embryonic stem cells

No

Imaging procedures or radiation

No

Medical Devices

No

Surgical procedures that would not otherwise be conducted or are beyond standard of care

No

Will any of the following qualitative research methods be used?

Survey/interview/questionnaire

No

Systematic observation of public or group behavior

No

Program evaluation

No

Will any of the following tests or evaluations be used?

Cognitive testing

No

Educational testing

No

Non-invasive physical measurements

No

Taste testing

No

Is there an external protocol that describes ALL procedures in this study?

No

Please describe ALL study procedures in detail.

NOTE: Be sure to detail all of the procedures above to which a "yes" response was selected. Also detail any additional procedures that may or may not fall into the categories listed above.

This is a retrospective study, no study instruments will be used during the time of investigation.

Data will be collected from paper and electronic medical records, which are protected by standard privacy mechanisms adopted by NYPH. Information and data will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study or other research for which the use or disclosure has been approved. Electronic data containing PHI will be stored in secure CUMC IT certified systems and encrypted/ password protected endpoint devices.

Columbia University IRB
Approved for use until: 08/16/2017

Analysis of Existing Data and/or Prospective Record Review

Indicate whether the data that will be collected or utilized for the proposed study are in existence as of the current IRB submission date.

All of the data are in existence

Provide the date range of the existing data, documents, or records (e.g., medical charts, school records, census data)

Beginning Date: 01/01/2003
End Date: 06/30/2014

Note that end dates beyond the initial IRB Protocol submission date or future requests for a date parameter extension beyond the provided end date may require informed consent and HIPAA Authorization to be obtained from subjects.

Data will be obtained from (select all that apply):

[x] Columbia and/or NYP (e.g., departmental databases/systems, patient charts, Eclipsys, WebCIS, administrative/billing records, etc.)

Select all that apply:

[x] Data to be analyzed were or will be collected for clinical care

[ ] Data to be analyzed were or will be collected for nonresearch purposes other than for clinical care (e.g., student records, class evaluation, administrative records, etc.,)

[ ] Data originate from an IRB approved protocol

[ ] Other

[ ] Outside Columbia and/or NYP:

Will a member of the research team be abstracting data directly from source documents?

Yes

If there is a data abstraction document/spreadsheet, attach it to the submission to complete study records. Though the IRB does not approve these documents, for reference purposes they are extremely helpful in understanding the scope of the proposed data collection.

Columbia University IRB
Approved for use until: 08/16/2017

Select the applicable responses:

[x] The data, documents, or records to be reviewed/abstracted are those to which a member of the research team has legitimate access for non-research purposes (e.g., departmental patient database, physicians' patient clinical records, student records).

[ ] Special authorization is necessary to review the records as the research team does not have access to the data, and a request will be or has been made to access the data.

If any existing data was obtained from a prior research study, was any member of the current research team involved (e.g., obtained consent, performed study procedures, conducted data analysis) in the project or procedures that collected and/or used identifiable information?

N/A

Indicate the manner in which the existing data and/or the records to be reviewed prospectively will be collected or received:
(Select all that apply. At least one must be selected.)

[x] Contains direct identifiers (e.g., name, MRN, date of birth)
[ ] Coded and the research team has the key and can link the data to direct identifiers
[ ] Coded and the research team does not have access to the key to link data to direct identifiers
[ ] Prior to the receipt of the data by the research team submitting this protocol, the identifiers will be removed and no link will remain.
[ ] The information was originally or will be collected without identifiers

If data are collected or received at any point in time with direct identifiers or linked to identifiers, then the data are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of the submission.

Recruitment And Consent

Recruitment:

Describe how participants will be recruited:
Data will be collected from paper and electronic medical records, which are protected by standard privacy mechanisms adopted by NYPH. Information and data will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study or other research for which the use or disclosure has been approved. Electronic data containing PHI will be stored in secure CUMC IT certified systems and encrypted/

Columbia University IRB
Approved for use until: 08/16/2017

password protected endpoint devices.

Select all methods by which participants will be recruited:

[x] Study does not involve recruitment procedures
[ ] Person to Person
[ ] Radio
[ ] Newspapers
[ ] Direct Mail
[ ] Website
[ ] Email
[ ] Television
[ ] Telephone
[ ] Flyer/Handout
[ ] Newsletter/Magazine/Journal
[ ] ResearchMatch
[ ] CUMC RecruitMe

Informed Consent Process:

Informed Consent Process, Waiver or Exemption: Select all that apply

[ ] Informed consent with written documentation will be obtained from the research participant or appropriate representative.

[ ] Informed consent will be obtained but a waiver of written documentation of consent (i.e., agreement to participate in the research without a signature on a consent document) is requested.

[x] A waiver of some or all elements of informed consent (45 CFR 46.116) is requested.

Waiver of consent is applicable to:
The study in its entirety

Select the applicable situation:

[x]This study qualifies for a waiver of consent as per 45CFR46.116(d) as the following criteria are met in this study (provide justification for EACH of these criteria):

(1)The research involves no more than minimal risk to the subjects
Provide justification:
This is a retrospective study: no more than minimal risk from prior data collected during clinical care,

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects
Provide justification:
This is a retrospective study: the waiver will not adversely affect the rights and welfare of the subjects

(3) The research could not practicably be carried out without the waiver or alteration

Columbia University IRB
Approved for use until: 08/16/2017

Provide justification:
This is a retrospective study: this research could not practicably be carried out without the waiver

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation

Provide justification:
This is a retrospective study, no study procedures will be used during the time of investigation.

[ ]This study qualifies for a waiver of consent as per 45CFR46.116(c) as the following criteria are met for this study (provide justification for EACH of these criteria):

[ ] Planned Emergency Research with an exception from informed consent as per 21 CFR 50.24.

[x] Informed consent is not required; this is exempt research.

Although informed consent is not required for exempt research, when there will be interaction with potential subjects for the purpose of the project, it is recommended that there be a process to provide information about the research (e.g., the elements of informed consent could be provided in an information sheet or consent script) and allow subjects the opportunity to confirm their agreement to participate.

Describe how participants will be informed about the research, if applicable:
This a retrospective study. We request a waiver of consent for this study. We anticipate that we will not be able to
obtain informed consent from the majority of the study subjects due

1) no more than minimal risk from prior data collected during clinical care,
2) the waiver will not adversely affect the rights and welfare of the subjects; and
3)thisresearch could not practicably be carried out without the waiver.

Subject Language

Enrollment of non-English speaking subjects is expected.

Languages anticipated:

Spanish

As you plan on enrolling non-English speaking subjects, administrative IRB approval of the translated documents (e.g., consent, recruitment materials, questionnaires) in the above selected languages are required. Please see the IRB's policy on the Enrollment of Non-English Speaking Subjects in Research for further details

(http://www.cumc.columbia.edu/dept/irb/policies/documents/Nonenglishspeakingsubjects.Revised.FINALDRAFT.111909.website.doc).

Capacity to Provide Consent:

Columbia University IRB
Approved for use until: 08/16/2017

Do you anticipate using surrogate consent or is research being done in a population where capacity to consent may be questionable?

No

Research Aims & Abstracts

Research Question(s)/Hypothesis(es):

Hypothesis: We hypothesize that cases with NAFLD and HCC will have a significant association with insulin resistance/existence of diabetes.

Scientific Abstract:

Nonalcoholic fatty liver disease (NAFLD) affects approximately 30% of the U.S. population. Up to 10% of patients with NAFLD have nonalcoholic steatohepatitis (NASH). Patients with NASH can develop cirrhosis of the liver with all the inherent complications of end stage liver disease (ESLD) including HCC. In fact, it is projected that NAFLD will be the leading indication for liver transplantation in the next decade. The yearly risk of HCC in NASH cirrhosis has been estimated to be approximately 1%, with a five year cumulative incidence of up to 8%. The incidence of HCC has increased dramatically over the last decade, and early identification of HCC is critical so that different modalities of treatment, including transplantation, can be offered in a timely fashion. Unfortunately, many patients with NAFLD do not develop symptoms early in the disease process and often present at the time of hepatic decompensation or with a new diagnosis of HCC. Identifying risk factors that predispose NAFLD patients to develop HCC may be beneficial in order to help stratify at risk patients for more intensive surveillance. The aim of this study is to retrospectively review the patients with HCC associated with nonalcoholic fatty liver disease (NAFLD) and compare them to patients with NAFLD without HCC to identify risk factors that may contribute to the development of HCC. This study will be part of a multi-center effort, led by Columbia, to investigate these associations.

Lay Abstract:

Nonalcoholic fatty liver disease (NAFLD) affects approximately 30% of the U.S. population. Up to 10% of patients with NAFLD have nonalcoholic steatohepatitis (NASH). Patients with NASH can develop cirrhosis of the liver with all the inherent complications of end stage liver disease (ESLD) including HCC. In fact, it is projected that NAFLD will be the leading indication for liver transplantation in the next decade. The yearly risk of HCC in NASH cirrhosis has been estimated to be approximately 1%, with a five year cumulative incidence of up to 8%. The incidence of HCC has increased dramatically over the last decade, and early identification of HCC is critical so that different modalities of treatment, including transplantation, can be offered in a timely fashion. Unfortunately, many patients with NAFLD do not develop symptoms early in the disease process and often present at the time of hepatic decompensation or with a new diagnosis of HCC. Identifying risk factors that predispose NAFLD patients to develop HCC may be beneficial in order to help stratify at-risk patients for more intensive surveillance. The aim of this study is to retrospectively review the patients with HCC associated with nonalcoholic fatty liver disease (NAFLD) and compare them to patients with NAFLD without HCC to identify risk factors that may contribute to the development of HCC. This study will be part of a multi-center effort, led by

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Columbia, to investigate these associations.

Risks, Benefits & Monitoring

Abbreviated Submission:
The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the overall objectives. .
If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone protocol, you will need to go back and provide this information in your submission.

Potential Risks:
Provide information regarding all risks to participants that are directly related to participation in this protocol, including any potential for a breach of confidentiality. Risks associated with any of the items described in the Procedures section of this submission should be outlined here if they are not captured in a stand-alone protocol. Risks of procedures that individuals would be exposed to regardless of whether they choose to participate in this research need not be detailed in this section, unless evaluation of those risks is the focus of this research. When applicable, the likelihood of certain risks should be explained and data on risks that have been encountered in past studies should be provided.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

This is a minimal risk study. The only risk would be potential loss of confidentiality, and every effort will be made to prevent this.

Potential Benefits:
Provide information regarding any anticipated benefits of participating in this research. There should be a rational description of why such benefits are expected based on current knowledge. If there is unlikely to be direct benefit to participants/subjects, describe benefits to society. Please note that elements of participation such as compensation, access to medical care, receiving study results, etc. are not considered benefits of research participation.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Patients with NAFLD are currently being screened according to paradigms for other chronic liver diseases. If specific risk factors are associated with the development of HCC in a background of NAFLD, better screening, earlier detection and earlier treatment may portend better outcomes (survival).

Alternatives:
If this research involves an intervention that presents greater than minimal risk to participants, describe available alternative interventions and provide data to support their efficacy and/or availability. Note, participants always have the option not to participate in research.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next

Columbia University IRB
Approved for use until: 08/16/2017

question
N/A

Data and Safety Monitoring:

Describe how data and safety will be monitored locally and, if this is a multi-center study, how data and safety will be monitored across sites as well.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

N/A

Subjects

Unless otherwise noted, the information entered in this section should reflect the number of subjects enrolled or accrued under the purview of Columbia researchers, whether at Columbia or elsewhere.

Target enrollment:

256

Number enrolled to date:

55

Number enrolled since the last renewal or, if this is the first renewal, since the initial approval:

0

Number anticipated to be enrolled in the next approval period:

20

Does this study involve screening/assessment procedures to determine subject eligibility?

No

Of the number of subjects enrolled, or the number accrued for interventional studies with a screening process:

How many remain on the study?

55

How many are off study?

0

How many completed the study?

0

Have any withdrawn of their own initiative?

No

Have any been removed by PI?

No

Have any been lost to follow-up?

No

Have any died while on study?

No

Have any subject complaints been received?

No

Is this a multi-center study?

Yes

Target number of eligible subjects to be included at all sites:

256

Does this study have one or more components that apply to a subset of the overall study population (e.g. Phase

Columbia University IRB
Approved for use until: 08/16/2017

1/2, sub-studies)?

No

Of the number enrolled, or the number accrued for interventional studies with a screening process, indicate:

Population Gender

Females	Males	Non Specific
50%	50%	0%

Population Age

0-7	8-17	18-65	>65	Non Specific
0%	0%	90%	10%	0%

Population Race

American Indian/Alaskan Native	Asian	Native Hawaiian or Other Pacific Islander	Black or African American	White	More than One Race	Non-Specific
0%	0%	0%	20%	30%	0%	50%

Population Ethnicity

Hispanic or Latino	Not Hispanic or Latino	Non-Specific
40%	50%	10%

Vulnerable Populations as per 45 CFR 46:

Will children/minors be enrolled

No

Will pregnant women/fetuses/neonates be targeted for enrollment?

No

Will prisoners be targeted for enrollment?

No

Other Vulnerable Populations:

[ ]Individuals lacking capacity to provide consent

[ ]CU/NYPH Employees/Residents/Fellows/Interns/Students

[ ]Economically disadvantaged

[ ]Educationally disadvantaged

[ ]Non-English speaking

[ ]Other Vulnerable populations

[x]None of the Populations listed above will be targeted for Enrollment

Subject Population Justification:

The subject population distribution is based on clinic population estimates within our liver clinic.

Does this study involve compensation or reimbursement to subjects?

No

Attached HIPAA Forms

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Number	Type	Title	Status
AAAK9400	B	AAAO0410	Approve

Documents

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	CreatedBy
No	Will be submitted at next submission	Local IRB/Ethics/Site Approval	irb.docx	Y		08/11/2016	Samina Munir (sm3417)
No	NASH-HCC IRB form	Other	NASH-HCC IRB form.pdf	Y		09/09/2014	Julia Wattacheril (jjw2151)
No	Response to IRB_HCC_NAFLD	Other	Response to IRB_HCC_NAFLD.docx	Y		09/24/2014	Grace Bayona (geb2122)
No	Study Description NAFLD-HCC_IRB-2-clean	Other	Study Description NAFLD-HCC_IRB-2-clean.docx	Y		09/24/2014	Grace Bayona (geb2122)
No	Study Description NAFLD-HCC_IRB-2-tracked	Other	Study Description NAFLD-HCC_IRB-2-tracked.docx	N		09/24/2014	Grace Bayona (geb2122)
No	Study Description NAFLD-HCC_IRB	Other	Study Description NAFLD-HCC_IRB.docx	N		09/10/2014	Grace Bayona (geb2122)

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CAROLINAS HEALTHCARE SYSTEM
Institutional Review Board / Privacy Board

RECEIVED
NOV 7 2016
CHS IRB

Protocol / Consent Change Report Form

Any change to a proposed research study needs to be approved by the IRB. If the change is minor, the revision may go through expedited approval. Any changes that are not minor (e.g., increased risk or discomfort from a procedure, increase in drug dose, addition of another drug) will go through Full-Board review.

Submission Date: 11/7/16	IRB File #: 8-14-15E
Investigator: Andrew deLemos, MD	Dept: Hepatology
Coordinator: Krista Bossi, MS	Phone: 6-4834

Study Title: Hepatocellular carcinoma (HCC) in patients with underlying nonalcoholic fatty liver disease (NAFLD)
Sponsor: None

Does this change require a Full Board Review?

☐ Yes ☒ No

Are there any substantive changes in the potential risks and benefits of study participation that will impact patient safety?

☒ No ☐ Yes (explain)

PROTOCOL

		Date	Version #
X	Amendment	02 November 2016	v5
	Revision		
	Update		
	Addendum		

Description of changes:

1. Addition of Aim 2 to determine temporal trends in etiology of liver disease predisposing HCC
2. Expansion of time frame from 01/2005 to 01/2000
3. Increase total number of charts to be reviewed from 500 to 1000

Has this revised Protocol been submitted to the Pharmacy?

☐ YES ☐ NO NA

Highlight changes and attach copy of amendment/revision/update/addendum in Protocol

Find included

CONSENT FORM NA

Indicate the number of CONSENTS approved by the IRB (NOT the # of signed consents):

Indicate the number of ASSENTS approved by the IRB (NOT the #of signed assents):

Revision Date:

NA

Description of changes (Clarify which Consents/Assents are being changed):

NA

Study Enrollment:

48	Number of patients enrolled (charts reviewed at CHS)
	Number of active patients
	Number of patients in long-term follow-up
	Anticipated duration of study

Plan for Re-Consenting: (If no plan, state "no plan on reconsenting")

NA

Attach copy of consent with deletions lined through and additions highlighted and a clean copy

NA

CERTIFICATION OF PRINCIPAL INVESTIGATOR: Your signature here certifies that you have assessed the information concerning the Protocol/Consent changes detailed above.

Signature of Investigator

11/7/16
Date

(For IRB Use Only)

IRB File Number 08-14-15E

Your documentation has been received, reviewed, and approved by the Chair or Vice Chair of the IRB on 10 NOV 16 (Date). **It will be placed on file.**

Michael Brennan, DDS
Vice Chair, IRB

Rachel Seymour, PhD
Vice Chair, IRB

Michael Runyon, MD
Chair, IRB

PARTNERS HEALTHCARE
FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL AND MASSACHUSETTS GENERAL HOSPITAL

Partners Human Research Committee
116 Huntington Avenue, Suite 1002
Boston, MA 02116
Tel: (617) 424-4100
Fax: (617) 424-4199

Continuing Review: Notification of IRB Approval/Activation
Protocol #: 2014P000924/MGH

Date: April 12, 2016

To: Kathleen S Corey, MD
MGH
Medical Services / GI Unit

From: Partners Human Research Committee
116 Huntington Avenue, Suite 1002
Boston, MA 02116

Title of Protocol:	Prevalence of Hepatocellular Carcinoma in Patients with Nonalcoholic Fatty Liver Disease
IRB Continuing Review #:	1
IRB Review Type:	Expedited
Expedited Category/ies:	(5)
IRB Approval Date:	4/11/2016
Approval Activation Date:	4/12/2016
IRB Expiration Date:	5/9/2018

This project has been reviewed by MGH IRB . During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Please note that if an IRB member had a conflict of interest with regard to the review of this project, consistent with IRB policies and procedures, the member was required to leave the room during the discussion and vote on this project except to provide information requested by the IRB.

NOTES: *Use of Medical Records - ongoing. A data collection form is noted and approved with Continuing Review #1 submission*

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

1. Submission of any and all proposed changes to this project (e.g., protocol, recruitment materials, consent form, status of the study, etc.) to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB as an unanticipated problem.
2. Submission of continuing review submissions for re-approval of the project prior to expiration of IRB approval and a final continuing review submission when the project has been completed.

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3. Submission of any and all unanticipated problems, including adverse event(s) in accordance with the IRB's policy on reporting unanticipated problems including adverse events.
4. Obtaining informed consent from subjects or their legally authorized representative prior to initiation of research procedures when and as required by the IRB and, when applicable, documenting informed consent using the current IRB approved consent form(s)with the IRB-approval stamp in the document footer.
5. Informing all investigators and study staff listed on the project of changes and unanticipated problems, including adverse events, involving risks to subjects or others.
6. When investigator financial disclosure forms are required, updating your financial interests in Insight and for informing all site responsible investigators, co-investigators and any other members of the study staff identified by you as being responsible for the design, conduct, or reporting of this research study of their obligation to update their financial interest disclosures in Insight if (a) they have acquired new financial interests related to the study and/or (b) any of their previously reported financial interests related to the study have changed.

The IRB has the authority to terminate projects that are not in compliance with these requirements.
Questions related to this project may be directed to Thelma L Bennett, TBENNETT1@PARTNERS.ORG, 617-424-4116.

CC: James M Cleary, MGH - MGH Cancer Center - Hematology/Oncology, Non-Study Staff
James M Cleary, MGH - MGH Cancer Center - Hematology/Oncology, Non-Study Staff

Vanderbilt University
Institutional Review Board
504 Oxford House Nashville, Tennessee 37232-4315
(615) 322-2918 Fax: (615) 343-2648
www.mc.vanderbilt.edu/irb

March 13, 2015

Andrew Scanga, M.D.
Transplant
1660 TVC 37232-5280

Tina Higginbotham, MS,CCRP
Medicine - Gastroenterology
103C MAB 1610

RE: IRB# 150360 "HCC in Patients with Underlying NAFLD"

Dear Andrew Scanga, M.D.:

A sub-committee of the Institutional Review Board reviewed the research application identified above. The sub-committee determined the study poses minimal risk to participants, and the application is approved under 45 CFR 46.110 (F)(5). Approval is extended for the Application for Human Research dated 03/11/2015.

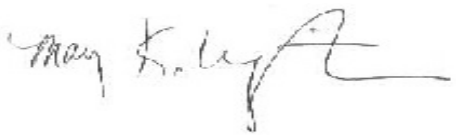
Documentation of informed consent is waived in accordance with 45 CFR 46.117 (c) (2).

As the Principal Investigator, you are responsible for the accurate documentation, investigation and follow-up of all possible study-related adverse events and unanticipated problems involving risks to participants or others. The IRB Adverse Event reporting policy III.G is located on the IRB website at http://www.mc.vanderbilt.edu/irb/.

Please note that approval is for a 12-month period. Any changes to the research study must be presented to the IRB for approval prior to implementation.

DATE OF IRB APPROVAL: 3/13/2015 DATE OF IRB EXPIRATION: 3/12/2016

Sincerely,



M. Kay Washington, M.D., Ph.D., Vice-Chair
Institutional Review Board
Health Sciences Committee #3

MKW/aep
Electronic Signature: Kay Washington/VUMC/Vanderbilt : (711C8FF56D09658061E7058D4499F5E4)
Signed On: 03/26/2015 04:08:01 PM CDT