Carilion IRB Application (Version 1.22)

1.0 General Information

*Please enter the full title of your study (#[%irb_number%]):		
Evaluation of Innovative Placental Imaging Techniques in Fetal Growth Restriction		
***Please enter an abbreviated study title or key words you would like to use to reference the study:**		
Placental Imaging Techniques * This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.		

2.0 Add departments

2.1 Add the departments of all Key Study Personnel that will be involved with the design, conduct, or reporting on this project:

Is Primary?	Department Name
◉	**CC** - Department of Obstetrics and Gynecology
○	**CC** - Research & Development

3.0 ■ Assign key study personnel (KSP) access to the study

3.1 * Please add a Principal Investigator for the study:

Name	Role	Training Record
Whitham, Megan	**Principal Investigator**	View Training Record

3.2 Please add the Research Staff, if applicable:

A) Additional Investigators

Name	Role	Training Record
Durica, Allison	**Sub-Investigator**	View Training Record
Gbozah, Korene, MD	**Sub-Investigator**	View Training Record
Hennis, Lauren	**Sub-Investigator**	View Training Record
Prinster, Teresa	**Sub-Investigator**	View Training Record
Yohannes, Falen, DO	**Sub-Investigator**	View Training Record

B) Research Support Staff

Name	Role	Training Record
CATALDO JOHNSON, Christy	Other	View Training Record
Degraaf, Amanda	Student	View Training Record
Gabby, Maegan	Student	View Training Record
Grossheim, Tyler	Research Coordinator	View Training Record
Issel, Sofia	Student	View Training Record
Joseph, Nicholas	Research Coordinator	View Training Record
Miller, Makayla, Associates of Applied Science	Other	View Training Record
Nichols, Jessica	Research Coordinator	View Training Record
Purcell, Emily	Other	View Training Record

3.3 *Please add a Study Contact:

Name	Role	Training Record
Grossheim, Tyler	Study Contact	View Training Record
Joseph, Nicholas	Study Contact	View Training Record
Nichols, Jessica	Study Contact	View Training Record
Whitham, Megan	Study Contact	View Training Record

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The study contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

4.0 Key Study Personnel (KSP) Info

4.1 Provide the following information below for each Carilion Clinic research team member: You will be asked to provide information about members of the research team that are outside Carilion at a later time.

Click "add another entry" to respond to this item.

****CITI Training in Human Subjects Research Biomedical Researchers and GCP (for FDA-regulated and NIH-funded) will be verified for each team member before the application will be reviewed by the IRB. Detailed instructions for Carilion's CITI training requirements can be found at https://www.carilionclinic.org/irb/education . Please ask all team members to ensure their Carilion email address is added to their CITI account profile so that their CITI training is pulled into this system. This feed occurs on a nightly basis.***

Entry 1

Research team member name:	Whitham, Megan
Degree:	M.D.

Status:	Physician **If other, specify:**
Email address:	mdwhitham@carilionclinic.org
Phone number:	7038197703
Alternate phone number (optional):	
Affiliation:	Carilion Clinic **If other, specify:**
Research Duties (check all that apply):	☑ PI: Ultimately responsible for the study including conduct by all study team members ☑ Identification of potential subjects ☑ Contacting potential subjects ☑ Screening of subjects, including assessing eligibility criteria ☑ Obtain Informed Consent ☐ Randomization ☑ Conduct of study procedures that result in research data ☐ Prepare or dispense study drug/device ☑ Research specimen collection/shipping ☑ Adverse Event documenting and reporting ☑ Data entry ☑ Data Analysis - Identifiable ☑ Data Analysis - De-identified ☑ Regulatory document maintenance ☐ Other (specify):

Entry 2

Research team member name:	Nichols, Jessica
Degree:	MSHSc
Status:	Carilion Staff/Employee **If other, specify:**
Email address:	jlnichols1@carilionclinic.org
Phone number:	540-491-2324
Alternate phone number (optional):	
Affiliation:	Carilion Clinic **If other, specify:**

Research Duties (check all that apply):	☐ PI: Ultimately responsible for the study including conduct by all study team members ☑ Identification of potential subjects ☑ Contacting potential subjects ☑ Screening of subjects, including assessing eligibility criteria ☑ Obtain Informed Consent ☐ Randomization ☑ Conduct of study procedures that result in research data ☐ Prepare or dispense study drug/device ☐ Research specimen collection/shipping ☑ Adverse Event documenting and reporting ☑ Data entry ☑ Data Analysis - Identifiable ☑ Data Analysis - De-identified ☑ Regulatory document maintenance ☐ Other (specify):

Entry 3

Research team member name:	Joseph, Nicholas
Degree:	B.S.
Status:	Carilion Staff/Employee **If other, specify:**
Email address:	ncjoseph@carilionclinic.org
Phone number:	540-655-8670
Alternate phone number (optional):	
Affiliation:	Carilion Clinic **If other, specify:**
Research Duties (check all that apply):	☐ PI: Ultimately responsible for the study including conduct by all study team members ☑ Identification of potential subjects ☑ Contacting potential subjects ☑ Screening of subjects, including assessing eligibility criteria ☑ Obtain Informed Consent ☐ Randomization ☑ Conduct of study procedures that result in research data ☐ Prepare or dispense study drug/device ☐ Research specimen collection/shipping ☑ Adverse Event documenting and reporting ☑ Data entry

- [x] Data Analysis - Identifiable
- [x] Data Analysis - De-identified
- [x] Regulatory document maintenance
- [ ] Other (specify):

Entry 4

Research team member name:	CATALDO JOHNSON, Christy
Degree:	RDMS
Status:	Carilion Staff/Employee **If other, specify:**
Email address:	cljohnson2@carilionclinic.org
Phone number:	9546739761
Alternate phone number (optional):	
Affiliation:	Carilion Clinic **If other, specify:**
Research Duties (check all that apply):	☐ PI: Ultimately responsible for the study including conduct by all study team members ☑ Identification of potential subjects ☑ Contacting potential subjects ☑ Screening of subjects, including assessing eligibility criteria ☑ Obtain Informed Consent ☐ Randomization ☑ Conduct of study procedures that result in research data ☐ Prepare or dispense study drug/device ☐ Research specimen collection/shipping ☑ Adverse Event documenting and reporting ☑ Data entry ☐ Data Analysis - Identifiable ☐ Data Analysis - De-identified ☐ Regulatory document maintenance ☐ Other (specify):

Entry 5

Research team member name:	Miller, Makayla, Associates of Applied Science
Degree:	RDMS
Status:	Carilion Staff/Employee

	If other, specify:
Email address:	msmiller@carilionclinic.org
Phone number:	4349600456
Alternate phone number (optional):	
Affiliation:	Carilion Clinic **If other, specify:**
Research Duties (check all that apply):	☐ PI: Ultimately responsible for the study including conduct by all study team members ☑ Identification of potential subjects ☑ Contacting potential subjects ☑ Screening of subjects, including assessing eligibility criteria ☑ Obtain Informed Consent ☐ Randomization ☑ Conduct of study procedures that result in research data ☐ Prepare or dispense study drug/device ☐ Research specimen collection/shipping ☑ Adverse Event documenting and reporting ☑ Data entry ☐ Data Analysis - Identifiable ☐ Data Analysis - De-identified ☐ Regulatory document maintenance ☐ Other (specify):

Entry 6

Research team member name:	MORIN, Sonya
Degree:	RDMS
Status:	Carilion Staff/Employee **If other, specify:**
Email address:	smgeorge1@carilionclinic.org
Phone number:	5405105361
Alternate phone number (optional):	
Affiliation:	Carilion Clinic **If other, specify:**

Research Duties (check all that apply):	☐ PI: Ultimately responsible for the study including conduct by all study team members ☑ Identification of potential subjects ☑ Contacting potential subjects ☑ Screening of subjects, including assessing eligibility criteria ☑ Obtain Informed Consent ☐ Randomization ☑ Conduct of study procedures that result in research data ☐ Prepare or dispense study drug/device ☐ Research specimen collection/shipping ☑ Adverse Event documenting and reporting ☑ Data entry ☐ Data Analysis - Identifiable ☐ Data Analysis - De-identified ☐ Regulatory document maintenance ☐ Other (specify):

Entry 7

Research team member name:	Gabby, Maegan
Degree:	MS
Status:	VTCSOM Medical Student **If other, specify:**
Email address:	megabby@carilionclinic.org
Phone number:	540-985-9985
Alternate phone number (optional):	
Affiliation:	VTCSOM **If other, specify:**
Research Duties (check all that apply):	☐ PI: Ultimately responsible for the study including conduct by all study team members ☑ Identification of potential subjects ☑ Contacting potential subjects ☑ Screening of subjects, including assessing eligibility criteria ☑ Obtain Informed Consent ☐ Randomization ☐ Conduct of study procedures that result in research data ☐ Prepare or dispense study drug/device ☐ Research specimen collection/shipping ☐ Adverse Event documenting and reporting ☑ Data entry ☑ Data Analysis - Identifiable ☑ Data Analysis - De-identified ☐ Regulatory document maintenance

☐ Other (specify):

Entry 8

Research team member name:	Durica, Allison
Degree:	MD
Status:	Physician **If other, specify:**
Email address:	ARDurica@carilionclinic.org
Phone number:	540-985-9985
Alternate phone number (optional):	
Affiliation:	Carilion Clinic **If other, specify:**
Research Duties (check all that apply):	☐ PI: Ultimately responsible for the study including conduct by all study team members ☑ Identification of potential subjects ☑ Contacting potential subjects ☑ Screening of subjects, including assessing eligibility criteria ☑ Obtain Informed Consent ☐ Randomization ☑ Conduct of study procedures that result in research data ☐ Prepare or dispense study drug/device ☑ Research specimen collection/shipping ☑ Adverse Event documenting and reporting ☑ Data entry ☑ Data Analysis - Identifiable ☑ Data Analysis - De-identified ☑ Regulatory document maintenance ☐ Other (specify):

Entry 9

Research team member name:	Degraaf, Amanda
Degree:	MS
Status:	VTCSOM Medical Student **If other, specify:**

Email address:	amandadegraaf@vt.edu
Phone number:	443-813-1644
Alternate phone number (optional):	
Affiliation:	VTCSOM **If other, specify:**
Research Duties (check all that apply):	☐ PI: Ultimately responsible for the study including conduct by all study team members ☑ Identification of potential subjects ☑ Contacting potential subjects ☑ Screening of subjects, including assessing eligibility criteria ☑ Obtain Informed Consent ☐ Randomization ☐ Conduct of study procedures that result in research data ☐ Prepare or dispense study drug/device ☐ Research specimen collection/shipping ☐ Adverse Event documenting and reporting ☑ Data entry ☑ Data Analysis - Identifiable ☑ Data Analysis - De-identified ☐ Regulatory document maintenance ☐ Other (specify):

Entry 10

Research team member name:	Prinster, Teresa
Degree:	MD
Status:	Physician **If other, specify:**
Email address:	tbprinster@carilionclinic.org
Phone number:	540-985-9715
Alternate phone number (optional):	
Affiliation:	Carilion Clinic **If other, specify:**
Research Duties (check all that apply):	☐ PI: Ultimately responsible for the study including conduct by all study team members ☑ Identification of potential subjects

- [x] Contacting potential subjects
- [x] Screening of subjects, including assessing eligibility criteria
- [x] Obtain Informed Consent
- [ ] Randomization
- [ ] Conduct of study procedures that result in research data
- [ ] Prepare or dispense study drug/device
- [ ] Research specimen collection/shipping
- [ ] Adverse Event documenting and reporting
- [x] Data entry
- [x] Data Analysis - Identifiable
- [x] Data Analysis - De-identified
- [ ] Regulatory document maintenance
- [ ] Other (specify):

Entry 11

Research team member name:	Yohannes, Falen, DO
Degree:	DO
Status:	Physician **If other, specify:**
Email address:	fgyohannes@carilionclinic.org
Phone number:	(540) 988-3971
Alternate phone number (optional):	
Affiliation:	Carilion Clinic **If other, specify:**
Research Duties (check all that apply):	

- [ ] PI: Ultimately responsible for the study including conduct by all study team members
- [x] Identification of potential subjects
- [x] Contacting potential subjects
- [x] Screening of subjects, including assessing eligibility criteria
- [x] Obtain Informed Consent
- [ ] Randomization
- [ ] Conduct of study procedures that result in research data
- [ ] Prepare or dispense study drug/device
- [ ] Research specimen collection/shipping
- [ ] Adverse Event documenting and reporting
- [x] Data entry
- [x] Data Analysis - Identifiable
- [x] Data Analysis - De-identified
- [ ] Regulatory document maintenance
- [ ] Other (specify):

Entry 12

Research team member name:	Issel, Sofia
Degree:	MS
Status:	Carilion Staff/Employee **If other, specify:**
Email address:	sofiai@vt.edu / sfissel@carilionclinic.org
Phone number:	540-985-9985
Alternate phone number (optional):	
Affiliation:	Carilion Clinic **If other, specify:**
Research Duties (check all that apply):	☐ PI: Ultimately responsible for the study including conduct by all study team members ☑ Identification of potential subjects ☑ Contacting potential subjects ☑ Screening of subjects, including assessing eligibility criteria ☑ Obtain Informed Consent ☐ Randomization ☐ Conduct of study procedures that result in research data ☐ Prepare or dispense study drug/device ☐ Research specimen collection/shipping ☐ Adverse Event documenting and reporting ☑ Data entry ☑ Data Analysis - Identifiable ☑ Data Analysis - De-identified ☐ Regulatory document maintenance ☐ Other (specify):

5.0 Application Type

IRB-24-2156

5.2 Select the application type:

- ◉ Human Subject Research Study
- ○ Determination of Human Subjects Research (including QA/QI Determination)
- ○ Establishing a prospective Data or Specimens Research Repository
- ○ Humanitarian Use Device (non-research use)

- ○ Expanded Access or Compassionate Use
- ○ Single Patient Emergency Use
- ○ Preparatory to Research Application
- ○ IRB Grant Review ONLY for preliminary approval if required by funder
- ○ Requesting Carilion Clinic RELY on another IRB of Record (WIRB, CIRB, VT, UVA, Advarra etc.)
- ○ Conversion of a paper application due for Continuing Review or Annual Check-In

Please ensure the PI has completed and submitted the R&D Application Department Level Review Form (eCRAF), and that the PI's Department Chair or signatory has signed off on the R&D Department Level Review eCRAF Form BEFORE you proceed any further with this IRB application. Please read the below bullet points carefully and acknowledge your understanding.

- **The R&D Application Department Level Review eCRAF Form must be submitted by the PI and signed off by Department Chair or signatory through RedCap BEFORE you may proceed with this IRB application.**
- **The R&D Application Department Level Review eCRAF Form serves a major function for section and department level review and may result in this study not being permitted due to resources, scientific validity, or other reasons.**
- **You must submit a copy of the signed R&D Application Department Level Review eCRAF Form with this IRB application in the supplemental document section.**
- **Failure to complete the steps in the above order will result in a significant delay in the IRB's review of this study.**

- ◉ Acknowledged

6.0 Funding Information and Outside Services

6.1 Select the applicable funding source(s).

- ☐ None (no money, equipment, supplies, and/or services will be provided by external source)
- ☐ No monetary funding BUT equipment, supplies, and/or services will be provided
- ☐ Federal Government
- ☐ Foundation or Non-profit
- ☐ Industry/Commercial Sponsor
- ☐ State or Local Government
- ☐ Investigator or Departmental/Unit Funds
- ☑ Carilion RAP Grant
- ☐ Other

6.2 Select services from all areas outside of the Research Team members' affiliations that are necessary to conduct the work.

Research and Development (R&D) will contact you to arrange a Feasibility Meeting based on your responses below. This will ensure roles, responsibilities, and costs associated with this project are understood by all parties. Final sign-off from leadership in the additional service areas, as well as contracts, may be required.

- ☐ Animals
- ☐ Basic Science Laboratory Services
- ☐ Center for Simulation, Research & Patient Safety (CSRPS)
- ☐ Department of Medicine
- ☐ Department of Pediatrics
- ☐ Department of Psychiatry
- ☐ Department of Surgery
- ☐ Emergency Department
- ☐ Hazardous Materials
- ☑

Health Analytics Research Team (HART), including Epic Data Extraction, Statistics Services, Carilion RedCap, Epic Research Access

- [ ] Human Resources
- [ ] Jefferson College
- [ ] Nuclear Medicine
- [ ] Nursing
- [ ] Pathology
- [ ] Pharmacy
- [ ] Physical Therapy
- [ ] Radiology
- [ ] Recombinant DNA/RNA
- [ ] Respiratory
- [ ] Solstas Lab
- [ ] Technology Services Group (TSG)
- [ ] Other
- [ ] None

6.3 You have selected that HART services are needed for this research. Specify the resources needed.

- [x] Epic Data Extract
- [x] Statistics Support (biostatisticians)
- [x] Carilion REDCap (Data management)
- [x] Epic Research Access for Chart Review
- [x] TriNetX Identifiable Patient List/Data Set
- [ ] SPARC Carilion Secure Research Environment

Note: If you have not yet discussed this project with the HART team, please contact them at HART@carilionclinic.org before proceeding any further with this application. This will ensure that your request for this project is feasible.

7.0 Regulatory Compliance

7.1 How many studies is the PI currently responsible for?

1

7.2 Does the PI have protected or dedicated time available to conduct this research?

- (•) Yes
- ( ) No

7.3 Has any member of the research team ever received a FDA 483, "Warning Letter", Notice of Disqualification, or other warning or disciplinary action from an agency or licensing authority?

- ( ) Yes
- (•) No

7.4 Has this study been disapproved or terminated by another IRB?

- ( ) Yes
- (•) No

8.0 Conflict of Interest

8.1 A Conflict of Interest, per the Carilion Clinic Organizational Policy, is a situation in which an Investigator's and/or their Family Member's financial, professional, or other personal consideration may directly or indirectly affect, or reasonably appear to affect, the Investigator's professional judgement in performing their Institutional Responsibilities. A Conflict of Interest may be actual, apparent, or potential. Any research team member listed on the IRB application is considered to be an Investigator. It is the Principal Investigator'

s responsibility to query all Carilion research team members on this study to ensure they have honestly completed their Annual COI Disclosure and that it is current. The Principal Investigator should be notified by the study team member if the study team member has disclosed any related interests. Carilion Clinic's Conflicts of Interest in Research Policy **can be found** here.

If this study has any external funding or support, have all Carilion research team members filed an Annual COI Disclosure through Carilion Clinic's Office of Organizational Integrity and Compliance via the COI-Smart online disclosure system?

- ○ Yes
- ○ No
- ◉ N/A - this study does not have any external funding or support

If the funding status or support of this study changes, you must submit a modification to the IRB immediately with the updates funding or support source and note if any research team member now has a potential Conflict of Interest. The IRB will work with the Carilion Clinic Office of Organizational Compliance and Integrity to ensure any potential conflicts of interest are reported and managed.

It is the Principal Investigator and conflicted employee's responsibilities to ensure the conflict or any changes that result in a potential conflict are disclosed to the Office of Integrity and Compliance who will refer it to the Carilion Clinic's Research Conflict of Interest Commitee for appropriate management when necessary. Disclosure and management must occur before the conflicted employee is permitted to engage in any research activities. Any employee who violates the Conflict of Interest policy is subject to disciplinary actions, up to and including termination.

9.0 Collaboration

9.1 Is this research project a collaboration between Carilion Clinic and another institution (including, but not limited to Fralin Biomedical Research Institute at VTC, VTCSOM, VT, UVA)?

- ◉ Yes ○ No

9.2 Please provide the name(s) of the collaborating institution(s) and the name(s) and contact information of the lead PI(s) at that institution.

VT - Aiguo Han, aiguohan@vt.edu and Yuanbin Zhu
Aiguo Han is lead P.I. for VT

9.3 Is Carilion acting as one site of a multicenter study?

- ○ Yes ◉ No

9.7 Are any members of the research team listed on this IRB application under the jurisdiction of another institution's IRB?

- ◉ Yes ○ No

Please state specifically which external personnel are under the jurisdiction of another IRB, their role on this research study and the type of interaction they will have with the subjects, the name of the institution's IRB(s), and an explanation as to why they are listed on this IRB application.

Dr. Aiguo Han, collaborator, as listed above, is under the jurisdiction of the Virginia Tech IRB and is lead P.I. for VT.
aiguohan@vt.edu

- Conduct of study procedures that result in research data
- Adverse event documenting and reporting
- Conduct of study procedures that result in research data
- Research specimen collection
- Data entry
- Data analysis – de-identified

Yuanbin Zhu, collaborator, is under the jurisdiction of the Virginia Tech IRB
yuanbinz@vt.edu

- Conduct of study procedures that result in research data
- Adverse event documenting and reporting
- Conduct of study procedures that result in research data
- Research specimen collection
- Data entry
- Data analysis – de-identified

Jingyi Zuo, collaborator, is under the jurisdiction of the Virginia Tech IRB
jingyizuo@vt.edu

- Conduct of study procedures that result in research data
- Adverse event documenting and reporting
- Research specimen collection
- Data entry
- Data analysis – de-identified

sDr. Maegan Gabby, collaborating MEDICAL STUDENT, VTCSOM, is under the jurisdiction of the Virginia Tech IRB
megabby@carilionclinic.org

- Identification of potential subjects
- Contacting potential subjects
- Screening of subjects, including assessing eligibility criteria
- Obtain Informed Consent
- Data entry
- Data Analysis - Identifiable
- Data Analysis - De-identified

Dr. Emmanuel Nartey, PhD, collaborator, is under the jurisdiction of the Virginia Tech IRB.
narte1en@vt.edu

- Conduct of study procedures that result in research data
- Research specimen collection
- Data entry
- Data analysis – de-identified

sDr. Amanda Degraaf, MS, Collaborating Medical Student, VTCSOM, under jurisdiction of the Virginia Tech IRB
amandadegraaf@vt.edu

- Identification of potential subjects
- Contacting potential subjects
- Screening of subjects, including assessing eligibility criteria
- Obtain Informed Consent
- Data entry
- Data Analysis - Identifiable
- Data Analysis - De-identified

Arlo Gow, collaborator, is under the jurisdiction of the Virginia Tech IRB
arlo@vt.edu

- Conduct of study procedures that result in research data
- Research specimen collection
- Data entry
- Data analysis – de-identified

Zoya Amer, VTCSOM Medical Student Collaborator is under the jurisdiction of the Virginia Tech IRB.
zoyaamer@vt.edu

- Identification of potential subjects
- Contacting potential subjects

- Screening of subjects, including assessing eligibility criteria
- Obtain Informed Consent
- Data entry
- Data Analysis - Identifiable
- Data Analysis - De-identified

Yitian Lu, VT collaborator, is under the jurisdiction of the Virginia Tech IRB

- Conduct of study procedures that result in research data
- Research specimen collection
- Data entry
- Data analysis - de-identified

9.8 Are you requesting that Carilion Clinic serve as the IRB of record for the other participating institutions or organizations?

For more information on IRB reliance requests, please visit the Carilion Clinic IRB website or contact the IRB Office.

○ Yes ◉ No

9.11 Describe any plans for initial and ongoing training of the other sites on important aspects of the protocol.

N/A

9.12 Describe the plan to manage communication of information at the other sites that is relevant to the conduct of the research and the protection of human subjects, such as reporting of unexpected problems, protocol modifications, and interim results for all sites to the Carilion Clinic IRB.

For FDA-regulated clinical trials, the plan must include the plan for reporting serious adverse events or serious adverse device effects, significant new risk information, and any other reports mandated by regulation or policy.

N/A

9.13 Describe the Carilion Clinic investigator's plan for oversight of research activities at other sites including verification of Institutional approvals, data safety monitoring, and ensuring data quality and integrity.

For FDA-regulated clinical trials, the plan must include the use of trained and qualified monitors to oversee the progress of the research.

N/A

9.14 Will identifiable data or specimens be transferred, transmitted, or shared outside of Carilion?

For example, transfer of data or specimens from Carilion Clinic to an external collaborator (including VT, VTCRI, UVA, etc.).

○ Yes ◉ No

9.15 Provide information about the types of specimens and/or data, including specific datapoints, that will be shared and the methods of storage of the data at the collaborating site. Include a description of the process for shipping the specimens and/or transmitting the data to the collaborator, including the method of encryption if sharing data electronically.

Research Ultrasounds:

Upon enrollment to the study, subjects will be assigned a 3-digit coded ID, [001, 002, 003..] based on the sequence in which they are enrolled to the study; the code will have no other relation to the participant or their medical chart. Participants' 3-digit, coded, research ID and exam date for each research ultrasound will be recorded. Gestational age, estimated fetal weight

in grams and percentile measurements for biometric parameters will be recorded during the research visit. Any previous, routine, abnormal Dopplers will be recorded by the IRB-approved research sonographer delegated to collect research data on the delegation of authority log (DOA).

Acquired images, QUS and uPDI data, ultrasound research visit date, and research ID, without PHI /HIPAA identifiers, will be stored on the Verasonics machine, run with a computer terminal that has a password only shared with research team members delegated to collect research data. The computer will connect to the "Carilion Public Network" Wifi and use this network to transfer deidentified data to the network-attached storage (NAS) device belonging to Dr. Han at VT; the transfer uses a secure data transfer computer protocol to encrypt data as it is transferred over the Carilion public wifi network. This method of transferring data has been approved by the Carilion Information Security officer and HART team director. Read below for further details regarding the NAS device.

Alternatively, this deidentified data may be transmitted to the NAS using a secure data transfer computer protocol to encrypt data as it is transferred via a Virginia-Tech computer located at Carilion Clinic's Center for Simulation, Research and Patient Safety [5 Old Woods Ave, Roanoke, VA 24016] or 2 Riverside Circle, via the Virginia Tech network. The data will get to these VT computers via the external hard drive described below. It will be driven there by an IRB-approved, Carilion study team member; the distance from the Maternal Fetal Medicine department where the ultrasound machine is, is approximately 1/2 a mile. Absolutely no PHI will be transferred or added to the external hard drive. This second method has been suggested and approved by the HART Team Director and the HART team, as well as a VT IT specialist.

Alternatively, the deidentified data may be transmitted to our VT collaborator, Dr. Han, via a dedicated VT study computer set up for us by VT/VTCSOM at 1316 S. Jefferson St, Roanoke, VA, which is 0.4 miles away from the Carilion Maternal Fetal Medicine offices where the study is being conducted. The data will get to the VT computer via the external hard drive described below. It will be driven there by an IRB-approved, Carilion study team member. Absolutely no PHI will be transferred or added to the external hard drive. VTCSOM's Information Technology Director has provided VT login credentials and access passes to the locked 1316 S. Jefferson St building to Nicholas Joseph, CRC, and Amanda deGraaf, VTCSOM medical student. The computer will remain securely at this location at all times and is maintained by the VT IT Security Office. The computer will transfer deidentified data [ultrasounds] via a LAN connection through a HIPAA-compliant transfer protocol/program called Globus, which VT has a High Assurance license to use. This very secure transfer program includes high authentication assurance for data access, isolation of applications and devices, forced encryption of protected data during transit, option to require multi-factor authentication for data access, prevention of anonymous or public data sharing, data sharing only with identities from identity providers recognized by Globus, and local audit logging. More information about Globus is attached to this application.

Data will be transferred via Globus directly into the VT Advanced Research Computing (ARC) cluster(s) dedicated to Dr. Han & the approved research team. These clusters allow for secure, password-protected, encrypted storage of research data but also for high-throughput computing power for analysis of the large ultrasound files. This additional storage and ultrasound analysis location compliments Dr. Han's existing, approved NAS storage.

ARC clusters provide ultra high-cybersecurity meeting National Institute of Standards and Technology (NIST) 800-53 Priority 1 controls, NIST CSF Tier 4 [sufficient security for Department of Defense *controlled unclassified information* up to Impact Level 4 [IL-4] as well as clusters sufficient for DoD national security data], and NIST 800-171 (healthcare cybersecurity guidelines) standards for compliance on private and federal projects. Some of these measures include management by the VT Information Technology Security Office (ITSO), continuous real-time monitoring and hunting for threats by the VT Cyber Security Operations Center (SOC) for compromised machines and facilitating remediation, intrusion detection sensors which merge data with GIS mapping and VT building architecture to provide a precise location of any compromised device, and a VT-IT-maintained Centralized Logging Service (CLS) to monitor access and use of the clusters. Please see attachment on ARC for additional information about cybersecurity.

The use of Globus and ARC as described above for this project are supported by the Director of IT for VTCSOM, Dustin Womack; Julie Cook, the VT Director of Privacy and Research Data Protection; and Alberto Cano-Rojas, Associate Vice President for Research Computing, Advanced Research Computing.

Also alternatively, the hard drive may be driven by an IRB-approved study team member to Dr. Han at VT, who will upload the data to the NAS described above via his VT computer, then wipe the drive clean before returning it to the IRB-approved team member to drive back to the Maternal Fetal Medicine Clinic site where the research scans are occurring.

Physical Item Storage:

The research machine and associated computer will be stored together on a cart, in a locked consult room within the Maternal Fetal Medicine (Room 455) suite of the Carilion Clinic Medical Office Building (CC-MOB) at 102 Highland Ave, Roanoke, VA. The device will be clearly labelled "For Research Use Only- Carilion Clinic," to further prevent the device from being accidentally used for routine care.

Ultrasound images, video, and data as described above, will be transferred to IRB-approved VT collaborators from the Verasonics machine directly. An encrypted external hard drive, formatted for security, will back-up deidentified ultrasound videos, images, measurements, and radiofrequency (rf) data from the Verasonics machine. This ultrasound backup will only be connected/re-connected to the Verasonics research ultrasound machine; it will not be plugged into any Carilion computer or personal computer. The external hard drive will be locked in the PI's desk in her locked office, when not in use.

NAS Storage:

Upload directly from the Verasonics machine over the "Carilion Public Network" wifi will be to a password-protected, encrypted, private NAS device belonging to Dr. Han and located physically at VT. This device functions similarly to a network drive on a server, allowing password-protected, encrypted data transfer remotely from Carilion Clinic to the IRB-approved study team members at VT. [See attached "NAS Instructions- for collaborators" document for specifics on this type of storage and upload instructions.]

Only the PI and IRB-approved study personnel delegated the role of research data collection or data analysis on the delegation of authority (DOA) log will have access to the study NAS device's files containing deidentified ultrasound data and ultrasounds, which are linked only through the alpha-numeric subject ID number.

RedCap & Participant IDs:

A randomly generated, research ID will be created at enrollment for each participant. A physical copy of the file linking this number to the patient will be created. The 3-digit research ID number will identify subjects within Redcap. An electronic copy of the key will also be stored on a password-protected, secure drive in a Carilion server, "shared drive (S:)" folder. Only IRB-approved study team members will have access. The physical key will be stored in a locked file cabinet in the PI's office.

The demographic and clinical data listed on the currently approved data collection sheet will be stored in REDCap. No PHI or identifiers will be uploaded to REDCap. REDCap (research electronic data capture) provides a secure, web-based application designed to support data management and collection for research/QA/QI studies. Carilion's REDCap servers are securely housed on site in a limited access data center, and all data are stored on Carilion's firewall-protected network. The Health Analytics Research Team (HART) supports the proper development of projects and surveys in REDCap, observing appropriate change control and enforcing appropriate security controls. Data collection projects are built with a study-specific data dictionary, enforcing intuitive, accurate, consistent and complete data entry. REDCap also provides a survey tool for building and managing online surveys. Health Analytics Research team restricts user access to the IRB-approved project research team utilizing the approved processes and standards of TSG. REDCap is HIPAA compliant and provides audit trails.

Only the above-described data will be shared or transferred to REDCap or OneDrive. No PHI or information not described above will be transferred, shared, or removed from Carilion Clinic.

10.0 Human Subjects Research Description

10.1 In the opinion of the Principal Investigator, does this research impart minimal risk or greater than minimal risk to subjects?

As defined by regulation, minimal risk means 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 examinations or tests. Please note that the IRB makes the final determination of risk level and may ask you to change this based on their decision.

If this is a Conversion of a Paper Application, select the risk level that has been determined already by the IRB at most recent review per the most recent approval letter (expedited review = minimal risk, full board review = greater than minimal risk).

- ○ Minimal Risk
- ◉ Greater than minimal

10.2 Does the research offer the prospect of direct benefits to the individual subjects?

- ○ Yes ◉ No

10.3 Select ALL the types of research activities that will be involved in your human subject research subject, or select None.

- ☐ Drugs, biologics or other FDA-regulated products (other than devices)
- ☑ Medical devices
- ☑ Review of data/records (i.e. prospective clinical data collection from medical records, reviewing previously collected data)
- ☐ Biospecimen collection (i.e. blood, tissue, urine, saliva)
- ☐ Analysis of existing specimens from patients and/or bank or repository
- ☐ Human genetic analysis or Recombinant DNA, or Gene Therapy
- ☐ Invasive medical procedures (i.e. lumbar puncture, biopsy, endoscopy, surgery, etc.)
- ☐ Non-invasive medical procedures routinely employed in medical practice (i.e., physical measurements, EKG, EEG, moderate exercise, etc.)
- ☑ Imaging (i.e., x-ray, CT, DEXA, MRI, ultrasound, etc.), Use of Therapeutic or Diagnostic Radiation, Radioactive Drugs
- ☐ Task-based activities or games, or Psychometric Testing
- ☑ Surveys, questionnaires, focus groups, or interviews
- ☐ Examination of educational practices, instructional techniques, curricula or classroom management
- ☐ Observations of public behavior
- ☐ Interventions or procedures involving deception
- ☐ Use of Internet
- ☐ Audio or Video recording
- ☐ International Research
- ☐ NONE OF THE ABOVE

10.4 Briefly describe the proposed research in language that can be understood by a non-scientist.

This description should summarize the objectives of the research and the procedures to be used, with an emphasis on what will happen to the subjects. If this is an application for the establishment of a research repository, summarize the objectives of the repository and how data/specimens will be used in the future.

Background: Our study is a proof-of-concept, case-control exploration of quantitative ultrasound (QUS) and ultrafast power Doppler imaging (uPDI) imaging techniques, applied to the placenta to evaluate health of the placenta, blood flow visualized by the colored doppler imaging, fetal growth and age, as well as its restriction. We will utilize the Verasonics Vantage 256 research ultrasound machine for this study, which is not FDA approved/experimental, along with a standard-of-care Phillips ultrasound machine which is FDA approved. Use of QUS gained interest within the 1980s to evaluate the health of a range of tissues, from myocardial [heart muscle], to artery plaques, to breast masses, to bone density. More recently, there has been great interest in QUS for evaluation of fetal tissue health, including fetal liver and lung tissue, as well as placental tissue to gauge both gestational age as well as placental health. QUS imaging creates a number of values including an attenuation coefficient estimate (*ACE*), specified in decibels (dB) which is a measurement of the ultrasound waves' absorption and scattering as they move through human tissue. QUS also generates other values including a frequency-dependent attenuation value. These numerical estimates of absorption and scattering along with others provided by QUS are believed to change within the placenta with increased gestational age due to increasing deposition of collagen and fibrin, two types of connective fibers. As well, measures of absorption, scattering, and related tissue properties may be altered in unhealthy versus healthy placental tissue. Thus, QUS is believed to provide a means for non-invasive estimation of fetal growth and its restriction.

QUS will be combine in our study with ultrafast power Doppler imaging (uPDI), a newer ultrasound modality that uses an ultra-high frame rate and clutter filtering to increase the Doppler imaging sensitivity. Traditional Doppler ultrasound displays color onto the normally greyscale ultrasound where blood flow is seen by the machine. However, traditional ultrasound with Doppler has difficulty in detecting blood flow within smaller vessels, such as the smallest spiral arteries of the placenta which provide nutrition to both the placenta and fetus. It is therefore believed uPDI can better visualize these and other small areas of blood flow or pooled blood within the placenta, providing the sonographer with improved indications of placental tissue perfusion and health.

Our primary objective is to investigate the efficacy of combine QUS and uPDI imaging techniques obtained from subject placental ultrasounds in distinguishing healthy pregnancies from those affected by fetal growth restriction (FGR); FGR is defined as a fetus demonstrating a fetal weight in less than the 10th percentile for that fetus's gestational age or abdominal circumference in the 10th percentile or less for age, as estimated by conventional ultrasound measurements. We will use ACE and other QUS parameters along with uPDI imaging, all performed every 3 weeks throughout gestation, in this case-control, proof-of-concept study.

Our secondary aims will include evaluation of differences in QUS and uPDI imaging and numbers, in the setting of utero-placental insufficiency including evolution of abnormal umbilical artery Doppler testing, diagnosis of severe FGR with uPDI/QUS, identification of stillbirth with uPDI /QUS, and detection of preeclampsia and preterm births with uPDI/QUS.

Sample: Our study is a proof-of-concept, prospective, case-control, cohort study composed of ultrasound imaging of placentas from pregnancies with and without a diagnosis of FGR by traditional ultrasound measurement. Cohort one (the "Case" cohort) will comprise of 30 subjects diagnosed with FGR by traditional ultrasound measurements; Cohort two (the "Control" cohort) will comprise of 30 controls without an FGR diagnosis. Further inclusion and exclusion criteria for the "Case" and "Control" cohorts are listed below in the eligibility criteria.

Procedure: Ultrasounds will be performed every 3 weeks until delivery for both cohorts following informed consent. The first ultrasound will take place within 1 week of enrollment to allow for the sonographer to be scheduled. Ultrasounds will be performed by trained MFM sonographers. Ultrasounds will take place within the Maternal Fetal Medicine suite of Carilion Clinic [102 Highland Ave, Roanoke, VA], in clinical exam rooms with dimmable lights and calming music to reduce patient stress. Upon entering the exam room, IRB-approved study team members and/or sonographers will introduce themselves by name and capacity, then ask the name and date of birth of the subject to verify subject identity against the research enrollment log and EMR. The purpose for the visit will be reiterated and the subject's wish to continue to participate in the research will be verified to ensure continued consent. Any questions the subject has will be answered to the subject's satisfaction. An agenda for the encounter will be set by the IRB-approved study team member or sonographer, so the patient knows what to generally expect and how long the visit will take. The subject will be seated in a reclined position and asked to raise the bottom portion of their shirt, while the sonographer drapes the patient according to standard clinical procedure. Ultrasound gel will be applied to the subject's abdomen and the sonographer will then begin the ultrasound using the machine's transducer [part held in sonographer's hand].

To begin, an ultrasound using a standard-of-care, Philips ultrasound machine will be used to first verify continued fetal viability and perform a basic anatomical survey to ensure continued eligibility for the subject's given cohort [either Case [FGR-positive] or Control [FGR-negative]]. These Philips ultrasound machines are located in each of the standard MFM exam rooms. Color Doppler images using the standard-of-care machine may also be obtained for control-group subjects, of <40 kg/m^2, <32 wks gestational age, with anterior placentas [as confirmed by the standard-of-care ultrasound], who speak/read English, and who otherwise meet the study eligibility criteria, starting on 19 Feb 2026. These Doppler images from the standard-of-care ultrasound machine will allow the study team to compare clarity of the Doppler images to those of the research machine's uPDI images. Color Doppler images are not standardly collected for routine care and will add approximately one minute to the overall exam [standard-of-care images + research images]. Informed consent will be obtained prior to any procedure performed for research [the color Doppler w/ standard-of-care ultrasound or use of the research ultrasound.] Following these standard-of-care machine ultrasound images, the sonographer will transition to the research ultrasound machine for the rest of the visit.

Participants will have research ultrasounds performed of their placentas using a Verasonics Vantage 256 system (a popular research ultrasound platform used for human imaging under IRB approval). The gestational age of the fetus, estimated fetal weight in grams, and growth/weight percentile measurements for that gestational age will be recorded during the research visits. The placenta will be scanned at a central, peripheral, and 'mid-disc' region to acquire QUS and uPDI

images with the Verasonics research ultrasound as well. Three measurements will be acquired at these locations. The Verasonics machine will be programmed to project B-mode (brightness mode) images for the sonographer at the time of the research ultrasound for confirmation of correct placental location. These B- or *brightness* mode images will project a 2-dimensional, greyscale image of the placenta (or fetus) to the sonographer to orient him/her to the location they are scanning and find the placenta. The machine will be programmed to display thermal index (TI) and mechanical index (MI) during all exams, which are derived estimates of the heat and pressure created by ultrasound waves' energy. These are displayed for safety and kept within International Society of Ultrasound of Obstetrics and Gynecology (ISUOG) guidelines. The Verasonics machine will be programmed with a "hard stop" not to exceed these limits. The energy exposure from Ultrasound has no cumulative effect.

Following the ultrasound procedure, the subject will be cleaned of ultrasound gel with a cloth and drapes removed. The subject's will be told of any changes noticed since the last visit to the growth or health of their baby or placenta. Incidental findings obtained during the research ultrasound will be shared with the subject's routine clinical provider and the patient by IRB-approved and qualified physicians on the research team. The PI will advise the participant's routine clinical provider that all results obtained with the research ultrasound should be validated using an FDA Approved ultrasound and standard of care ultrasound techniques.

Following all research ultrasound procedures during the visit, subjects will be given an opportunity to ask any further questions they wish and receive answers to their satisfaction. Printouts of their baby from the standard-of-care ultrasound machine will be provided to subjects. Subjects will then be led back out of the MFM suite to the front desk where they will be scheduled for their next research visit.

Participants will not be under the primary care of the research physicians. The research physicians will not be involved in decisions regarding the timing, method, or procedures used to terminate a pregnancy or determining the viability of a neonate.

Analysis: We will evaluate QUS and uPDI images of the placentas. We will evaluate which QUS parameters are most strongly associated with FGR diagnosis by comparing them to numbers obtained by QUS in normal estimated fetal growth pregnancies. We will examine uPDI images in FGR pregnancies versus those obtained from normal growth weight pregnancies.

Secondary analysis: We will perform multimodal analysis to determine whether these ultrasound modalities can distinguish between pregnancies with: A.) confirmed diseases deriving from a placental origin; B.) abnormal umbilical artery assessments, severe FGR, preeclampsia and stillbirth; C.) no complications.

References:

1. Deeba F, Ma M, Pesteie M, et al. Attenuation coefficient estimation of normal placentas. *Ultraso und in medicine & biology*. 2019;45(5):1081-1093. doi:10.1016/j.ultrasmedbio.2018.10.015
2. Huang L, Wang Y, Wang R, et al. High-quality ultrafast power doppler imaging based on spatial angular coherence factor. *Ieee transactions on ultrasonics, ferroelectrics, and frequency control*. 2023;70(5):378-392. doi:10.1109/TUFFC.2023.3253257

10.5 Provide background information about the research question(s.) Explain why the research is needed and include the relevance of this research to the contribution of this field of study.

Please include the current state of knowledge about your project topic by summarizing and synthesizing the available research (including published data) to provide justification for the study. Include a reference list of literature cited to support the protocol statement, either in your response below or as a supplemental document as part of the application packet.

Fetal growth restriction (FGR)is a comprehensive term that describes a pathologic failure of a fetus to reach its individual growth potential and is a leading cause of poor obstetric outcomes. This condition is intimately linked to early childhood and developmental outcomes, with lifelong lasting health implications[1]. FGR has multi-factorial causes, including underlying genetic abnormalities, environmental or infectious exposures, or maternal medical co-morbidities. By classical definition, FGR refers to the smallest 10% of fetal patients in utero. Identification of a truly "growth restricted" fetus at risk of perinatal morbidity and mortality has many challenges. In fact, many of these fetuses are in fact demonstrating their true growth potential and the appearance of delayed growth is simply constitutional.

A myriad of strategies have been proposed to identify, classify and manage patients with FGR[2,3]. There is good evidence that antenatal identification of this condition reduces adverse perinatal outcomes. This improvement in fetal outcomes is achieved through adoption of antenatal fetal testing protocols[4,5].

The most feared complication of FGR is a progression to insufficient nutrient exchange in the placenta, leading to stillbirth. Currently, the placental function is assessed clinically by assessment of fetal umbilical artery Doppler blood flow which demonstrates characteristic changes in velocities and waveforms when placental resistance is significantly increased[6]. These changes in the waveform for umbilical artery velocity are an indirect upstream measure of the placenta and placental blood flow itself. These changes in waveform are also present when there is clear uteroplacental insufficiency that has been well-established and there is already an increased risk for stillbirth and severe growth restriction. It is unclear whether detection of patients with microvascular damage might be accomplished more directly at the placental interface, perhaps allowing for better identification of which patients need heightened surveillance. Additionally, assessment of features of the microvascular placental bed itself has the potential to correlate with disease progression.

Recently, there has been growing enthusiasm toward developing non-invasive placental imaging technologies[7]. Superb microvascular imaging (SMI) is an emerging sonographic placental imaging method that has been shown to be useful for evaluating FGR and placenta vascularization[8,9]. Compared to conventional blood flow imaging methods, SMI uses advanced techniques to reduce motion artifacts and allows the visualization of low-velocity blood flow in small vessels. While SMI demonstrates the power of microvascularity imaging, this method is only available from a single ultrasound vendor (Toshiba Medical Systems, Tokyo, Japan) and has its own limitations. We propose advancing non-invasive placental imaging by combining two emerging technologies, quantitative ultrasound (QUS)[10,11] and ultrafast power Doppler imaging (uPDI)[12]. The two modalities provide complementary information for placenta evaluation. One of the modalities, QUS, relies on extracting tissue microstructure information and mechanical properties from radiofrequency (RF) data to provide information unavailable from clinical B-mode images. Investigations using QUS have resulted in improvements in quantifying hepatic fat fraction[12] and assessing preterm birth risk[13]. There are few studies evaluating QUS in placental imaging. However, a recent ex-vivo evaluation of QUS parameters obtained from ultrasounds of placentas is able to detect placental-mediated diseases and distinguish those affected by preeclampsia or FGR[14]. The other modality, uPDI, relies on the use of revolutionary ultrafast ultrasound techniques to image the blood flow with a high spatio-temporal resolution simultaneously at several locations, thus providing previously unavailable information about the flow behavior. uPDI has shown tremendous success in imaging organs such as the kidney,and has also been shown to be promising for placental imaging[15,16] by providing enhanced sensitivity to slow blood flow and small vessels. However, no human studies have been performed to date to use uPDI to assess pregnancies affected by FGR. Our study is a preliminary exploratory step evaluating whether placental QUS and uPDI imaging may be applied to evaluate pregnancies affected by FGR. It is anticipated that multi-modal, multi-scale imaging techniques may be able to provide insight into placental microvascular development and function[17]. QUS and uPDI can be implemented on the same ultrasound scanner, which will facilitate eventual clinical adoption.

1 Galjaard, S., Devlieger, R. & Van Assche, F. A. Fetal growth and developmental programming. J Perinat Med 41, 101-105 (2013). https://doi.org/10.1515/jpm-2012-0020
2 Blue, N. R. et al. A Comparison of Methods for the Diagnosis of Fetal Growth Restriction Between the Royal College of Obstetricians and Gynaecologists and the American College of Obstetricians and Gynecologists. Obstet Gynecol 131, 835-841 (2018). https://doi.org/10.1097/aog.0000000000002564
3 Monier, I. et al. Comparison of the Hadlock and INTERGROWTH formulas for calculating estimated fetal weight in a preterm population in France. Am J Obstet Gynecol 219, 476.e471-476.e412 (2018). https://doi.org/10.1016/j.ajog.2018.08.012
4 Martins, J. G., Biggio, J. R. & Abuhamad, A. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction. American Journal of Obstetrics and Gynecology 223, B2-B17 (2020). https://doi.org/10.1016/j.ajog.2020.05.010
5 Hernandez Andrade, E. et al. Doppler evaluation of normal and abnormal placenta. Ultrasound in Obstetrics & Gynecology 60, 28-41 (2022). https://doi.org/10.1002/uog.24816
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7 Slator, P. et al. Placenta Imaging Workshop 2018 report: Multiscale and multimodal approaches. Placenta 79, 78-82 (2019). https://doi.org/10.1016/j.placenta.2018.10.010
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11 Deeba, F. et al. Attenuation Coefficient Estimation of Normal Placentas. Ultrasound Med Biol 45, 1081-1093 (2019). https://doi.org/10.1016/j.ultrasmedbio.2018.10.015
12 Han, A. et al. Assessment of Hepatic Steatosis in Nonalcoholic Fatty Liver Disease by Using Quantitative US. Radiology 295, 106-113 (2020). https://doi.org/10.1148/radiol.2020191152
13 McFarlin, B. L. et al. Predicting Spontaneous Pre-term Birth Risk Is Improved When Quantitative Ultrasound Data Are Included With Historical Clinical Data. Ultrasound Med Biol 49, 1145-1152 (2023). https://doi.org/10.1016/j.ultrasmedbio.2022.12.018
14 Deeba, F. et al. in 2021 IEEE International Ultrasonics Symposium (IUS). 1-3.
15 Osmanski, B.-F. et al. Discriminative imaging of maternal and fetal blood flow within the placenta using ultrafast ultrasound. Scientific Reports 5, 13394 (2015). https://doi.org/10.1038/srep13394
16 Li, Y. L. et al. in 2020 IEEE International Ultrasonics Symposium (IUS). 1-4.
17 Leung, K. Y. & Wan, Y. L. Update on Color Flow Imaging in Obstetrics. Life (Basel) 12 (2022). https://doi.org/10.3390/life12020226

10.6 State the research hypothesis or the question that the research will answer.

List the research objectives and expected outcomes. A primary outcome or objective must be identified. After the statement of the primary objective, secondary objectives may be listed. Objectives should be simple and specific.

Our primary objective is to investigate whether QUS and uPDI imaging techniques obtained from in-vivo ultrasound imaging of the placenta can distinguish between patients with healthy pregnancies from those affected by FGR. We will compare individual QUS parameters and uPDI images obtained of the placentas in utero acquired by ultrasound studies performed throughout gestation in this case-control study. Our secondary aims will include evaluation of differences in these imaging parameters in the setting of complications of uteroplacental insufficiency including evolution of abnormal umbilical artery Doppler testing, severe FGR, stillbirth, preeclampsia and preterm births.

10.7 State how qualitative and/or quantitative data will be analyzed in order to answer the research questions.

Include an analysis from a statistician (or someone familiar with statistical methods) that either indicates the power calculation for the sample size necessary to meet the primary study outcome or objective OR a statement from the statistician indicating reasons why a power calculation is waived or not necessary for this study. Also include the statistical test(s) that will be used to analyze your primary study objective (t-test, chi-square, etc.). Secondary outcomes may be listed as descriptive.

If this is a proof of concept or feasibility study that includes limited efficacy testing, please provide a description on how your design will determine if an intervention should be recommended for broader efficacy testing. If a study is meant to be solely descriptive, then the primary outcome or objective must be limited in scope. As such, the study results apply only to the sample being studied, and conclusions cannot be drawn about the larger population.

This is required for ALL studies, as this section helps the IRB confirm the data being collected are relevant to the study aims and planned analysis.

Primary Objective Analysis: QUS and uPDI parameters (continuous variables) will be described as means and standard deviations. Comparisons will be performed between healthy pregnancies and those affected by FGR. Comparisons will be performed for each matched time point. Student's t-test will be performed for normally distributed data for between-group comparison and Mann-Whitney U-test will be performed for non-normally distributed data. The significance level will be set at $p<0.05$. Multivariable logistic regression will be performed to test whether combination of multiple parameters will show improved discriminative values.
Secondary Objectives Analysis: Statistical analyses will be similar to those used in primary objective analysis, except that between-group comparisons will be made between different groups considering normal versus 1) abnormal umbilical artery Doppler testing, 2) severe FGR, 3) stillbirth, 4) preeclampsia, and 5) preterm births
A power calculation is waived given the preliminary investigatory nature of this project / pilot study.

10.8 Statistical Review

Name of statistician or person who prepared the statistical plan:	Department/Institution:	Date statistical review was conducted:
Nicholas Joseph	Department of Research and Development, Carilion Clinic	04 March 2024

Note: The statistician or individual that prepared the statistical plan must also be included on the study team if they meet the definition of key research personnel (ex: significantly involved in the study design, conduct, or reporting of the research).

If a statistical review has not been submitted, explain why:

An a priori power analysis was conducted to estimate sample size requirements for statistical significance of study results. A similarly designed, controlled, cohort, prospective clinical trial of predictive power of historical data [Hx cohort] versus historical data + quantitative ultrasound data [Hx+QUS cohort] in spontaneous preterm birth risk assessment (McFarlin et al. 2023) (N=274) was used. The effect size in McFarlin et al. was calculated from a given AUC of 0.53 in the control cohort, with odds ratio 1.21, and a calculated effect size of 0.11 (Chinn, Stat Med.) (2000), and Cohen's d of 0.11 and small per (Cohen et al.)(1988) classification.
The treatment group [Hx data + QUS data] effect size was calculated from a given AUC of 0.68 with an odds ratio of 3.319 and a calculated effect size of 0.66 (Chinn, Stat Med.)(2000) and Cohen's d of 0.661 and large per (Cohen et al.)(1988) classification.
A 95% CI of (0.57-0.78) was found for the Hx+QUS cohort on spontaneous preterm birth prediction, yielding a CI length of 0.21 with standard error width 3.92 utilized. Two-sided Z (alpha) is 1.96, Z(1-beta) is 0.8416. An alpha-error rate of .05 along with a power of 0.80 is accepted.
The effect delta is found to be 0.150, and a minimum N= 190 patients per arm, 381 total subjects estimated (Kadam et al.) (2010) to be needed in a two-cohort clinical trial of similar design.

The current study takes into account the lack of pilot studies into the use of a dual QUS and ultrafast power Doppler imaging (uPDI) placental ultrasound to detect fetal growth restriction (FGR). The current study is an initial, proof-of-concept study similar to a phase IIb clinical trial [but not FDA-regulated]. Given this similarity, use of Fleming et al. (1982)'s method of one-sample, proof-of-concept, phase IIb trial recruitment is appropriate. This method notes that in addition to the interest of a large sample size in order to improve chances of finding results of statistical significance in their p-value, there also exists a benefit to both researchers and subjects in a recruitment methodology which allows for 'interim' data analysis of the treatment's effect and of safety, adverse events, and other points of significance at the conclusion of a proof-of-concept / phase IIb study, prior to moving to a larger cohort size study.
This 'interim' analysis of a phase IIb-similar design allows the principle investigator (PI) to make a decision regarding continuation or termination of the study, be it for futility, safety, or another reason. This method of utilizing a small cohort within proof-of-concept studies with an 'interim' analysis and decision as to the appropriateness of moving into a second study with a greater number of patients to prove the effectiveness of the intervention over other contemporary methods of detecting FGR benefits subject safety as fewer subjects will be enrolled in the research and thus fewer subject exposed to previously described study risks. This design also benefits researchers who may avoid conducting greater amounts of futile research.
We will thus utilize 60 subjects, 30 control subjects without known FGR and 30 subjects with known FGR in this phase IIb-similar, proof of concept, non-FDA regulated, two-cohort, prospective human research study.

References:
1. McFarlin, B. L. et al. Predicting Spontaneous Pre-term Birth Risk Is Improved When Quantitative Ultrasound Data Are Included With Historical Clinical Data. Ultrasound Med Biol 49, 1145-1152 (2023). **https://doi.org/10.1016/j.ultrasmedbio.2022.12.018**
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5. *1. Fleming TR (1982). One-sample multiple testing procedure for phase II clinical trials. Biometrics 38: 143-151.*

11.0 Subject Population

11.1 Please select the population(s) being targeted, or likely to be included in this research study. (select all that apply)

- [ ] Medical Chart Review of patients only (no in-person contact)
- [x] Normal Adults/Healthy Volunteers
- [ ] In-Patient Population
- [x] Out-Patient Population
- [ ] Patients in emergency situations
- [ ] Terminally ill patients
- [ ] Employees/Staff
- [ ] Students
- [ ] Children/Minors (anyone younger than 18 years of age in the state of Virginia. For research conducted outside of the state of Virginia, age of majority is dependent on state/local law)
- [ ] Prisoners
- [x] Pregnant Women
- [x] Fetuses
- [ ] Neonates of uncertain viability and/or nonviable neonates
- [ ] Adults with Impaired Decision-Making Capacity
- [x] Persons with Limited-English proficiency (LEP) or Non-English Speakers
- [ ] Individuals of Childbearing Potential

11.2 Please indicate the total number of subjects anticipated to be enrolled at this site/by this investigator.

For the purposes of the IRB, a subject is enrolled once they have provided consent to participate, or for studies approved with a waiver of consent, once data has been collected on the subject.

60

11.3 If the research involves multiple subject groups or cohorts at this site, provide the anticipated number of subjects in each of group or cohort (e.g., control/experimental, adults/children, etc.).

Control - 30
Case - 30

11.4 Provide the age range for the proposed subject population (e.g., 0-5 years old):

18-45 years old

11.5 Specify the inclusion criteria for each of the subject groups to be included in the research.

If there are multiple different groups being recruited with different eligibility criteria, instead add an Eligibility Criteria checklist for each group as a supplemental document after you complete this application. Please make note of this in the Inclusion Criteria below.

Order Number	Criteria

1	Control Group: Patient at least 18 to 45 years of age at screening
2	Control Group: Non-anomalous, singleton gestation without suspected genetic disorders or growth abnormalities
3	Control Group: Low-risk aneuploidy screening, if performed
4	Control Group: Intention to deliver at Carilion Roanoke Memorial Hospital (CRMH) or Carilion New River Valley Medical Center (CNRVMC)
5	Control Group: Anatomical survey has been performed
8	Control Group: Pregnancy without current fetal growth restriction (FGR) diagnosis
9	Control Group: 9. Subject willing and able to provide informed consent **Note:** *Verify that the most recent version of the ICF was used to consent the subject*
10	Case Group: Patient at least 18 to 45 years of age at screening
11	Case Group: Non-anomalous, singleton gestation without suspected genetic disorders
12	Case Group: Low-risk aneuploidy screening, if performed
13	Case Group: Intention to deliver at Carilion Roanoke Memorial Hospital (CRMH) or Carilion New River Valley Medical Center (CNRVMC)
14	Case Group: Anatomical survey has been performed
15	Case Group: Pregnancy diagnosed with fetal growth restriction (FGR) by estimated fetal weight <10th centile or abdominal circumference measurements <10th centile
16	Case Group: Subject willing and able to provide informed consent **Note:** *Verify that the most recent version of the ICF was used to consent the subject*

11.6 Specify the exclusion criteria for each of the subject groups to be included in the research.

If there are multiple different groups being recruited with different eligibility criteria, instead add an Eligibility Criteria checklist for each group as a supplemental document after you complete this application. Please make note of this in the Exclusion Criteria below.

Order Number	Criteria
1	Control Group: Multiple gestations
2	Control Group: Known fetal anomaly affecting biometric measurements
3	Control Group: Suspected fetal genetic disorder(s)
4	Control Group: Suspected fetal infection(s)
	Control Group: Non-English or Spanish-speaking

5	
6	Control Group: Unstable housing or transportation
7	Control Group: Any other criterion which, in the clinical judgement of the investigator, would make the subject unsuitable for study enrollment.
8	Case Group: Multiple gestations
9	Case Group: Known fetal anomaly affecting biometric measurements
10	Case Group: Suspected fetal genetic disorder(s)
11	Case Group: Suspected fetal infection(s)
12	Case Group: Non-English or Spanish-speaking
13	Case Group: Unstable housing or transportation
14	Case Group: Any other criterion which, in the clinical judgement of the investigator, would make the subject unsuitable for study enrollment.

11.7 Is information being obtained about individuals other than the "target subjects" (such as a family member or colleague of the subject), making the other individuals "secondary subjects"?

○ Yes ◉ No

11.8 What languages do you expect the subjects with Limited English Proficiency will be fluent in?

Spanish

11.9 How will you ensure that subjects with Limited English Proficiency will understand the information provided to them and will be able to ask questions and communicate with the researchers during recruitment, the consent process, and throughout participation (i.e., plan for interpretation).

Subjects with limited English proficiency (LEP) who read and understand Spanish may be enrolled in this study. A certified translation of the latest IRB-approved informed consent form (ICF) in Spanish will be provided to these LEP, Spanish-speaking subjects so that they will be able to read the same information that is contained in the latest IRB-approved English informed consent form.

IRB-approved study personnel meeting with these subjects will have the latest IRB-approved English ICF for their use during the informed consent process and discussion of the study while the subject reads the latest IRB-approved Spanish-translated ICF. A certified interpreter is available in the clinic for all Spanish-speaking-only patients for routine clinical care. This same interpreter will assist in the informed consent process, assist IRB-approved study personnel in understanding and responding to questions by subjects, to that subject's satisfaction. The interpreter will also interpret the discussion of the study by IRB-approved study personnel into Spanish so the subject can understand what is being said. An ask-tell-ask format of questioning will be used to verify the subject's understanding, just as in the English informed consent process but via the interpreter.

The interpreter will sign/date the Spanish informed consent form if the subject wished to participate in the study and signs/dates the latest IRB-approved Spanish-translated ICF to indicate this desire to participate. The IRB-approved study personnel will then also sign the Spanish-translated ICF and make a photocopy of the triple-signed, IRB-approved, latest ICF and provide this photocopy to the subject so they may review the information whenever they would like.

As with English-speaking subjects, LEP, Spanish-speaking subjects will be asked if they wish to continue to participate in the study by the PI or IRB-approved study personnel at each research visit prior to the research procedures for that visit beginning; what will occur at the research visit

if the subject wishes to continue to participate will be reviewed, via the interpreter to ensure continued informed consent to participation is being provided by the subject.

Interpreter services are also available on the phone from Carilion Clinic if subjects should call the PI with research-related questions between research visits.

IRB-approved study personnel will follow the Spanish informed consent process discussed previously in this IRB application in the Informed Consent for Adult Subjects section.

Neither 'long-form' nor 'short-form' consent procedures are expected to be used during this study for other languages than Spanish as we do not anticipate meeting subjects not speaking either English or Spanish and due to a lack of available in-person interpreters for languages other than Spanish at the clinic.

11.10 Will consent forms and other subject materials be translated?

NOTE: Cost alone is typically insufficient justification for not translating materials when recruitment of persons with LEP is anticipated.

- (●) Yes
- ( ) Some, but not all materials
- ( ) No

Once the English version of the consent form and subject materials are approved, translated materials must be submitted to the IRB as a Change Request, along with a certificate of translation or certified back translation for review and approval prior to use.

12.0 Pregnant Individuals, Individuals of Childbearing Potential, Breastfeeding Infants, Fetuses, or Neonates

12.2 Are there any additional risks to pregnant individuals by participating in this study?

If your research involves fetuses or neonates, please contact the IRB prior to submission.

(●) Yes ( ) No

12.3 Are there any additional risks to individuals of childbearing potential, individuals who become pregnant, breastfeeding infant, or fetus or neonate by participating in this study?

(●) Yes ( ) No

12.4 Describe the additional risks.

Ultrasounds will be used on the study subject for placental and fetal imaging. Therefore, there will be ultrasound exposure beyond routine clinical care indications by participating in the study. For this reason, all study personnel will be informed of ultrasound principles and principles of *as low as reasonably achievable* (ALARA) as applied to ultrasound imaging (limiting time during the study and radiofrequency exposure). In addition, the Verasonics machine will be programmed to project B-mode images for the sonographer at the time of the research ultrasound for confirmation of correct placental location. The machine will be programmed to display thermal index (TI) and mechanical index (MI) during all exams, not to exceed 1.0 and the ALARA principles will be adhered to during the examinations as indicated by ISUOG guidelines. The Verasonics machine will be programmed with a "hard stop" not to exceed these limits. The energy exposure from Ultrasound has no cumulative effect.

12.5 Provide justification for including this population.

The study population requires fetal and placental imaging as this is the population affected by fetal growth restriction requiring evaluation.

12.6 Please provide the following information, as applicable:

- **For individuals of childbearing potential: How participants will be asked their current pregnancy status.**
- **For individuals of childbearing potential: The type and timing of pregnancy testing to be used.**
- **For individuals of childbearing potential: How participants will be informed that they should prevent pregnancy including use of adequate methods of birth control.**
- **For individuals of childbearing potential: Investigator's evaluation of the participant's willingness to, and reliability to practice effective birth control.**
- **For individuals of childbearing potential: Instructions for the participant if they suspect they may have become pregnant**
- **For individuals of childbearing potential: Plan in case a participant suspects pregnancy, or becomes pregnant (pregnancy testing, termination from the study, assistance with obstetrical follow up).**
- **For breastfeeding infant, fetus, or neonate if individual does become pregnant: Plan to monitor and minimize risk.**

Please address the following points if applicable:

- *In research where individuals of childbearing potential will have one or more MRI (magnetic resonance imaging) scan conducted solely for research purposes, special protections include informing the individual that they should not have the MRI scan unless they are certain they are not pregnant.*
- *In research on drugs where there is a concern about the female partners of male subjects receiving the drugs, special protections include provisions for informing males of the precautions they should take to prevent pregnancy in the individuals of childbearing potential.*

N/A

12.7 Please provide the following information for pregnant individuals, as applicable:

- **How participants will be asked if they are pregnant, and how this will be confirmed, if applicable**
- **How participants will be informed of additional risks**
- **Plan to monitor and minimize risk.**
- **For breastfeeding infant, fetus, or neonate: Plan to monitor and minimize risk.**

Participants will be recruited from the CMC OB clinics and pregnancy confirmation will be performed at the time of ultrasound. Estimated delivery date will be provided by the patient based on best clinical gestational age (based on LMP and previous ultrasound dating).

Ultrasounds will be used on the study subject for placental and fetal imaging. Therefore, there will be ultrasound exposure beyond routine clinical care indications by participating in the study. The consent form and process will confirm this intention. All study personnel will be informed of ultrasound principles and principles of ALARA as applied to ultrasound imaging (limiting time during the study and radiofrequency exposure). In addition, the Verasonics machine will be programmed to project B-mode images for the sonographer at the time of the research ultrasound for confirmation of correct placental location. The machine will be programmed to display thermal index (TI) and mechanical index (MI) during all exams, not to exceed 1.0 and the ALARA principles will be adhered to during the examinations as indicated by ISUOG guidelines. The Verasonics machine will be programmed with a "hard stop" not to exceed these limits. The energy exposure from Ultrasound has no cumulative effect.

13.0 Informed Consent for Adult Subjects

13.1 How do you plan to obtain consent from ADULT subjects or their Legally Authorized Representative?

Check all that apply:

- [x] Written consent document with signature (ie: obtaining signature from subject or Legally Authorized Representative)
- [ ] Waiver of written documentation of consent (ie: consent will be obtained through verbal confirmation from the subject or Legally Authorized Representative rather than through a signed document)

- ☐ Waiver of informed consent for minimal risk research (ie: typically appropriate only when the study does not involve any interaction or intervention with subjects)
- ☐ Waiver or alteration of the elements of informed consent (ie: research involving deception)
- ☐ Waiver of the informed consent document and process for PLANNED EMERGENCY RESEARCH. Contact the IRB before submission.
- ☐ No adults are being enrolled; this study is only enrolling children. (You will answer questions about the assent and parental permission process later.)

You must attach all consent forms, consent scripts, and information sheets in the Initial Submission Packet.

13.2 Is it expected that surrogate consent will need to be obtained from Legally Authorized Representatives (LARs) for some or all adult subjects?

○ Yes ◉ No

13.3 If the research includes more than one subject group or you have selected multiple responses above due to the inclusion of multiple subject groups, please specify the requested consent method for each group, or state N/A.

N/A

13.4 How will written consent be documented?

Click the Help bubble to the right for more information about requirements for eConsent before selecting this option.

- ☑ Traditional signed written consent form on paper document
- ☑ eConsent: signed via an REDCap or other electronic or web-based form
- ☐ Short Form Method (for non-English speaking subjects only)
- ☐ Other

13.5 Describe the process of obtaining consent and documenting the process, including the following:

- **Circumstances under which consent will be obtained, including how the potential participant will first be approached;**
- **Where the consent process will take place (ex: in person in a private clinic room, over the phone, through WebEx, etc.);**
- **When the consent process will take place and how long participants will be given to decide;**
- **If eConsent is being utilized, describe how you will first contact the potential participants and provide the consent form to them to review;**
- **Steps that will be taken to ensure voluntary participant and to minimize the possibility of coercion or undue influence;**
- **Any cultural considerations (ex: tribal or group permission requirements, age of majority, technological implications, etc.);**
- **If any participants do not speak English, whether a translator with witness will be used, whether translated materials will be used, whether the consent process changes based on the language;**
- **If multiple participant groups or consent procedures are to be included, these need to be clearly delineated;**
- **how participants will be provided with a copy of their signed consent;**
- **Describe the method you will use to document the consent PROCESS within each participants' research record /medical record (state which). This should include a process note or checklist that will document all the components listed above, the start and end time of the discussion, and is in addition to the signed and dated consent form (if applicable).**

For example, describe it consent will take place in the research office, in a private conference room, in the doctor's office, in a group setting, over the phone, etc.

IRB-approved study personnel will conduct pre-screenings within the electronic medical record to identify subjects meeting the inclusion and exclusion criteria listed in the protocol. When a potential subject is identified and found to meet inclusion and exclusion criteria within the EMR, verbal consent from their treating physician will be sought by the study team. The treating physician will be given adequate information concerning the research protocol to determine the

appropriateness of the qualified clinical trial for their patient. The treating physician will next speak in a private location or by phone to determine the subject's interest in speaking with the research team.
Subjects expressing interest in speaking to the research team will be approached by study personnel in the CMC OB offices or via telephone call from a designated study personnel. A second in-person pre-screening will then take place. The informed consent process will then take place, and consist of the following:
The informed consent document will be provided as a physical or electronic document to the participant or as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts, and benefits. In order to minimize potential coercion, at least 30 minutes, or as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members, and other advisors, and to ask questions of any designated study investigator. The patient will be assured by study staff that their medical care will not be influenced by their decision to participate or decline to participate in the study. The study participant will be informed that gift cards distributed upon completion of the study are compensation for the subject's time and travel expenses incurred for research ultrasounds. A signed informed consent document will be obtained prior to any research activities taking place.
The initial consent process as well as re-consent, when required, may take place in person or remotely (via telephone or Microsoft Teams call per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators and participant when in person, will be located in a private area of the CMC OB Clinic. When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed. If the consent process is occurring remotely, participants and investigators will view individual copies of the approved consent document on screens at their respective locations; the same screen may be used when both the investigator and the participant are co-located but this is not required. The study team will request verbal permission via telephone or Microsoft Teams call to send the eConsent via a REDCap link. The email/text will not include PHI. The request will state: "Because Carilion Clinic can't control the security of email or text messages once we send them, we need your permission to text or email you. Do you want to receive the link to the eConsent via text or email?" Subject permission will be documented electronically, via EPIC.
When required, the witness signature will be obtained similarly as described for the investigator and participant below.
An IRB approved study team member will review each section of the consent form in detail with the participant.
Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to the participant) or on the electronic document. The process for documenting signatures on an electronic document is described below.
A hand signature on the electronic consent form may be used to document informed consent. The consent document will be created using a REDCap-based electronic consent form. The IRB-approved consent form will be uploaded to REDCap, a secure, web-based, HIPAA- compliant, data collection platform with a user management system allowing project owners to grant and control varying levels of access to data collection instruments and data (e.g. read only, de-identified-only data views) for other users.
Both the individual obtaining consent and the participant will sign the electronic document using a finger, stylus or mouse. Electronic signatures (i.e., the "signature" and a timestamp are digitally generated) will not be used.
Once the consent form is signed and submitted, subjects will be able to receive a printout of the paper copy, download a pdf, and/or receive an email with a PDF attachment of the signed consent form. They will also be able to request that a paper copy of the signed consent form be mailed to their home address.
An electronic research note within the subject's EMR will be created. This note will detail the process employed by the investigator or designated key personnel to obtain informed consent from the subject. This note is to include: a brief description of critical topics discussed from the informed consent form; an attestation that the subject was given a copy of the signed informed consent form; notice the subject was provided with adequate time to review and discuss the form with others if desired and then ask questions of the study team member that were appropriately addressed; documentation of the start and end times of the informed consent discussion.
Study team members will also document that the subject understands that their participation in any research procedure is completely voluntary, and that they may withdraw consent for this study at any time; withdrawing consent for continued study procedures will not adversely affect the subject's ability to receive routine clinical care. The note will be signed and dated by the consenting study team member.

Spanish Informed Consent:
Per the study's eligibility criteria, subjects who do not read, speak, or understand English to the level needed to provide informed consent but do read, speak, and understand Spanish may still be enrolled. The enrollment process for this particular population of potential subjects will only be

consented with in-person, paper informed consent forms; eConsent will not be used, due to the added complexity of explaining the technology through an interpreter. The informed consent process will follow the same procedures specified above for English-speaking subjects, but with the added aid of a Carilion interpreter. As a standard of care procedure, all non-English-speaking patients at the Carilion Clinic Maternal Fetal Medicine unit will already be followed by an interpreter throughout their visit(s). This same interpreter will aid with the informed consent procedure. Interpreters working on the Maternal Fetal Medicine unit will be spoken to in advance of study enrollment to familiarize them with the basic research procedure, informed consent procedures, and what their responsibilities would be. As with English-speaking subjects, IRB-approved study personnel will speak to the treating physician who will ask the patient via the interpreter if they would consent to speaking to the IRB-approved study personnel. If verbal consent from the subject is given to meet, the IRB-approved study personnel will provide the subject with a written, long-form, Spanish-language-translated, IRB-approved, informed consent form (ICF) and briefly explain the purpose of the research and what the ICF is, via the interpreter. The procedures for informed consent described above will then commence. All questions about the study will be answered to the patient's satisfaction via the interpreter prior to signing the informed consent form. If the subject chooses to participate in the research, they will document this by printing their name, signing, and dating the Spanish-language-translated, long-form, ICF; the IRB-approved study personnel will sign the Spanish-language version of the long-form ICF that was most recently approved by the IRB also; the interpreter will print their name, sign, and date as a witness to the informed consent process on the Spanish-translated ICFs. A photocopy of the Spanish-language informed consent form will be provided to the subject.

Documenting the process used to obtain informed consent by the subject will be documented in the EMR in the same way as it is for English-speaking participants, as described above.

No research procedures will begin until after the subject, IRB-approved study personnel, and witness have signed the proper ICF.

Approximately 80% of subjects are expected to be consented in English and 20% are expected to be consented in Spanish.

13.6 How will you ensure that subjects or LARs have sufficient opportunity to consider whether or not to participate?

Check all that apply:

- ☐ Subjects will be provided the consent form to take home for consideration prior to signing.
- ☑ Subjects will be allowed a waiting period to consider their decision.
- ☐ Other

Please specify waiting period:

30 minutes

13.7 How will the subjects' or LARs understanding of the consent information presented be assessed?

Check all that apply:

- ☐ Subjects will be asked to "Teach-Back" the study to the researchers
- ☑ Subjects will be asked open-ended questions about the research (purpose, procedures, risks, alternatives, voluntary nature)
- ☐ A tool or post-consent assessment will be used
- ☐ Other

Specify the "teach back" questions or open-ended questions that the subject will be asked to describe in their own words in order to assess their understanding.

What is the purpose of the study?
To see if new ultrasound techniques can evaluate fetal growth abnormalities

How often are the ultrasounds?
Every 3 weeks

What will happen if you choose not to participate?
You will no longer be scheduled for research ultrasounds and nothing will happen to change your clinical care

13.8 Utilizing eConsent has additional requirements. Please describe the following:

- **The method to verify the identity of the individual providing consent;**
- **How participants will sign the eConsent (ex: type their name, use stylus or finger to sign);**
- **If potential participants will sign the consent while having a virtual conversation or if they will have additional time to consider their participation;**
- **If use of LAR is being requested, how you will ensure this individual is an appropropriate LAR per Virginia requirements and verify their identity.**

The initial consent process as well as re-consent, when required, may take place in person or remotely (via telephone or Microsoft Teams call per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Verification of the patient will occur by asking the participant to provide their name and date of birth. Consenting investigators and participant/consent designee when in person, will be located in a private area of the MFM Clinic. When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed. If the consent process is occurring remotely, participants and investigators will view individual copies of the approved consent document on screens at their respective locations; the same screen may be used when both the investigator and the participant are co-located but this is not required. The study team will request verbal permission via telephone or Microsoft Teams call to send the eConsent via a REDCap link. Subject permission will be documented electronically, via EPIC.
When required, the witness signature will be obtained similarly as described for the investigator and participant below.
Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to the participant) or on the electronic document. The process for documenting signatures on an electronic document is described below.
A hand signature on the electronic consent form may be used to document informed consent. The consent document will be created using a REDCap-based electronic consent form. The IRB-approved consent form will be uploaded to REDCap, a secure, web-based, HIPAA- compliant, data collection platform with a user management system allowing project owners to grant and control varying levels of access to data collection instruments and data (e.g. read only, de-identified-only data views) for other users.
Both the individual obtaining consent and the participant will sign the electronic document using a finger, stylus or mouse. Electronic signatures (i.e., the "signature" and a timestamp are digitally generated) will not be used.
Once the consent form is signed and submitted, subjects will be able to receive a printout of the paper copy, download a pdf, and/or receive an email with a PDF attachment of the signed consent form. They will also be able to request that a paper copy of the signed consent form be mailed to their home address.
An electronic *research note* within the subject's EMR will be created. This note will detail the process employed by the investigator or designated key personnel to obtain informed consent from the subject. This note is to include: a brief description of critical topics discussed from the informed consent form; an attestation that the subject was given a copy of the signed informed consent form; notice the subject was provided with adequate time to review and discuss the form with others if desired and then ask questions of the study team member that were appropriately addressed; documentation of the start and end times of the informed consent discussion.
Study team members will also document that the subject understands that their participation in any research procedure is completely voluntary, and that they may withdraw consent for this study at any time; withdrawing consent for continued study procedures will not adversely affect the subject's ability to receive routine clinical care. The note will be signed and dated by the consenting study team member.

13.9 If the enrollment of subjects who cannot read the consent form, due to visual impairment, literacy, or other issues, is anticipated, how will consent be obtained and documented?

Refer to 45 CFR 46.117(b)(2) or 21 CFR 50.27(b)(2) for information regarding when the use of a short form is appropriate. A witness to the consent process is needed.

- ☐ N/A
- ☐ Short form
- ☐ Other mechanism
- ☑ Consent form read to participant with witness present

13.10 How will you ensure research participants remain informed about the study and continue to agree to participate in the research study after their initial informed consent has been obtained?

☐ N/A

At each study ultrasound, prior to initiating performing the ultrasound, the study participant will be asked if they still desire to remain enrolled and agree to participate in the research study. Interpreters are available to assist in this process for Spanish-speaking subjects at ultrasound visits; phone interpreter services may be used if in-person interpreters are not available or seeing another patient after the initial consent [which will always have an in-person interpreter present]

14.0 Privacy and Confidentiality

14.1 Does the research include interaction with or observation of subjects?

◉ Yes ○ No

14.3 Select the data points that will be reviewed, collected, recorded, or created for research purposes, including screening or recruitment.

Check all that apply:

- ☑ name
- ☑ all geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census:
- ☑ an element of a date, except year, for dates related to an individual, including birth date, admission date, discharge date and date of death; and all ages over 89 and all elements of such ages may be aggregated into a category of age 90 or older
- ☐ telephone numbers
- ☐ fax numbers
- ☑ electronic mail address
- ☐ social security number
- ☑ medical record number/ master patient index (MPI)
- ☐ health plan beneficiary numbers
- ☐ account numbers
- ☐ hospital account receivable (HAR)/contact serial number (CSN)
- ☐ certificate/license numbers
- ☐ vehicle identifiers, including license plate number
- ☐ device identifiers and serial numbers
- ☐ Web Universal Resource Locators (URLs)
- ☐ Internet Protocol (IP) address numbers
- ☐ biometric identifiers, including finger and voice prints
- ☐ full face photographic images and any comparable image
- ☐ any other unique identifying number, characteristic, code
- ☐ None of the above

14.4 Will any of the above data points be reviewed, collected, recorded, or created from the medical record (or other healthcare records)?

◉ Yes ○ No

Since you plan to access or use PHI from the Medical Record, you must contact the HART Team at Carilion Clinic immediately to ensure the data you will need is accessible and to discuss data management and storage. Do not proceed with the submission of this application until you have done so.

14.5 Is the private information being requested the minimum necessary to meet the research goals?

(●) Yes ( ) No

14.6 Under the HIPAA Privacy Rule, when accessing or using PHI, a HIPAA Authorization of the subject must be obtained, or the IRB must grant a waiver.

Indicate which of the following apply (more than one may be selected):

- [x] The HIPAA Authorization is embedded in the research consent document.
- [x] A partial waiver of the requirement for HIPAA Authorization is requested (e.g., for screening or for some subjects, such as a retrospective cohort)
- [ ] A full waiver of the requirement for HIPAA Authorization is requested
- [ ] The HIPAA Authorization will be sought but one or more required elements will be eliminated or altered
- [ ] The PHI accessed or used for this research is a Limited Data Set (LDS) and a Data Use Agreement (DUA) is or will be in place prior to accessing or obtaining the LDS.
- [ ] HIPAA Authorization will be obtained as a separate document (only permitted if required by sponsor)
- [ ] Other

14.7 Will educational records protected under the Family Educational Rights and Privacy Act (FERPA) be accessed or used for the research?

( ) Yes (●) No

14.8 Does the research involve the administration or use of surveys, interviews, or other evaluations or examinations protected under the Protection of Pupil Rights Amendment (PPRA)?

( ) Yes (●) No

14.9 Will the research records (other than the consent form) and/or specimens contain data that is identifiable, coded, or de-identified?

- [ ] Identifiable (includes direct identifiers or information such that subject identities could be ascertained)
- [x] Coded or linked (identifying information that would enable the investigator or collaborator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, etc., and a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens)
- [ ] De-identified or unlinked (specimens/data cannot be linked to specific individuals by anyone, including the Carilion investigator, either directly or indirectly through coding systems)

14.10 Where will research data be stored during the period the research is active? Describe the security controls in place, including physical safeguards for paper records and technical safeguards for electronic records

Storage options other than those listed below are NOT currently permitted, including the use of Carilion provided or personal laptops, flash drives or other portable devices, non-Carilion cloud or other hosted environment. Any exceptions to the list above must be approved by the Carilion Privacy and Information Security Officer and documentation provided to the IRB.

- [x] Hardcopy data in a locked office in a locked cabinet
- [x] Electronic data on a password protected, secure drive on a Carilion server (contact mmtenzer@carilionclinic.org to set up a shared drive)
- [x] REDCap (contact mmtenzer@carilionclinic.org to discuss use of REDCap)
- [ ] Sponsor's electronic data capture system

☐ SPARC Carilion Secure Research Environment (contact mmtenzer@carilionclinic.org to discuss)

14.11 Provide any additional information pertaining to the storage and management of the research data.

Best research pratice is to have data management plan which will help you manage and protect your data, meet funder requirements, and help others use and protect your data, if shared. A well structured project can help protect the confidentiality of patient and participant data. Carefully planned data management also allows for a better use of your time and resources. For guidance on data management pratices, please review the Harvard Catalyst document and upload your data management plan into the Supplemental documents.

There are no collaborating sites for this study. All research-related activities, recruitment, and research procedures will be occurring at Carilion Clinic. Deidentified data may be analyzed by collaborating VT, IRB-approved study team members delegated the duty of data analysis. Analysis may occur at that collaborating member's office at VT. Collaborators' computers are protected by a username and password personal to that researcher and by VT's firewall.

Research Ultrasounds:

Participants' 3-digit, coded, research ID and exam date for each research ultrasound will be recorded. Gestational age, estimated fetal weight in grams and percentile measurements for biometric parameters will be recorded during the research visit. Any previous, routine, abnormal Dopplers will be recorded by the IRB-approved research sonographer delegated to collect research data on the delegation of authority log (DOA).

Acquired images, QUS and uPDI data, ultrasound *research visit* date, and research ID, without PHI /HIPAA identifiers, will be stored on the Verasonics machine, run with a computer terminal that has a password only shared with research team members delegated to collect research data. The computer will connect to the "Carilion Public Network" Wifi and use this network to transfer deidentified data to the network-attached storage (NAS) device belonging to Dr. Han at VT; the transfer uses a secure data transfer computer protocol to encrypt data as it is transferred over the Carilion public wifi network. This method of transferring data has been approved by the Carilion Information Security officer and HART team director. Read below for further details regarding the NAS device.

Alternatively, this deidentified data may be transmitted to the NAS using a secure data transfer computer protocol to encrypt data as it is transferred via a Virginia-Tech computer located at Carilion Clinic's Center for Simulation, Research and Patient Safety [5 Old Woods Ave, Roanoke, VA 24016] or 2 Riverside Circle, via the Virginia Tech network. The data will get to these VT computers via the external hard drive described below. It will be driven there by an IRB-approved, Carilion study team member; the distance from the Maternal Fetal Medicine department where the ultrasound machine is, is approximately 1/2 a mile. Absolutely no PHI will be transferred or added to the external hard drive. This second method has been suggested and approved by the HART Team Director and the HART team, as well as a VT IT specialist.

Alternatively, the deidentified data may be transmitted to our VT collaborator, Dr. Han, via a dedicated VT study computer set up for us by VT/VTCSOM at 1316 S. Jefferson St, Roanoke, VA, which is 0.4 miles away from the Carilion Maternal Fetal Medicine offices where the study is being conducted. The data will get to the VT computer via the external hard drive described below. It will be driven there by an IRB-approved, Carilion study team member. Absolutely no PHI will be transferred or added to the external hard drive. VTCSOM's Information Technology Director has provided VT login credentials and access passes to the locked 1316 S. Jefferson St building to Nicholas Joseph, CRC, and Amanda deGraaf, VTCSOM medical student. The computer will remain securely at this location at all times and is maintained by the VT IT Security Office. The computer will transfer deidentified data [ultrasounds] via a LAN connection through a HIPAA-compliant transfer protocol/program called Globus, which VT has a High Assurance license to use. This very secure transfer program includes high authentication assurance for data access, isolation of applications and devices, forced encryption of protected data during transit, option to require multi-factor authentication for data access, prevention of anonymous or public data sharing, data sharing only with identities from identity providers recognized by Globus, and local audit logging. More information about Globus is attached to this application.

Data will be transferred via Globus directly into the VT Advanced Research Computing (ARC) cluster(s) dedicated to Dr. Han & the approved research team. These clusters allow for secure,

password-protected, encrypted storage of research data but also for high-throughput computing power for analysis of the large ultrasound files. This additional storage and ultrasound analysis location compliments Dr. Han's existing, approved NAS storage.

ARC clusters provide ultra high-cybersecurity meeting National Institute of Standards and Technology (NIST) 800-53 Priority 1 controls, NIST CSF Tier 4 [sufficient security for Department of Defense *controlled unclassified information* up to Impact Level 4 [IL-4] as well as clusters sufficient for DoD national security data], and NIST 800-171 (healthcare cybersecurity guidelines) standards for compliance on private and federal projects. Some of these measures include management by the VT Information Technology Security Office (ITSO), continuous real-time monitoring and hunting for threats by the VT Cyber Security Operations Center (SOC) for compromised machines and facilitating remediation, intrusion detection sensors which merge data with GIS mapping and VT building architecture to provide a precise location of any compromised device, and a VT-IT-maintained Centralized Logging Service (CLS) to monitor access and use of the clusters. Please see attachment on ARC for additional information about cybersecurity.

The use of Globus and ARC as described above for this project are supported by the Director of IT for VTCSOM, Dustin Womack; Julie Cook, the VT Director of Privacy and Research Data Protection; and Alberto Cano-Rojas, Associate Vice President for Research Computing, Advanced Research Computing.

Also alternatively, the hard drive may be driven by an IRB-approved study team member to Dr. Han at VT, who will upload the data to the NAS described above via his VT computer, then wipe the drive clean before returning it to the IRB-approved team member to drive back to the Maternal Fetal Medicine Clinic site where the research scans are occurring.

Physical Items Storage:

The research machine and associated computer will be stored together on a cart, in a locked consult room within the Maternal Fetal Medicine (Room 455) suite of the Carilion Clinic Medical Office Building (CC-MOB) at 102 Highland Ave, Roanoke, VA. The device will be clearly labelled "For Research Use Only- Carilion Clinic," to further prevent the device from being accidentally used for routine care.

Ultrasound images, video, and data as described above, will be transferred to IRB-approved VT collaborators from the Verasonics machine directly. An encrypted external hard drive, formatted for security, will back-up deidentified ultrasound videos, images, measurements, and radiofrequency (rf) data from the Verasonics machine. This ultrasound backup will only be connected/re-connected to the Verasonics research ultrasound machine; it will not be plugged into any Carilion computer or personal computer. The external hard drive will be locked in the PI’s desk in her locked office, when not in use.

Upload directly from the Verasonics machine over the “Carilion Public Network” wifi will be to a password-protected, encrypted, private NAS device belonging to Dr. Han and located physically at VT. This device functions similarly to a network drive on a server, allowing password-protected, encrypted data transfer remotely from Carilion Clinic to the IRB-approved study team members at VT. [See attached "NAS Instructions- for collaborators" document for specifics on this type of storage and upload instructions.]

Only the PI and IRB-approved study personnel delegated the role of research data collection or data analysis on the delegation of authority (DOA) log will have access to the study NAS device's files containing deidentified ultrasound data and ultrasounds, which are linked only through the alpha-numeric subject ID number.

RedCap:

A randomly generated, research ID will be created at enrollment for each participant. A physical copy of the file linking this number to the patient will be created. The 3-digit research ID number will identify subjects within Redcap. An electronic copy of the key will also be stored on a password-protected, secure drive in a Carilion server, "shared drive (S:)" folder. Only IRB-approved study team members will have access. The physical key will be stored in a locked file cabinet in the PI's office.

The demographic and clinical data listed on the currently approved data collection sheet will be stored in REDCap. No PHI or identifiers will be uploaded to REDCap. REDCap (research electronic data capture) provides a secure, web-based application designed to support data management and collection for research/QA/QI studies. Carilion's REDCap servers are securely housed on site in a limited access data center, and all data are stored on Carilion's firewall-protected network. The Health Analytics Research Team (HART) supports the proper development of projects and

surveys in REDCap, observing appropriate change control and enforcing appropriate security controls. Data collection projects are built with a study-specific data dictionary, enforcing intuitive, accurate, consistent and complete data entry. REDCap also provides a survey tool for building and managing online surveys. Health Analytics Research team restricts user access to the IRB-approved project research team utilizing the approved processes and standards of TSG. REDCap is HIPAA compliant and provides audit trails.

Only the above-described data will be shared or transferred to REDCap. No PHI or information not described above will be transferred, shared, or removed from Carilion Clinic.

14.12 How long will research records, data, and specimens be retained following completion of the study? Where will study records will be retained when the study has been closed (long-term storage)?

Describe when and how the identifiers, if applicable, will be destroyed. If specimens will be retained, describe where.

Please note that any data involving PHI must be maintained for a minimum of 6 years, and data that does not contain PHI must be maintained for a minimum of 3 years. In many cases, identifiers will need to be retained after the research is completed (e.g., for publication or data verification purposes or because of contractual requirements or grant terms).

Please click the Help bubble to the right for more information on minimum storage requirements.

Data will be maintained for a minimum of 6 years following the completion of the study according to Carilion SOP.

Carilion Clinic's REDCap software will be used as the central location for data collection. REDCap (research electronic data capture) provides a secure, web-based application designed to support data management and collection for research/QA/QI studies. Carilion's REDCap servers are securely housed on site in a limited access data center, and all data are stored on Carilion's firewall protected network. The Health Analytics Research Team supports the proper development of projects and surveys in REDCap, observing appropriate change control and enforcing appropriate security controls. Data collection projects are built with a study-specific data dictionary, enforcing intuitive, accurate, consistent and complete data entry. REDCap also provides a survey tool for building and managing online surveys. Health Analytics Research team restricts user access to the IRB-approved project research team utilizing the approved processes and standards of TSG. REDCap is HIPAA compliant and provides audit trails. Data can be easily exported in several formats to a secure network directory for combination with extracted data, if appropriate, and analysis with common statistical packages.

14.13 Describe the structure of the code (e.g., randomly generated number, sequential number plus initials, etc.) and indicate whether a linking file (key) will be created and, if so, how it will be protected.

A three digit number will be created at study enrollment for each participant. A physical copy of the linking file will be created in addition to recording the coded study ID number into RedCAP. An electronic copy of the key will also be stored on a password protected, secure drive on a Carilion server, shared drive.
The physical key will be stored in a locked file cabinet in the PI's office which is located in an area locked to entry for non-Carilion employees.
Carilion Clinic's REDCap software will be used as the central location for data collection. REDCap (research electronic data capture) provides a secure, web-based application designed to support data management and collection for research/QA/QI studies. Carilion's REDCap servers are securely housed on site in a limited access data center, and all data are stored on Carilion's firewall protected network. The Health Analytics Research Team supports the proper development of projects and surveys in REDCap, observing appropriate change control and enforcing appropriate security controls. Data collection projects are built with a study-specific data dictionary, enforcing intuitive, accurate, consistent and complete data entry. REDCap also provides a survey tool for building and managing online surveys. Health Analytics Research team restricts user access to the IRB-approved project research team utilizing the approved processes and standards of TSG. REDCap is HIPAA compliant and provides audit trails. Data can be easily exported in several formats to a secure network directory for combination with extracted data, if appropriate, and analysis with common statistical packages.

14.15 Who will have access to identifiers?

The following team members will have access to identifiers:
Megan Whitham, P.I.
Jessica Nichols, CRC
Nicholas Joseph, CRC
Lauren Hennis, MD
Sofia Issel, MS
sDr. Amanda DeGraaf, VTCSOM Candidate
Zoya Amer, VTCSOM medical student

14.16 How will access to the identifiers be protected?

Patient identifiers will be stored along with the coded patient ID number in the following locations: A 3 digit number will be created at study enrollment for each participant. A physical copy of the linking file will be created in addition to recording the study ID number into RedCAP. An electronic copy of the key will also be stored on a password protected, secure drive on a Carilion server, shared drive.
The physical key will be stored in a locked file cabinet in the PI's office which is located in an area locked to entry for non-Carilion employees.
Carilion Clinic's REDCap software will be used as the central location for data collection. REDCap (research electronic data capture) provides a secure, web-based application designed to support data management and collection for research/QA/QI studies. Carilion's REDCap servers are securely housed on site in a limited access data center, and all data are stored on Carilion's firewall protected network. The Health Analytics Research Team supports the proper development of projects and surveys in REDCap, observing appropriate change control and enforcing appropriate security controls. Data collection projects are built with a study-specific data dictionary, enforcing intuitive, accurate, consistent and complete data entry. REDCap also provides a survey tool for building and managing online surveys. Health Analytics Research team restricts user access to the IRB-approved project research team utilizing the approved processes and standards of TSG. REDCap is HIPAA compliant and provides audit trails. Data can be easily exported in several formats to a secure network directory for combination with extracted data, if appropriate, and analysis with common statistical packages.

All other identifying HPI will be stored in REDCap.

14.17 Describe whether data will be aggregated/summarized in publications or presentation, or whether individual participant results will be published/presented.

Data will be aggregated for analysis and summarized in publications.

14.18 Will research records include information that subjects or others might consider to be sensitive in nature?

E.g.,communicable disease status, substance abuse, mental health information, illegal behaviors, etc.

(●) Yes ( ) No

Explain what sensitive information is included, why it is needed, and any additional safeguards that will be taken to protect it:

Subjects during screening and/or their EMR during pre-screening by IRB-approved study personnel, will be queried about active cocaine use during their pregnancy. Active cocaine use is a substantial risk factor for development of fetal growth restriction; we will include only control subjects which do not have substantial risk factors for developing fetal growth restriction in the study. Therefore, this information needs to be asked.

Additional safeguards include only documenting this information on the physical eligibility criteria study document and not otherwise transmitting it, even deidentified, into REDCap or OneDrive. The information is also included within a group of possible risk factors for FGR that would exclude a control subject. The exclusionary risk factors include, along with active cocaine use, a large list of non-sensitive factors such as hypertension, in-vitro fertilization (IVF), anemia, vascular disease, diabetes, and other risk factors. Therefore, it is impossible for anyone but the study team member who asked the patient about these criteria to tell for which of these reasons a subject was excluded from the study under this particular "substantial risk factor for FGR" criteria.

Cocaine use is not asked of case-group subjects.

14.19 Do you plan to obtain a Certificate of Confidentiality (CoC) from NIH for this research or is one already in place (ex: for NIH-funded research) that covers this site and any recipient site or organization?

Per Section 2012 of the **21st Century Cures Act** as implemented in the **2017 NIH Certificates of Confidentiality Policy**, all ongoing or new research funded by NIH as of December 13, 2016 that is collecting or using identifiable, sensitive information is automatically issued a CoC. Please note that for research that is not NIH-funded, the IRB may require you to obtain a CoC if it deems the data to be sensitive.

(•) Yes ( ) No

Please do not apply for the CoC until your study receives full IRB approval. Please reference the approval letter for instructions on completing this process. This should be done before enrolling subjects in the study.

15.0 Request for Partial Waiver, Full Waiver, or Alteration of HIPAA Authorization

15.6 Describe how you will utilize PHI for purposes of recruitment and describe how the use of PHI in this study poses no greater than minimal risk to participants' privacy.

IRB-approved study team members will perform a limited review in the Epic EMR of potential subjects identified only within the maternal fetal medicine schedule as potential participants [correct age range, pregnant, being seen for either routine, singleton neo-natal care or being seen for FGR-related appointment]; these factors will be visible on the schedule and appointment notes without opening the patient's individual chart. Patients identified on the schedule as meeting these basic criteria will have limited chart review then performed on their chart to determine eligibility based on their intended cohort [Control or FGR cohort].

This limited chart review will look at items within the inclusion and exclusion criteria:

For control cohort-intended patients:

- non-anomalous, singleton pregnancy without suspected genetic disorders or growth anomalies
- low risk aneuploidy screening
- intention to deliver at CRMH or CNRVMC
- Anatomical survey performed
- 18-26 weeks gestational age without concern for FGR in mid-trimester
- English or Spanish listed as patient language
- no notes stating patient is experiencing an unstable housing or transportation situation
- without any other criterion which, in the clinical judgement of the investigator, would make the subject unsuitable for study enrollment.

For case cohort-intended patients:

- non-anomalous, singleton pregnancy without suspected genetic disorders or growth anomalies,
- low risk aneuploidy screening
- intention to deliver at CRMH or CNRVMC
- Anatomical survey performed
- Pregnancy diagnosed with FGR by estimated fetal weight of <10th percentile or adnominal circumference measurements <10th percentile
- without multiple gestations
- without known fetal anomalies affecting biometric measurements
- without suspected fetal infections
- English or Spanish listed as patient language
- no notes stating patient is experiencing an unstable housing or transportation situation
- without any other criterion which, in the clinical judgement of the investigator, would make the subject unsuitable for study enrollment

This question will remain part of the inclusion/exclusion criteria previously described, however potential subjects will be asked this question after informed consent has been obtained to participate in the study. Additionally, notes marked as 'sensitive' will not be accessed.

A pre-screening log will be maintained to provide an audit trail of who has accessed medical records, as well as the outcome of the pre-screening and the date it was performed. This log may be audited by the IRB or proper regulatory body upon proper and valid request. The log will be maintained on a secure, firewall protected, Carilion Clinic server which only IRB-approved study team members will have access to after entering their personal Carilion username and password known only to them.

All IRB-approved study team members who will be performing pre-screening within the Epic EMR for Carilion Clinic have undergone training on subjects of privacy and confidentiality, have undergone a background check, drug screening, conflict of interest disclosure, HIPAA training, and training on how to use the Epic EMR. These team members have all completed the CITI-approved courses regarding Good Clinical Practices and courses on biomedical research safety and best practice. These study team members will not print or otherwise remove any information from the EMR prior to patient's providing informed consent and HIPAA waiver. All Epic EMR access for the purpose of pre-screening will occur on Carilion Clinic computers which are password protected and behind a Carilion Clinic firewall. The EMR will not be accessed anywhere that non-IRB-approved study team members might be able to view, intentionally or accidentally, patient health information or charts. A rigorous standard operating procedures (SOPs) is in place by Carilion Clinic for reporting any possible breaches of patient confidentiality and all IRB-approved study team members who will be performing pre-screening for this study are aware of and have agreed to follow these SOPs.

15.7 Describe why the research could not practicably be carried out without the use of PHI for recruitment.

Patient protected health information (PHI) is needed in order to determine whether subjects are likely to meet the inclusion and exclusion criteria of the study. These criteria are needed to eliminate confounding factors which could confound the results of the study's outcomes which would negate the value of the research. Whether subjects meet the inclusion and exclusion criteria will need to be pre-screened for the reasons listed in the next paragraph. These criteria can only be determined prior to in-person meeting of patients and the informed consent process by pre-screening of the Epic EMR. PHI is needed in order to identify the patient EMR charts which do [and don't] appear to meet the eligibility criteria so IRB-approved study team members can then approach the patients [identified by their PHI] meeting eligibility criteria to present the study and go through the informed consent process.

Without the ability to pre-screen prospective subjects, IRB-approved study team members would need to meet with every patient attending the Maternal Fetal Medicine clinic without any prior knowledge of why that patient might be presenting. This would involve a massive number of research-related visits, unnecessary patient inconvenience, and would interrupt clinical care within the clinic. Due to the large patient volume being seen in the clinic, large volumes of ineligible patients would need to undergo the informed consent procedure without actually being enrolled in the study come the screening process. As well, this would entail the collection of large amounts of patient health information within the screening eligibility documents for the study, from patients who will not be ultimately enrolled. This presents a greater potential risk to patient confidentiality than does the limited pre-screening procedure described above by IRB-approved study team members within the Epic EMR of only patients on the Maternal Fetal Medicine schedule who first meet the basic criteria described above [age, pregnancy, singleton gestation], which can be seen on the schedule within the "appointment notes" column prior to opening individual medical charts.

15.8 Describe why the research could not be practicably carried out without the partial waiver for recruitment.

Without the ability to pre-screen prospective subjects, IRB-approved study team members would need to meet with every patient attending the Maternal Fetal Medicine clinic without any prior knowledge of why that patient might be presenting. This would involve a massive number of research-related visits, unnecessary patient inconvenience, and would interrupt clinical care within the clinic. Due to the large patient volume being seen in the clinic, large volumes of ineligible patients would need to undergo the informed consent procedure without actually being enrolled in the study come the screening process. As well, this would entail the collection of large amounts of patient health information within the screening eligibility documents for the study, from patients who will not be ultimately enrolled. This presents a greater potential risk to patient confidentiality than does the limited pre-screening procedure described above by IRB-approved study team members within the Epic EMR of only patients on the Maternal Fetal Medicine schedule who first meet the basic criteria described above [age, pregnancy, singleton gestation], which can be seen on the schedule within the "appointment notes" column prior to opening individual medical charts.

15.9 Do you assure that any data identifying subjects used in this study will not be disclosed to anyone other than the research team, sponsor, and oversight groups?

(•) Yes ( ) No

15.10 Do you assure that you will not re use or disclose this data for any other research unless you receive IRB approval?

(•) Yes ( ) No

16.0 Research Settings/Performance Sites

16.1 Indicate the sites where research activities will occur, or from which subject data or specimens will be obtained, and a brief summary of the activities that will occur at each.

☐ N/A (Select this option if this research is a Medical/Chart Review ONLY)

	Site	Summary
☑	CRMH	Subject recruitment
☐	CRCH	
☑	CNRVMC	Subject recruitment
☐	CFMH	
☐	JCHS	
☐	CRMH Rehab	
☑	Riverside	A VT computer at Riverside 2 may be used to transfer de-identified ultrasound data to our VT collaborator's NAS via a VT computer an network [see collaboration section.]
☐	Crystal Spring Medical Office Building	
☑	Other Carilion Clinic Physician's Office	Research ultrasound data will be obtained at the Maternal Fetal Medicine offices located at 102 Highland Ave, Suite 455. Research ultrasounds will be performed in clinical ultrasound rooms

		following clinical exams or in the case of controls, in the ultrasound room that is currently not in use.
☐	Blue Ridge Cancer Care (BRCC) / US Oncology	
☐	Fralin Biomedical Research Institute at VTC	
☐	VT Blacksburg Campus	
☐	Assisted Living Facility or Nursing home	
☑	Other Locations (specify): Carilion Clinic's Center for Simulation, Research and Patient Safety	A VT computer at Carilion Clinic's Center for Simulation, Research and Patient Safety [15 Old Woods Ave, Roanoke, VA 24016] may be used to transfer de-identified ultrasound data to our VT collaborator's NAS via a VT computer and network [see collaboration section.] 1316 S. Jefferson St., a VT-owned office location, may be used to transfer deidentified data via a VT computer to Dr. Han's Arc storage.

17.0 Applicable Regulations for ClinicalTrials.gov Registration

17.1 Is this study FDA-regulated?

◉ Yes ○ No

17.2 Is this research funded wholly or in part by NIH?

○ Yes ◉ No

17.3 Is this study a Clinical Trial, as defined by FDA or NIH, and therefore needing registration on ClinicalTrials.gov? Click the help button to the right to learn more about the definition of a clinical trial.

◉ Yes ○ No

17.5 Is the clinical trial already registered in ClinicalTrials.gov?

- ○ Not yet, but clinical trial will be registered prior to enrolling any subjects
- ◉ Yes
- ○ No, this clinical trial will not be registered

ClinicalTrials.gov #:

NCT06861309

Note: The following statement must be included verbatim in the consent form for trials that are/will be registered on ClinicalTrials.gov:

"A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time."

17.6 Who is responsible for registering this trial in ClinicalTrials.gov and ensuring information is updated, as necessary? Please provide a name if the person is at Carilion or listed on the research team, or state the sponsor or lead site if the sponsor or lead site will register the trial.

The responsible party for an applicable clinical trial (ACT) must register the trial and submit results information. The responsible party is defined as:

- ***The sponsor of the clinical trial, as defined in 21 CFR 50.3; or***
- ***The principal investigator (PI) of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the PI is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements for the submission of clinical trial information***

The responsible party for an ACT must submit the required clinical trial information **no later than 21 days** after enrollment of the first participant, but registration is highly recommended before enrollment begins due to some journal requirements.

Megan Whitham, P.I.

18.0 Study Procedures

18.1 Provide a step-by-step description of the research procedures and/or and interactions with human subjects.

Provide a study schedule and list all activities or procedures that will be performed and describe the frequency and duration of research procedures, diagnostic and research tests, questionnaires or surveys, specimen collection, and experiments, including screening, intervention, follow-up etc in step-by-step chronological order. State the length of time subjects will be in the study and the expected amount of time required for each study visit or activity. Describe how, when and where research activities will be administered and analyzed. If the research includes blinding, indicate whether researchers or subjects will be "unblinded" to study assignment and describe when and how this will be done.

Procedure:
Email address listed in Epic electronic health record (EHR) will be verified with patient at first visit immediately following informed consent to allow for compensation. If no email is listed, subject email will be added to their EHR.

Ultrasounds will be performed every 3 weeks until delivery for both cohorts following informed consent. The first ultrasound will take place within 1 week of enrollment to allow for the sonographer to be scheduled. Ultrasounds will be performed by trained MFM sonographers. Ultrasounds will take place within the Maternal Fetal Medicine suite of Carilion Clinic [102 Highland Ave, Roanoke, VA], in clinical exam rooms with dimmable lights and calming music to reduce patient stress. Upon entering the exam room, IRB-approved study team members and/or sonographers will introduce themselves by name and capacity, then ask the name and date of

birth of the subject to verify subject identity against the research enrollment log and EMR. The purpose for the visit will be reiterated and the subject's wish to continue to participate in the research will be verified to ensure continued consent. Any questions the subject has will be answered to the subject's satisfaction. An agenda for the encounter will be set by the IRB-approved study team member or sonographer, so the patient knows what to generally expect and how long the visit will take. The subject will be seated in a reclined position and asked to raise the bottom portion of their shirt, while the sonographer drapes the patient according to standard clinical procedure. Ultrasound gel will be applied to the subject's abdomen and the sonographer will then begin the ultrasound using the machine's transducer [part held in sonographer's hand].

To begin, an ultrasound using a standard-of-care, Philips ultrasound machine will be used to first verify continued fetal viability and perform a basic anatomical survey to ensure continued eligibility for the subject's given cohort [either Case [FGR-positive] or Control [FGR-negative]]. These ultrasound machines are located in each of the MFM ultrasound exam rooms. Color Doppler images using the standard-of-care machine may also be obtained for control-group subjects, of <40 kg/m^2, <32 wks gestational age, with anterior placentas [as confirmed by the standard-of-care ultrasound], who speak/read English, and who otherwise meet the study eligibility criteria, starting on 19 Feb 2026. These Doppler images from the standard-of-care ultrasound machine will allow the study team to compare clarity of the Doppler images to those of the research machine's uPDI images. Color Doppler images are not standardly collected for routine care and will add approximately one minute to the overall exam [standard-of-care images + research images]. Informed consent will be obtained prior to any procedure performed for research [the color Doppler w/ standard-of-care ultrasound or use of the research ultrasound.] Following this, the sonographer will transition to the research ultrasound machine for the rest of the visit.

Measurements of *fetal biometry* by standard-of-care-type, non-research ultrasound machine including head diameter, head length, abdominal circumference, and femur length, may be used to estimate fetal weight/growth compared to other fetuses at a similar estimated week of pregnancy; this will allow identification of fetuses in an average or large-for-age growth percentile versus those with a growth/size less than or equal to the 10th percentile of other fetuses. These babies may have fetal growth restriction (FGR).

Following these measurements, the placenta will be scanned at a central, peripheral, and mid-disc region to acquire quantitative ultrasound (QUS) and ultrafast power doppler imaging (uPDI) images which aid in visualizing blood flow. Three measurements will be acquired at these locations.

The experimental Verasonics machine will be programmed to project B-mode [*brightness-mode]* i mages for confirmation of correct placental location. Brightness-mode allows the sonographer to view greyscale images of the fetus and placenta, with lighter-colored areas corresponding to denser tissue. This image will allow sonographers to position the machine’s hand-held transducer over the structure the sonographer wishes to analyze with QUS or uPDI modes.

Participants will have research ultrasounds performed of their placentas using a Verasonics Vantage 256 system (a popular research ultrasound platform used for human imaging under IRB approval). The gestational age of the fetus, estimated fetal weight in grams, and growth/weight percentile measurements for that gestational age will be recorded during the research visits. The placenta will be scanned at a central, peripheral, and 'mid-disc' region to acquire QUS and uPDI images with the Verasonics research ultrasound as well. Three measurements will be acquired at these locations. The Verasonics machine will be programmed to project B-mode (brightness mode) images for the sonographer at the time of the research ultrasound for confirmation of correct placental location. These B- or *brightness* mode images will project a 2-dimensional, greyscale image of the placenta (or fetus) to the sonographer to orient him/her to the location they are scanning and find the placenta. The machine will be programmed to display thermal index (TI) and mechanical index (MI) during all exams, which are derived estimates of the heat and pressure created by ultrasound waves' energy. These are displayed for safety and kept within International Society of Ultrasound of Obstetrics and Gynecology (ISUOG) guidelines. The Verasonics machine will be programmed with a “hard stop” not to exceed these limits. The energy exposure from Ultrasound has no cumulative effect.

Following the ultrasound procedure, the subject will be cleaned of ultrasound gel with a cloth and drapes removed. The subject's will be told of any changes noticed since the last visit to the growth or health of their baby or placenta. Incidental findings obtained during the research ultrasound will be shared with the subject's routine clinical provider and the patient by IRB-approved and qualified physicians on the research team.

Following all research ultrasound procedures during the visit, subjects will be given an opportunity to ask any further questions they wish and receive answers to their satisfaction. Printouts of their baby from the standard-of-care ultrasound machine will be provided to subjects.

Subjects will then be led back out of the MFM suite to the front desk where they will be scheduled for their next research visit.

It is unlikely that any new safety information concerning participant risk will be learned of during this study given the largely observational nature of the procedure, however if such new safety information would become known to the PI or study team members, it will be reported to patients at their next study visit or by phone.

The findings of this research will be published and made available on **ClinicalTrials.gov** for subjects to read.

Additional Data Collection: Details regarding additional complications in the pregnancy will be collected.

Demographic and clinical information for enrolled participants will be extracted from the electronic health record *Epic* by Carilion Clinic IRB-approved study team members. This deidentified data will be stored on REDCap paired with a study participant ID number; details of the generation and storage of the key for these ID numbers is described within another section of this submission. Relevant demographic and clinical data will be gathered during this study as listed on the Data Collection Sheet.

Participants will be followed until delivery to record delivery outcomes. The electronic health record will be reviewed following delivery for extraction of the clinically-relevant pregnancy complications mentioned above.

Recruitment is expected to conclude 24 months from initial IRB approval; EMR data collection and analysis may continue for an additional 12 months.

You must attach surveys, instruments, interview questions, focus group questions, etc. in the Initial Submission Packet and label them clearly.

18.2 Specify which procedures, tests, visits, etc. described above are part of usual standard of care at Carilion Clinic and which are being performed solely for research purposes. If procedures, tests, visits are routinely performed for clinical care, but are providing data for this research study, state this as well.

Obstetric patients routinely undergo an anatomical survey as standard-of-care during their prenatal, mid-trimester checkup, typically between weeks 18-24 gestational age. This routine ultrasound on a Philips machine will occur with or without study enrollment. This anatomical survey's outcome in the electronic medical record and/or in person will likely be important to identifying potential fetal growth restriction pregnancies for possible enrollment to the study. Outcomes of this routine ultrasound will be recorded as the diagnosis [or lack of diagnosis] of fetal growth restriction for cohort allocation.

Enrolled subjects will undergo an ultrasound with the Philips machine which is used for standard-of-care ultrasounds but will, in this case, be used for research purposed to verify continued eligibility for the subject's given cohort and also the continued viability of the pregnancy. These ultrasounds take place at visit 1, occurring within 1 week of consent, and then every 3 weeks thereafter, at subsequent research visits up to delivery. Color Doppler images using the standard-of-care machine may also be obtained for control-group subjects, of <40 kg/m^2, <32 wks gestational age, with anterior placentas [as confirmed by the standard-of-care ultrasound], who speak/read English, and who otherwise meet the study eligibility criteria, starting on 19 Feb 2026. These Doppler images from the standard-of-care ultrasound machine will allow the study team to compare clarity of the Doppler images to those of the research machine's uPDI images. Color Doppler images are not standardly collected for routine care and will add approximately one minute to the overall exam [standard-of-care images + research images]. Informed consent will be obtained prior to any procedure performed for research [the color Doppler w/ standard-of-care ultrasound or use of the research ultrasound.]

Enrolled subjects will undergo an ultrasound with a Verasonics Vantage 256 ultrasound machine which is used for research purposes to obtain the previously explained quantitative ultrasound values and ultrafast power Doppler imaging.

Clinical data extracted from the maternal and neonatal charts as specified elsewhere in the data collection sections of this submission will come from routine standard-of-care check-ups, pre-natal check-ups, and any other recorded encounter in their medical record.

Genetic testing and phenotyping will occur as a standard-of-care during one of the subject's pre-natal visits. This is routine but will be recorded for enrollment purposes.

Complications during the pregnancy will be recorded in the electronic medical record as a routine standard of care but will be extracted and recorded for the purposes of research.

For research purposes to pre-screen patients for study eligibility prior to consenting, they will be asked the following questions by study personnel:

YES	NO	NA	Criteria
			1. How old are you?
			2. Did you conceive naturally?
			3. Have you had your anatomy ultrasound yet?
			4. Were there any concerns about baby's anatomy on your ultrasound?

Note: Details of the procedure for administering this questionnaire are found elsewhere in this submission.

18.3 Describe the data collection methods and how data be compiled and collected for assessment. State whether the data/specimens to be utilized in the repository are already in existence (retrospective) or if the data will be generated in the future (prospective).

- **"Retrospective data" is data that is already in existence at the time of application receipt by the IRB. Retrospective is in reference to the date the data was GENERATED, not the date the data is COLLECTED. If all data is retrospective, please provide the start date from which data will be collected and the end date, and note that ALL data must be in existence at time of submission of this application.**
  - **Example: This IRB application is being submitted on 12/1/21 and is collecting data on a standard of care surgery and looking at patient outcomes. All surgeries for this retrospective studies will be completed between 11/31/2018 and 11/31/2021 (the day before the study is submitted to the IRB). This study will likely qualify for a waiver of consent.**
- **"Prospective data" includes any data (including data from the medical record) that are not currently in existence at the time of receipt of the application by the IRB, even if the data is being collected solely for Standard of Care. Prospective data collection typically requires informed consent from the participant to be able to use their clinical data or specimens for research purposes. If all data is prospective, please state date range from which data will be generated.**
  - **Example: This IRB application is being submitted on 12/1/21 and the study is collecting data on a standard of care surgery and looking at patient outcomes. All surgeries for this prospective studies will be completed between 1/1/2022 and 1/1/2025. This study will require informed consent UNLESS a waiver of consent is requested and justified.**

Attach a copy of your data collection tool or spreadsheet listing exactly what data is to be gathered during this research study.

The study is collecting ultrasound imaging and radiofrequency data generated from research ultrasound performed specifically for research purposes. The study also includes data from demographic, medical details as well as obstetric and neonatal outcome data with no change in clinical care. All ultrasounds for this prospective study will be completed between 2/1/2024 and 2 /1/2026. This study will require informed consent of enrolled subjects. The data collection sheet is attached in a separate document. This document will be used by the HART team to create an eCRF for the electronic collection of study data.

18.4 Describe how long individual participants will be actively in the study. If there will be a period of time after the active component of the study where participants will still be in the study (ex: participants outcomes are being extracted from the medical record at 1 year, but the last research study visit was at 3 months), state this as well.

Participants will be actively enrolled in the study for the duration of their pregnancy. There will be a time period of 3 months following delivery during which participant outcomes will be extracted from the medical record.

18.5 Describe how long the entire study is expected to last, including data analysis.

The study is expected to last 3 years from enrollment through data analysis.

18.6 Describe the qualifications of study personnel conducting the research procedures. This could include medical training specific to conducting the interventional procedures in this research, phlebotomy training for those drawing blood, study protocol specific training to be provided by the sponsor, or any other training to demonstrate that the research personnel are appropriately quailified to conduct the study.

Megan Whitham, M.D. - Maternal Fetal Medicine specialist, trained in Obstetric ultrasound interpretation, Ultrasound training, Clinical Ultrasound Physics and with prior publications specific to fetal growth restriction ultrasound interpretation / management of fetal growth restriction. Involved in ongoing studies "Fetal Weight Prediction using Novel AI-guided Volumetric Predictive Modeling" and "Behavioral Health Modifiers in the Detection of Fetal Growth Disorders: An Integrative Machine Learning Approach to Novel AI-guided Fetal Weight Prediction" with Dr. Aiguo Han
Relevant Publications:
Whitham M, Dudley DJ. Delivering Neonates at High Risk in the Right Place: Back to the Future Again. JAMA Pediatr. 2020;174(4):329–330. doi:10.1001/jamapediatrics.2019.6059
Whitham, M.D., Reynolds, D.M., Urban, A.R., Ennen, C.S. and Dudley, D.J. (2023), Comparative Diagnostic Performance of Estimated Fetal Weight and Isolated Abdominal Circumference for the Detection of Fetal Growth Restriction. J Ultrasound Med, 42: 477-485.
Phillips A, Pagan M, Smith A, Whitham M, Magann EF. Management and Interventions in Previable and Periviable Preterm Premature Rupture of Membranes: A Review. Obstet Gynecol Surv. 2023 Nov;78(11):682-689. doi: 10.1097/OGX.0000000000001198. PMID: 38134338.
Whitham M, Gammon BL, Chronister BC, Urban A, Dudley D. Risk factors for Recurrent Stillbirth (SB): Results from the Stillbirth Collaborative Research Network (SCRN). Society for Maternal Fetal Medicine Annual Scientific Meeting 2020.

Aiguo Han, Ph.D., Assistant Professor at Virginia Tech- Dr. Han has extensive experience working on ultrasound imaging and is the recipient of a 2022 NIH NIBIB Trailblazer Award and is actively engaged in a project in the realm of Obstetric imaging, "Predicting Spontaneous Preterm Birth Risk is Improved when Quantitative Ultrasound Data are Included with Prior Clinical Data" as well as "Fetal Weight Prediction using Novel AI-guided Volumetric Predictive Modeling" and "Behavioral Health Modifiers in the Detection of Fetal Growth Disorders: An Integrative Machine Learning Approach to Novel AI-guided Fetal Weight Prediction" He has extensive expertise in biomedical ultrasound research and development as well as prior past experience with QUS.
Relevant Publications:
.Chen S, McFarlin BL, Meagher BT, Peters TA, Simpson DG, O'Brien WD Jr, Han A. A phantom-based assessment of repeatability and reproducibility of transvaginal quantitative ultrasound. IEEE Trans Ultrason Ferroelectr Freq Control, 2019; 66:1413-1421 [PMID: 31217100] [PMCID: PMC6774614]
McFarlin BL, Liu Y, Villegas-Downs M, Mohammadi M, Simpson DG, Han A, O'Brien WD Jr. Predicting spontaneous pre-term birth risk is improved when quantitative ultrasound data are included with historical clinical data. Ultrasound Med Biol, 2023; 49:1145-1152 [PMID: 36740462] [PMCID pending]
Zuo J, Simpson DG, O'Brien WD Jr, McFarlin BL, and Han A. Automated field of interest placement on cervical ultrasound images for assessing the risk of preterm birth. IEEE Trans Ultrason Ferroelectr Freq Control [Manuscript under review; submitted 11/28/2023]
McFarlin BL, Villegas-Downs M, Mohammadi M, Han A, Simpson DG, O'Brien WD Jr. Enhanced identification of at-risk women for preterm birth via quantitative ultrasound: A prospective cohort study. Am J Obstet Gyn
Han A, André MP, Erdman JW Jr, Loomba R, Sirlin CB, O'Brien WD Jr. Repeatability and reproducibility of a clinically based QUS phantom study and methodologies. IEEE Trans Ultrason Ferroelectr Freq Control, 2017; 64:218-231 [PMID: 27411218] [PMCID: PMC5283517] (Featured in Editor's Selection of Articles, Oct 2017)
Han A, André MP, Deiranieh L, Housman E, Erdman JW Jr, Loomba R, Sirlin CB, O'Brien WD Jr. Repeatability and reproducibility of the ultrasonic attenuation coefficient and backscatter coefficient measured in the right lobe of the liver in adults with known or suspected nonalcoholic fatty liver disease. J Ultrasound Med, 2018; 37:1913-1927 [PMID: 29359454] [PMCID: PMC6056350]

Han A, Zhang YN, Boehringer AS, André MP, Erdman JW Jr, Loomba R, Sirlin CB, O'Brien WD Jr. Interplatform reproducibility of ultrasonic attenuation and backscatter coefficients in assessing NAFLD. Eur Radiol, 2019; 29:4699-4708 [PMID: 30783789] [PMCID: PMC6684824]
Han A, Labyed Y, Sy EZ, Boehringer AS, André MP, Erdman JW Jr, Loomba R, Sirlin CB, O'Brien WD Jr. Inter-sonographer reproducibility of quantitative ultrasound outcomes and shear wave speed measured in the right lobe of the liver in adults with known or suspected non-alcoholic fatty liver disease. Eur Radiol, 2018; 28:4992-5000 [PMID: 29869170] [PMCID: PMC7235946]

Christy Johnson - Registered Diagnostic Medical Sonographer, with expertise in Obstetric imaging and High Risk Pregnancy Imaging, including interpretation of studies for FGR

Sonya Morin - Registered Diagnostic Medical Sonographer, with expertise in Obstetric imaging and High Risk Pregnancy Imaging, including interpretation of studies for FGR

Makayla Miller - Registered Diagnostic Medical Sonographer, with expertise in Obstetric imaging and High Risk Pregnancy Imaging, including interpretation of studies for FGR

Nicholas Joseph, B.S. - Clinical Research Coordinator II, Experience with prior investigator-initiated and industry-sponsored research programs

Jessica Nichols, MSHSc - Clinical Research Coordinator Manager, Experience with prior investigator-initiated and industry-sponsored research programs

Emmanuel Narty, PhD- VT collaborator- Research Scientist for the Center for Biostatistics and Health Data Science- He is a recent graduate from the Department of Statistics, Actuarial, and Data Sciences at Central Michigan University and beginning his career at the CBHDS. His research interests include supervised and unsupervised machine learning, statistical computing, complex sample data analysis, generalized linear models, and survival analysis. His dissertation studied internal indices for validating clustering solutions and using those indices to guide feature selection for classification. Emmanuel has experience working with national health surveys and electronic health records and has contributed to research studies in different health areas including eating disorders, HPV vaccination, and Medicare payments.

Dr. Teresa Prinster, MD- OB-GYN Resident physician with experience working with obstetric patients and will help with patient pre-screening for eligibility, recruitment, informed consent discussion, and data analysis/entry; as well as duties delegated to her per this application.

sDr. Amanda Degraaf, MS- VTCSOM Collaborating Medical Student- currently rotating with the maternal fetal medicine department, will assist in identifying patients meeting eligibility criteria on the maternal fetal medicine schedule, with the informed consent discussion, and with data entry/analysis; as well as duties delegated to her per this application. She is also a former CRC.

Dr. Falen Yohannes, DO- OB-GYN Resident physician with experience working with obstetric patients and will help with patient pre-screening for eligibility, recruitment, informed consent discussion, and data analysis/entry; as well as duties delegated to her per this application.

Ms. Sofia Issel, MS, is a Carilion Clinic Summer Intern and PhD candidate at VT studying biomedical engineering and will assist in the prescreening of subjects, the informed consent discussion and recruitment, and data collection, amongst other study needs as they arise. Her experience in biomedical engineering will benefit the study which focusses on a research ultrasound device.

Arlo Gow, BS, is a biomedical engineering PhD candidate at VT working in Dr. Han's lab and will be supporting technical aspects of research ultrasound data processing, analysis, and algorithm development.

sDr. Zoya Amer is a VTCSOM medical student that will be assisting in prescreening of potential subjects for enrollment, data entry, data analysis [identifiable and de-identifiable], and other study related tasks to bolster recruitment and support the study.

18.7 Please describe appropriate alternatives to the study procedures or course of treatment.

(For example: not to participate, standard of care treatment, other research study, same treatment offered off study)

Not to participate. Standard of care treatment without research ultrasound.

19.0 Research Involving Device(s)

19.1 Device Name:

View Details	Device Name	Is the Device FDA Approved
⊟	The Vantage™ Research Ultrasound System	No

Manufacturer/Supplier of Device	Verasonics
Will Devices be supplied at no Cost	Yes
Is the Device FDA Approved	No
Is an IDE necessary	No

⊟	Phillips Ultrasound Machine	Yes

Manufacturer/Supplier of Device	Phillips
Will Devices be supplied at no Cost	Yes
Is the Device FDA Approved	Yes
Is an IDE necessary	No

19.2 Describe any credentialing procedures and training in the use of the device that will occur prior to use.

Dr. Aiguo Han, one of the study team members, holds a PhD in electrical and computer engineering and works at VT's Biomedical Ultrasound Research Group (BURG) labs. His areas of focus are in biomedical engineering and ultrasound research. He is a fellow of the American Institute of Ultrasound in Medicine (AIUM), member of the IEEE UFFC IUS Medical Ultrasonics Technical Program Committee, and member of the Scientific Editorial Board (Ultrasound Section), European Radiology. He has extensive research experience in working with research ultrasound machines [please see references below.] Dr. Han has read and understood the operating manual for the research ultrasound device and has tested the device on non-human "phantom" models to ensure a practical understanding of the device, its functions, and its safe operation.

The device's function and mechanism for producing ultrasound images are substantially similar to those of the standard-of-care ultrasound. The machine will be programmed to display thermal index (TI) and mechanical index (MI) during all exams, not to exceed 1.0 and the ALARA principles will be adhered to during the examinations as indicated by ISUOG guidelines. It will be programmed with a “hard stop” not to exceed these limits. The energy exposure from Ultrasound has no cumulative effect. The primary differences in this machine are in its software and data processing capabilities. This study is not seeking market approval of this device, and is not seeking to "test" this device as a primary endpoint. Instead, this device is being used in conjunction with the standard-of-care Phillips ultrasound device to test a combine quantitative ultrasound - ultrafast power Doppler imaging (uPDI) methodology of diagnosing FGR in a proof-of-concept, non-FDA-regulated research study. We believe this study as a whole, poses minimal risk to study participants for reasons described prior in this submission. An ultrasound machine is a FDA grade I medical device. A 510(k) or PMA would therefore be inappropriate given the device grade and risk posed by the study.

Dr. Han will be training all IRB-approved research team members on the safe and proper use of the ultrasound machine, will inform sonographers about the differences they may see in using this research ultrasound machine as compared to the standard-of-care Phillips ultrasound machine, and be available for questions or concerns from other study team members throughout the study. As well, a copy of the device manual (Vantage system user guide, an extensive programming reference manual, and a programming tutorial) will be available to study team members on the study's secure, firewalled study server. The PI will review these manuals prior to study enrollment, and re-review them as needed.

Standard-of-care Phillips ultrasound machine will be operated by trained, certified ultrasonographers that are also IRB-approved study-team members, in accordance with the

machine's standard operating procedures and instructions. These sonographers use this machine for routine care many times per day at Carilion. These standard-of-care machines may be used to additionally collect color Doppler imaging in a specific subset of the control-group study cohort. While color Doppler is not typically used at Carilion for routine prenatal/growth/anatomy ultrasounds, it can be used if there is an indication to look at this type of image in some pregnant patients, and routinely employed at Carilion to scan other body parts such as the heart.

References:

K. Nagabhushana, Q. Wang, and A. Han, "Pulse-echo technique to compensate for laminate membrane transmission loss in phantom-based ultrasonic attenuation coefficient measurements," J. Ultrasound Med., vol. 42, pp. 45–58, 2023.
X. Chen, M. R. Lowerison, Z. Dong, A. Han, and P. Song, "Deep learning-based microbubble localization for ultrasound localization microscopy," IEEE Trans. Ultrason. Ferroelectr. Freq. Control, vol. 69, no. 4, pp. 1312–1325, 2022.
A. Han, M. Byra, E. Heba, M. P. Andre, J. W. Erdman, Jr., R. Loomba, C. B. Sirlin, and W. D. O' Brien, Jr., "Noninvasive diagnosis of nonalcoholic fatty liver disease and quantification of liver fat with radiofrequency ultrasound data using one-dimensional convolutional neural networks," Radiology, vol. 295, no. 2, pp. 342–350, 2020. (This paper was featured in an editorial in Radiology.)
A. Han, Y. N. Zhang, A. S. Boehringer, V. Montes, M. P. Andre, J. W. Erdman, Jr., R. Loomba, M. A. Valasek, C. B. Sirlin, and W. D. O'Brien, Jr., "Assessment of hepatic steatosis in nonalcoholic fatty liver disease using quantitative ultrasound," Radiology, vol. 295, no. 1, pp. 106–113, 2020.
S. Chen, B. L. McFarlin, B. T. Meagher, T. A. Peters, D. G. Simpson, W. D. O'Brien, Jr., and A. Han, "A phantom-based assessment of repeatability and reproducibility of transvaginal quantitative ultrasound," IEEE Trans. Ultrason. Ferroelectr. Freq. Control, vol. 66, pp. 1413–1420, 2019.
A. Han, Y. N. Zhang, A. S. Boehringer, M. P. Andre, J. W. Erdman, Jr., R. Loomba, C. B. Sirlin, and W. D. O'Brien, Jr., "Inter-platform reproducibility of ultrasonic attenuation and backscatter coefficients in assessing NAFLD," Eur. Radiol., vol. 29, no. 9, pp. 4699–4708, 2019.
A. Han, "A method for stereological determination of the structure function from histological sections of isotropic scattering media," IEEE Trans. Ultrason. Ferroelectr. Freq. Control, vol. 65, no. 6, pp. 1007–1016, 2018.
A. Han, M. P. Andre, J. W. Erdman, Jr., R. Loomba, C. B. Sirlin, and W. D. O'Brien, Jr., "Repeatability and reproducibility of a clinically based QUS phantom study and methodologies," IEEE Trans. Ultrason. Ferroelectr. Freq. Control, vol. 64, no. 1, pp. 218–231, 2017. (Editor's Selection of Articles - Oct 2017)
A. Han and W. D. O'Brien, Jr., "Structure function estimated from histological tissue sections," IEEE Trans. Ultrason. Ferroelectr. Freq. Control, vol. 63, no. 9, pp. 1296–1305, 2016.
A. Han and W. D. O'Brien, Jr., "Structure function for high-concentration biophantoms of polydisperse scatterer sizes," IEEE Trans. Ultrason. Ferroelectr. Freq. Control, vol. 62, no. 2, pp. 303–318, 2015.

19.3 Who will assume primary responsibility for the storage of the device used in this study?

Name:

Dr. Megan Whitham, MD

19.4 Describe storage and control of the device, including precautions being taken to minimize the chances of device use by health care providers not listed on this application.

(Ex: special ordering requirements, labeling, separate stocking, etc.).

The physical ultrasound machines [research and standard-of-care types] and associated computer will be stored together on a cart, in a locked consult room within the Maternal Fetal Medicine (Room 455) suite of the Carilion Clinic Medical Office Building (MOF) at 102 Highland Ave, Roanoke, VA. This locked room is further secured from outside access by two additional doors which are locked outside business hours. Only Carilion Clinic Maternal Fetal Medicine personnel have a key to this room. The research ultrasound machine will be clearly labelled "For Research Use Only- Carilion Clinic," to further prevent the device from being accidentally used for routine care.

Attach the PMA or cleared (510k) by FDA if used in accordance with labeling, or for investigational devices, attach sponsor/FDA risk assessment documentation if available in the Initial Submission Packet. Attach sponsor device manual of operations if available.

20.0 Research Review of Data/Records

20.1 What types of records will be reviewed for this research study?

- [x] Medical record/medical chart
- [ ] Films/x-rays
- [ ] Data in a database
- [ ] Hospital administrative/billing records
- [ ] Quality improvement records
- [ ] Publically available database
- [ ] Other

Provide a detailed description about your selection above, including if the records are already in existence at the time of this submission or if you will be accessing future records, and special permissions that may be needed to access the data/records:

The records to be accessed are future records and permission to review the records will be included during the informed consent process. The electronic health record data to be reviewed includes the data points listed on the Data Collection Sheet, the eligibility criteria, and the PHI data said to be collected within the *Privacy and Confidentiality* [Section 14] portion of this application.
Email address will be used for sending Amazon eGift Card as per compensation section procedure; email will not be recorded in study record but viewed within the subject's electronic medical record.

20.2 What is the original purpose of the data being reviewed?

- [x] Clinical Care
- [ ] Collected as part of routine business activities
- [ ] Research Study
- [ ] Collected under Repository Protocol
- [ ] Other

20.3 If collected as part of a previous research study or repository protocol, enter the IRB number for the study.

na

20.4 Is the data identifiable private information or Protected Health Information (PHI)?

- (•) Yes
- ( ) No

21.0 Incidental Findings

21.1 Does this study involve any imaging procedures (x-rays, CT, MRI, PET, ultrasound, etc.) specifically for research purposes?

- (•) Yes
- ( ) No

21.2 Does the research include any of the following?

- [ ] Exams, blood tests, genetic tests or markers, or other tests or procedures that may generate incidental or secondary findings, including disease or conditions other than the one under study, or familial relationships including paternity and ancestry.

☐ Testing for communicable diseases
☑ None

21.3 Specify the imaging procedures, exams, tests, or other procedures being done for the research that may generate incidental findings, including whether they will be of clinical quality.

Research Ultrasounds
Ultrasounds will be performed by trained MFM sonographers using the Verasonics Vantage 256 system. During the research ultrasound, fetal growth will be assessed using traditional biometry parameters and Hadlock's '91 estimation[18]. The gestational age of the fetus, estimated fetal weight in grams and percentile measurements for biometric parameters as well as estimation of fetal weight will be recorded during the research exam. Whether a participant has had a clinical exam with corresponding abnormal Dopplers will also be recorded. Following acquisition of fetal biometry, the placenta will be scanned at a central, peripheral and mid-disc region to acquire QUS and uPDI images. Three measurements will be acquired at these locations. The Verasonics machine will be programmed to project B-mode images for the sonographer at the time of the research ultrasound for confirmation of correct placental location. The machine will be programmed to display thermal index (TI) and mechanical index (MI) during all exams, not to exceed 1.0 and the ALARA principles will be adhered to during the examinations as indicated by ISUOG guidelines[19]. The acquired images, QUS and uPDI data will be paired with de-identified study participant ID for storage, post-processing and analysis. The images and ultrasound date, without HPI or participant identifiers, will be stored on the Verasonics machine and regularly transferred to more permanent storage and analysis to research computers located at Dr. Han's lab at Virginia Tech.
Cases: Research ultrasounds for cases will be performed the week after recruitment for baseline assessment, Q 3-week intervals during which FGR remains present, and following clinical exams demonstrating a change in U/A Doppler evaluations (e.g., at visits when Dopplers change from forward flow to absent or at visits when Dopplers change from absent to reversed). The research hard-drive will be regularly transported by Yuanbin Zhu to Dr. Han's lab. Dr. Han's computer is located within a locked office within Virginia Tech campus. This computer is password-protected and behind VT's firewall for a secondary layer of data protection and security. The images, with no patient identifiers, will be additionally uploaded to OneDrive.
Controls: Research ultrasounds for controls will be performed in the 1-2 weeks following enrollment, and at Q 3-week intervals throughout the remainder of the pregnancy. Any clinically-significant, incidental findings of abnormal fetal growth will be reported by the sonographer to the participating clinical team members and to the patient, so that an indicated formal clinical sonogram can be ordered by the managing Obstetrics provider.

The B-mode images paired with the QUD and uPDI data will be of clinical quality. Incidental findings will be disclosed to the patient by the study personnel and appropriate follow up for the enrollee will be coordinated by Dr. Whitham.

The PI will advise the participant's routine clinical provider that all results obtained with the research ultrasound should be validated using an FDA Approved ultrasound and standard of care ultrasound techniques.

Color Doppler images using the standard-of-care machine may also be obtained for control-group subjects, of <40 kg/m^2, <32 wks gestational age, with anterior placentas [as confirmed by the standard-of-care ultrasound], who speak/read English, and who otherwise meet the study eligibility criteria, starting on 19 Feb 2026. These Doppler images from the standard-of-care ultrasound machine will allow the study team to compare clarity of the Doppler images to those of the research machine's uPDI images. Color Doppler images are not standardly collected for routine care and will add approximately one minute to the overall exam [standard-of-care images + research images]. These images will be of clinical quality, on an FDA-approved, standard-of-care ultrasound machine used at Carilion, by a certified, Carilion-employed, IRB-approved, sonographer. Incidental findings will be referred by the PI to the subject's routine provider with patient verbal permission. This will be documented in Carilion Epic EMR if it occurs.

21.4 Describe the likelihood and nature of incidental or secondary findings and whether such findings could be clinically significant and if they may require additional interpretation (clinical imaging) or verification (e.g., certification by a CLIA lab).

There are incidental ultrasound findings which could include fetal anomalies or maternal abnormalities not previously detected on prior ultrasounds as well as new fetal growth abnormalities which could be discovered at the time of research ultrasound. These incidental findings may require additional clinical imaging with further obstetric ultrasound under clinical parameters. Arrangement for this follow up would be coordinated by Dr. Whitham.

21.5 Describe the plans for sharing such findings with subjects and their healthcare provider. If you will not be sharing findings with subjects, please provide your justification. The plans to share or not to share must be described in the Informed Consent document.

Incidental findings obtained during the research ultrasound will be shared with the subject's routine clinical provider and the patient by IRB-approved and qualified physicians on the research team. The PI will advise the participant's routine clinical provider that all results obtained with the research ultrasound should be validated using an FDA Approved ultrasound and standard of care ultrasound techniques.
Incidental findings during research color Doppler imaging with the standard-of-care Phillips machine will likewise be referred to the subject's routine OB provider, by the PI. Verbal permission by the subject to speak to their routine provider will be documented in a Carilion Epic note.

22.0 Imaging

22.1 Select the imaging procedures that will be completed for research purposes.

- ☐ X-ray
- ☐ CT scan
- ☐ Fluoroscopy
- ☐ Bone Density by X-ray Absorptiometry (DEXA)
- ☐ MRI/functional MRI
- ☑ Ultrasound
- ☐ Other

22.2 Provide a detailed description of the use of therapeutic or diagnostic radiation being administered for research purposes.

You may go to: https://vmw-oesoapps.duhs.duke.edu/radsafety/consents/irbcf_asp/default.asp for computation of Effective Dose Equivalent, and also a risk statement to be incorporated into the informed consent document.

If applicable, upload a Radiation Safety Approval letter to the Initial Submission Packet.

Ultrasound, without ionizing radiation, will be performed. The Verasonics machine will be programmed to project B-mode images for the sonographer at the time of the research ultrasound for confirmation of correct placental location. The machine will be programmed to display thermal index (TI) and mechanical index (MI) during all exams, not to exceed 1.0 and the ALARA principles will be adhered to during the examinations as indicated by ISUOG guidelines. The Verasonics machine will be programmed with a "hard stop" not to exceed these limits. The energy exposure from Ultrasound has no cumulative effect.

23.0 Identification/Recruitment of Subjects

23.1 How do you plan to identify potential subjects?

To "identify" a potential subject refers to procedures to determine which individuals may qualify to participate in the study in order to decide which individuals to contact about taking part.

Check all that apply:

	Existing Record Review, including Medical Chart Review, Clinic Schedule	Select all that apply: ☑ Patients' records reviewed will be those from research team's own patient population ☑ Patients' records will be those from other physicians or medical

☑	Review, or QA-QI Database Review.	practices' patient population ** You must request Waiver of Informed Consent and, if any HIPAA identifiers are collected, a Waiver of HIPAA Authorization for recruitment purposes.*
☐	Researchers who ARE NOT treating clinicians of potential subjects will ask treating clinicians for referrals of eligible patients interested in the study.	Select all that apply: ☐ Treating clinicians will identify potentially eligible patients and obtain patient permission before providing researchers with patient contact information. ☐ Treating clinician will provide documentation of patient permission in a email/letter to researcher, and researcher must document permission in research record. **You must request a Waiver of Informed Consent/HIPAA Authorization for recruitment purposes.*
☐	Potential subjects will not be directly identified by the researchers from existing records. The potential subject will obtain IRB-approved information about the study from an advertisement, flyer, brochure, website, grand rounds presentation, department meeting, etc. In most cases, the potential subject will contact the researcher if interested.	Comments:
☐	Review of Registry/Database in which individuals have previously signed a consent giving their permission to be contacted for future studies.	Comments:
☐	Student Records	Comments:
☐	Other	Please specify other:

23.2 Please describe the identification process.

List all information you plan to collect and record during the identification process PRIOR to contacting potential subjects. This includes the inclusion/exclusion criteria and demographics to determine if a person qualifies for a study before contacting that person to be a potential subject.

Subjects referred to the Maternal Fetal Medicine Clinic (MFM) or located within the MFM daily schedule and identified as potential case or control subjects will be pre-screened by reviewing their medical records for inclusion and exclusion criteria based on their potential group allocation [case or control].

Participants will not be under the primary care of the research physicians. The research physicians will not be involved in decisions regarding the timing, method, or procedures used to terminate a pregnancy or determining the viability of a neonate.

23.3 Through what methods will potential subjects be contacted or recruited?

Check all that apply. To "recruit" a potential subject refers to the initial contact method you plan to use to convey information to a potential subject to determine if he or she would be interested in taking part in your study.

- [x] Direct in-person contact
- [ ] Telephone call
- [ ] Letter
- [ ] E-mail
- [ ] Brochure
- [ ] Radio/Television script
- [ ] Newspaper Ad
- [ ] Online advertisement (including Facebook, Twitter, Craigslist, other websites, etc.)
- [ ] Flyer/Poster
- [ ] Snowball sampling
- [ ] Clinical trial website posting
- [ ] Other
- [ ] None (there will be no interaction or intervention with potential participants in this study)

23.4 Please provide any additional details about how potential subjects will initially be contacted, who will contact them, or how they will be introduced to the research.

- ***If recruitment material is being mailed, emailed, or otherwise distributed, describe where/how the distribution list will be obtained.***
- ***If potential subjects will be recruited by telephone, describe how many times the research team will attempt to call / leave a voice message.***
- ***When subjects respond to recruitment material, describe the information that will be provided to them about the study and the information that will be collected from subjects (e.g. name, telephone number, etc.). Describe also, how many times you will attempt to respond to call the subject back / leave a voice message.***

IRB-approved research personnel will conduct pre-screenings within the electronic medical record to identify subjects meeting the inclusion and exclusion criteria listed in the protocol. When a potential subject is identified and found to meet inclusion and exclusion criteria within the EMR, verbal consent from their treating physician will be sought by the study team. The treating physician will be given adequate information concerning the research protocol to determine the appropriateness of the qualified clinical trial for their patient. The treating physician will next speak in a private location or by phone to determine the subject's interest in speaking with the research team.

Subjects expressing interest in speaking to the research team will be approached by IRB approved study personnel in the CMC OB offices or via telephone call from a designated study

personnel. A second in-person pre-screening will then take place. The informed consent process will then take place."

23.5 After potential subjects are identified, describe the pre-screening process that will take place prior to obtaining informed consent.

This could include asking questions to a potential subject to determine whether he or she meets eligibility criteria, for example: patients will answer questions about their medical history, be expected to come to the first screening visit after fasting, stop taking medications, change diet, etc. To comply with HIPAA regulations, only the minimum necessary protected health information may be collected at this time. This means only questions relating to the inclusion and exclusion criteria may be asked.

☐ No prescreening will take place

The Maternal Fetal Medicine daily schedule will be pre-screened within the Carilion Clinic's electronic medical record *Epic*, to avoid consenting of large numbers of patients who do not meet the eligibility criteria.
Subjects may also be pre-screened in person using a pre-screening questionnaire which asks about their pregnancy and ability to undergo routine ultrasound; this questionnaire will not ask potential subjects about cocaine use; current cocaine use will remain one of the eligibility criteria which will be asked during screening *following* informed consent. This sensitive eligibility criterion has been grouped with 11 other identified risk factors for FGR. Only the investigator asking the subject the eligibility screening criteria will know which of those 12 total risk factors caused an ineligible patient to be denied study enrollment due to Control-cohort eligibility criterion 7 [FGR risk factors].

A partial HIPAA waiver is being sought for the purposes of pre-screening patients; the explanation for why this waiver is necessary is detailed elsewhere in this submission. Prior to asking any in-person, pre-screening questionnaire questions, the IRB-approved research team member will introduce their name, capacity, and purpose for speaking to the patient [to talk about a research study]; they will verify the patient's name and then verbally ask if they may speak to the patient about a research study. Following verbal consent, the IRB-approved study team member will give a short agenda for the conversation and that it should take around 5 minutes to complete. The IRB-approved team member will then explain that he/she is part of a research team from Maternal Fetal Medicine/Obstetrics conducting a research study, the title of this study, a lay explanation of the purpose for the research, and that they would like to ask the patient a few questions about their pregnancy and experience with previous ultrasound exams to see if they may qualify for the study. Any questions the patient may have will be answered to the patient's satisfaction before the questionnaire. If the patient verbally consents to be asked the questionnaire, they will first be informed they can stop answering these questions whenever they like. The questions will then be asked, and the patient subsequently informed as to whether the IRB-approved team member believes this patient *may* qualify for the research study. The subject will then be asked if they would be okay with hearing more about the study and the consent process will be conducted, or the patient will be asked for their permission to approach them at a subsequent routine visit to learn more about the research study [at which visit, the consent procedure would occur.] Whether the consent process is conducted will depend on the patient's answer [yes or no].

Following this encounter and questionnaire, the patient will be added to a prescreening log, detailing their name, date of the visit, whether the questionnaire was answered, the outcome of the prescreening questionnaire, whether the patient's EMR chart was reviewed for pre-screening purposes, the outcome of that EMR pre-screening, whether the patient provided informed consent, and whether the patient met screening criteria. This log will be kept on a secure Carilion Clinic Shared (S:) drive which is only accessible to Carilion Clinic employees with their username /password login, and only to those employees who are IRB-approved for this study. The drive is behind the Carilion Clinic firewall and is encrypted. The HART team will create a study-specific folder on this drive following IRB approval of the study.

Additionally, the process used by the IRB-approved study team member to obtain verbal consent from the patient as described above to conduct this prescreening questionnaire will be documented in a research note in the EMR *Epic.*

To pre-screen patients for participation, prior to consenting, they will be asked the following questions by study personnel:

1. How old are you?
2. Did you conceive naturally?

3. Have you had your anatomy ultrasound yet?
4. Were there any concerns about baby's anatomy on your ultrasound?

The questionnaire will ask the IRB-approved investigator if the subject was pre-screened in-person [with this questionnaire] or only the electronic medical record was needed to collect the above questionnaire information.

If subjects appear eligible for one of the cohorts [case or control] within the study based on this short pre-screening questionnaire, the above described methodology for performing the informed consent procedure will be followed.

23.6 Indicate whether pre-screening information will be retained on persons who do not ultimately participate in the study and what specific information, including identifiers, will be retained.

No pre-screening information will be retained on persons who do not participate in the study.

Attach all recruitment materials, letters, phone scripts, flyers, etc. in the Supplemental Documents section after you complete the IRB application.

24.0 Risks and Risk Minimization and Benefits

24.1 List the possible risks, discomforts, or harms to subjects associated with the research.

If the risks differ based on group assignment, describe for each group. Estimate the (1) probability of occurrence, (2) the seriousness, and (3) the duration of each risk. If this information is captured in the protocol or investigators brochure (IB) or other materials, indicate the document and page numbers where the information can be located.

The primary risk to participants is in the discovery of incidental findings which will be disclosed to the participants after confirmation with the Maternal Fetal Medicine team as previously-mentioned. Dr. Whitham will arrange for appropriate clinical follow up for these subjects and disclose the findings to their healthcare provider. The probability of this occurrence is minimized due to exclusion criteria of the patient not having suspected fetal anomalies, inclusion of having completed their anatomic survey evaluation and exclusion of patients in the control group with conditions related to increased risk of fetal growth restriction. Certainly, incidental findings can have serious implications; however, ultrasound for the detection of fetal anomalies is generally accepted as an expectation of routine clinical care.

Additional potential risks involve discomfort with the ultrasound exam, theoretical heat exposure to the fetus (not beyond those anticipated from routine clinical diagnostic ultrasounds) and the potential for breach of HPI/confidentiality. The risks of ultrasound exposure are minimized through principles of ALARA: The Verasonics machine will be programmed to project B-mode images for the sonographer at the time of the research ultrasound for confirmation of correct placental location. The machine will be programmed to display thermal index (TI) and mechanical index (MI) during all exams, not to exceed 1.0 and the ALARA principles will be adhered to during the examinations as indicated by ISUOG guidelines. Risks are theoretical and there are no documented cases of fetal damage with use of ultrasound when the abovementioned parameters used for diagnostic ultrasound imaging in pregnancy have been used.

Vasovagal episodes with ultrasound exam (rare event): The sonographer study team member will stop the exam and alert clinical staff members of the MFM Clinic. The patient will be provided rest and water, and the patient will be evaluated by a clinical team member. After resolution of any vasovagal symptoms, the sonographer will assess the patient's willingness to continue the research ultrasound on that day, reschedule or whether the patient wishes to forgo the research ultrasound altogether. Should the subject be wish to be rescheduled, this will be coordinated directly with Dr. Whitham or with study personnel, Nicholas Joseph or Jessica Nichols. The patient's desire to continue to be included in the study or desire to withdraw from the study will be determined prior to scheduling. Should the patient wish to completely withdraw, this will be noted and recorded in REDCap with no further study procedures or data collection planned for the patient.

Allergic Dermatitis (rare event): Ultrasound gel used during examination may contain propylene glycol or isothiazolinone chemicals. A small number of people may have an allergy or sensitivity

to one or more of these chemicals. This allergy or sensitivity usually manifests as a localized skin reaction such as mild erythema [redness] or itching. Should this occur, the ultrasound gel will be removed from the skin by the sonographer and the area cleansed with soap and water. Members of the clinical team will be alerted. Dr. Whitham will provide clinical care if needed. Should the subject wish to be rescheduled, this will be coordinated directly with Dr. Whitham or with study personnel, Nicholas Joseph or Jessica Nichols. The patient's desire to continue to be included in the study or desire to withdraw from the study will be determined prior to scheduling. Should the patient wish to completely withdraw, this will be noted and recorded in REDCap with no further study procedures or data collection planned for the patient.

There may be risks of stress, emotional distress, embarrassment, or inconvenience.

Breach of HPI is minimized through use of coded participant IDs and REDCap for storage of identifying data. Carilion Clinic's REDCap software will be used as the central location for data collection. REDCap (research electronic data capture) provides a secure, web-based application designed to support data management and collection for research/QA/QI studies. Carilion's REDCap servers are securely housed on site in a limited access data center, and all data are stored on Carilion's firewall protected network. The Health Analytics Research Team supports the proper development of projects and surveys in REDCap, observing appropriate change control and enforcing appropriate security controls. Data collection projects are built with a study-specific data dictionary, enforcing intuitive, accurate, consistent and complete data entry. REDCap also provides a survey tool for building and managing online surveys. Health Analytics Research team restricts user access to the IRB-approved project research team utilizing the approved processes and standards of TSG. REDCap is HIPAA compliant and provides audit trails. Data can be easily exported in several formats to a secure network directory for combination with extracted data, if appropriate, and analysis with common statistical packages.

24.2 Define adverse events (AEs), serious adverse events (SAEs), and unanticipated problems (UAPs) for the study. Describe the protocol-specific reporting procedures, including who will be responsible for each step (e.g., PI), timeframes for reporting, how reports will be distributed, and follow-up that will occur.

Ensure that the reporting procedures meet the reporting requirements of Carilion Clinic IRB, the FDA, NIH, OHRP, sponsor, study leadership and any other regulatory body that applies to the study, as applicable. Please note that all Carilion Privacy breaches must also be reported to the Privacy office by the PI. Noncompliance must be reported to the IRB as well as Office of Integrity and Compliance.

Adverse events:
Discomfort with ultrasound exam: The sonographer study team member will stop the exam, discuss the discomfort with the subject and discuss whether alterations in positioning can be made to improve comfort. The sonographer will assess the patient's willingness to continue the research ultrasound on that day, reschedule or whether the patient wishes to forgo the research ultrasound altogether. Should the subject wish to be rescheduled, this will be coordinated directly with Dr. Whitham or with study personnel, Nicholas Joseph or Jessica Nichols. The patient's desire to continue to be included in the study or desire to withdraw from the study will be determined prior to scheduling. Should the patient wish to completely withdraw, this will be noted and recorded in REDCap with no further study procedures or data collection planned for the patient.
Vasovagal episodes with ultrasound exam (rare event): The sonographer study team member will stop the exam and alert clinical staff members of the MFM Clinic. The patient will be provided rest and water, and the patient will be evaluated by a clinical team member. After resolution of any vasovagal symptoms, the sonographer will assess the patient's willingness to continue the research ultrasound on that day, reschedule or whether the patient wishes to forgo the research ultrasound altogether. Should the subject be wish to be rescheduled, this will be coordinated directly with Dr. Whitham or with study personnel, Nicholas Joseph or Jessica Nichols. The patient's desire to continue to be included in the study or desire to withdraw from the study will be determined prior to scheduling. Should the patient wish to completely withdraw, this will be noted and recorded in REDCap with no further study procedures or data collection planned for the patient.
Allergic Dermatitis (rare event): Ultrasound gel used during examination may contain propylene glycol or isothiazolinone chemicals. A small number of people may have an allergy or sensitivity to one or more of these chemicals. This allergy or sensitivity usually manifests as a localized skin reaction such as mild erythema [redness] or itching. Should this occur, the ultrasound gel will be removed from the skin by the sonographer and the area cleansed with soap and water. Members of the clinical team will be alerted. Dr. Whitham will provide clinical care if needed. Should the subject wish to be rescheduled, this will be coordinated directly with Dr. Whitham or with study personnel, Nicholas Joseph or Jessica Nichols. The patient's desire to continue to be included in

the study or desire to withdraw from the study will be determined prior to scheduling. Should the patient wish to completely withdraw, this will be noted and recorded in REDCap with no further study procedures or data collection planned for the patient.
Privacy breaches: Any reported privacy breaches will be directly reported to the P.I. The P.I. Will report any privacy breaches to the Privacy office.
Noncompliance: Any noncompliance with study procedures will be reported to the P.I. These will be directly reported to the IRB and Office of Integrity and Compliance by the PI.

24.3 Describe the actions that will be taken to minimize the risks associated with participation in this research.

If this research includes risks that might require immediate or prompt medical management, describe access to/availability of emergency medical equipment and trained personnel at each setting where procedures that impart physical/health risks will take place. If this information is available in the study protocol indicate the page numbers where the information can be located.

- The primary risk to participants is in the discovery of incidental findings which will be disclosed to the participants after confirmation with the Maternal Fetal Medicine team as previously-mentioned. Dr. Whitham will arrange for appropriate clinical follow up for these subjects and disclose the findings to their healthcare provider. The probability of this occurrence is minimized due to exclusion criteria of the patient not having suspected fetal anomalies, inclusion of having completed their anatomic survey evaluation and exclusion of patients in the control group with conditions related to increased risk of fetal growth restriction. Certainly, incidental findings can have serious implications; however, ultrasound for the detection of fetal anomalies is generally accepted as an expectation of routine clinical care.

- Discomfort with ultrasound exam: The sonographer study team member will stop the exam, discuss the discomfort with the subject and discuss whether alterations in positioning can be made to improve comfort. The sonographer will assess the patient's willingness to continue the research ultrasound on that day, reschedule or whether the patient wishes to forgo the research ultrasound altogether. Should the subject wish to be rescheduled, this will be coordinated directly with Dr. Whitham or with study personnel, Nicholas Joseph or Jessica Nichols. The patient's desire to continue to be included in the study or desire to withdraw from the study will be determined prior to scheduling. Should the patient wish to completely withdraw, this will be noted and recorded in REDCap with no further study procedures or data collection planned for the patient. The Verasonics machine will be programmed with a “hard stop” not to exceed these limits. The energy exposure from Ultrasound has no cumulative effect.

- Vasovagal episodes with ultrasound exam (rare event): The sonographer study team member will stop the exam and alert clinical staff members of the MFM Clinic. The patient will be provided rest and water, and the patient will be evaluated by a clinical team member. After resolution of any vasovagal symptoms, the sonographer will assess the patient's willingness to continue the research ultrasound on that day, reschedule or whether the patient wishes to forgo the research ultrasound altogether. Should the subject be wish to be rescheduled, this will be coordinated directly with Dr. Whitham or with study personnel, Nicholas Joseph or Jessica Nichols. The patient's desire to continue to be included in the study or desire to withdraw from the study will be determined prior to scheduling. Should the patient wish to completely withdraw, this will be noted and recorded in REDCap with no further study procedures or data collection planned for the patient.
    - Trained clinical personnel at the MFM clinic include RNs x 2, a CNA, and 2-4 MDs on any clinic day.

- Allergic Dermatitis (rare event): Ultrasound gel used during examination may contain propylene glycol or isothiazolinone chemicals. A small number of people may have an allergy or sensitivity to one or more of these chemicals. This allergy or sensitivity usually manifests as a localized skin reaction such as mild erythema [redness] or itching. Should this occur, the ultrasound gel will be removed from the skin by the sonographer and the area cleansed with soap and water. Members of the clinical team will be alerted. Dr. Whitham will provide clinical care if needed. Should the subject wish to be rescheduled,

this will be coordinated directly with Dr. Whitham or with study personnel, Nicholas Joseph or Jessica Nichols. The patient's desire to continue to be included in the study or desire to withdraw from the study will be determined prior to scheduling. Should the patient wish to completely withdraw, this will be noted and recorded in REDCap with no further study procedures or data collection planned for the patient.

- There may be risks of stress, emotional distress, embarrassment, or inconvenience. This is minimized by use of private maternal fetal medicine exam rooms for study-related discussions and visits. Study-related conversation and conversation pertaining to patient medical information will only be discussed in a private location where it won't be overheard by others not on the patient's care team or IRB-approved research study members. Exam rooms will have the lights dimmed and calming music played during ultrasounds to relax the patient and reduce stress. Should the patient appear to be in emotional distress, the IRB-approved study team member or sonographer will assess verbally, the patient's willingness to continue with the research study or ask if the patient would like to reschedule their research visit for another day.

- Privacy breaches: Any reported privacy breaches will be directly reported to the P.I. The P. I. Will report any privacy breaches to the Privacy office. The privacy office will work to minimize risk to the patient as they feel is best practice. This may include enrolling the patient in a credit monitoring program or other identity protection method.

- Breach of HPI is minimized through use of coded participant IDs and REDCap for storage of identifying data. Carilion Clinic's REDCap software will be used as the central location for data collection. REDCap (research electronic data capture) provides a secure, web-based application designed to support data management and collection for research/QA/QI studies. Carilion's REDCap servers are securely housed on site in a limited access data center, and all data are stored on Carilion's firewall protected network. The Health Analytics Research Team supports the proper development of projects and surveys in REDCap, observing appropriate change control and enforcing appropriate security controls. Data collection projects are built with a study-specific data dictionary, enforcing intuitive, accurate, consistent and complete data entry. REDCap also provides a survey tool for building and managing online surveys. Health Analytics Research team restricts user access to the IRB-approved project research team utilizing the approved processes and standards of TSG. REDCap is HIPAA compliant and provides audit trails. Data can be easily exported in several formats to a secure network directory for combination with extracted data, if appropriate, and analysis with common statistical packages.

- Noncompliance: Any noncompliance with study procedures will be reported to the P.I. These will be directly reported to the IRB and Office of Integrity and Compliance by the PI. An action plan for noncompliance as well as protocol deviations and unanticipated problems will be created to prevent such events from re-occurring. Study team members found to have made protocol deviations or are otherwise noncompliant with study procedures will be retrained by the PI. Continued protocol deviations, clinical research regulation or GCP violations, or breaches in local/state/federal law may result in that study team member being removed as the PI sees reasonable.

24.4 For studies involving drugs, devices, biologics, or imaging, describe the type of pregnancy testing that will occur and how frequently it will be conducted on women of reproductive potential.

Include:

- ***If pregnancy testing will not be conducted, provide the reason.***
- ***State the types of birth control methods women of reproductive potential will be instructed to use.***
- ***If women will not be instructed about acceptable methods of birth control, provide the reasoning.***

- ***Describe the birth control methods men of reproductive potential will be instructed to use. If men will not be instructed about acceptable methods of birth control, provide the reasoning.***

N/A All patients enrolled will be pregnant.

24.5 Does the research include screening tools, questionnaires, or procedures that may indicate the presence of serious depression and/or suicidal ideation?

○ Yes ◉ No

24.6 Describe the Data Safety Monitoring Plan or Data Safety Monitoring Board, or indicate the page(s) of the protocol or name of the document where this information can be located. While a robust Data Safety Monitoring Plan is REQUIRED for greater than minimal risk studies, a plan should also be in place for studies that are minimal risk. Please click on the Help circle to the right for information on writing a DSM plan based in risk levels of the research.

Include:

- ***The data that will be reviewed, including safety data, untoward events, and efficacy data;***
- ***Who is responsible for reviewing the data;***
- ***How the safety information will be obtained and documented (e.g., case report forms, by telephone calls with participants, printouts of laboratory results, etc.);***
- ***The frequency or periodicity of review of cumulative data;***
- ***The statistical tests for analyzing the safety data to determine whether harm is occurring;***
- ***Any conditions that trigger an immediate suspension of the research or other action for the research.***

Data Safety Monitoring Plan

1. Personnel responsible for the safety review and its frequency:

The principal investigator, Dr. Megan Whitham, will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews on a yearly basis, prior to the continuing review process; additionally, adverse events (AEs), serious adverse events (SAEs), Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), and other applicable information pertaining to subject safety will be reviewed by the PI following the completion of the study protocol by each patient. During both the individual subject and yearly review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator or the IRB have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed **minimal** by the research team due to the non-invasive and low-risk nature of the ultrasound imaging which comprises the main 'treatment' in our subjects. The main risks to subjects, as previously described in detail, comprise of a loss of confidentiality, learning of incidental findings concerning their fetus, minor discomforts during the scan, allergic dermatitis, allergies to ultrasound gel components, distress, embarrassment, or inconvenience, as well as other rare risks. We will not be otherwise modifying or altering the standard-of-care treatment of subjects within the "Case" / affected cohort, or the standard prenatal care received by the control group.

1. Although we have assessed the proposed study as one of minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur as it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator, Dr. Megan Whitham, according to the following categories:

a.) Definite: Adverse event is clearly related to the study.
b.) Probable: Adverse event is likely related to the study.
c.) Possible: Adverse event may be related to the study.
d.) Unlikely: Adverse event is likely not to be related to the study.
e.) Unrelated: Adverse event is clearly not related to the study.

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:
Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with Carilion Clinic IRB Policy HRP-071, Ed. 001, 21 CFR 56.108(b), and 45 CFR 46.107(a)(4), using the appropriate forms found on the Carilion Clinic PRIS3M IRB website. All related events involving risk but not meeting the *promp t* reporting requirements described in Carilion Clinic HRP-071 Ed. 001 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented***.***

7. Plan for reporting adverse events to co-investigators on the study

For the current study, the following individuals will be notified:

All Co-Investigators listed on the protocol.

The principal investigator, Dr. Megan Whitham, will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

All adverse events and unanticipated problems will be reported promptly to the Carilion Clinic IRB per Carilion Clinic reporting requirements.

References:

1. 21 CFR §56.108(b)
2. 45 CFR §46.107(a)(4)
3. Yale University IRB, 420 FR.1

24.7 Describe the plans and rationale for conducting an interim analysis.

○ Yes ◉ No

24.8 Have stopping rules been established for the study, including for reasons of futility?

◉ Yes ○ No

Describe the stopping rules:

After review of adverse events as mentioned in the DSMB section, the PI will determine if there is an increase in adverse events related to the study requiring consideration for stopping the study.

Safety of the study following any serious adverse events likely or possibly related to the study procedures will be reviewed by the PI who will make a determination whether the study should proceed along with the IRB who will be notified of these promptly reportable events.

Additionally, unanticipated problems or serious protocol deviations will also cause the PI to review the safety of continuing the study and make a determination whether or not to continue with enrollment or study procedures; these events are also reported to the IRB who will perform their own review.

24.9 Are there defined criteria (ex: rates of adverse events) for when study interventions should be discontinued?

○ Yes ◉ No

24.10 Are there exams or procedures that the subject will be asked to have done or follow to safely withdraw from the study?

○ Yes ◉ No

24.11 Will subjects who withdraw from the interventional component of the study be asked for their permission to continue to gather information about them through follow up visits, phone calls, records review, or other methods?

◉ Yes
○ No
○ N/A

Describe what the subjects will be asked to permit:
Note: Such plans should also be described in the consent.

The subjects will be asked whether their medical record can still be reviewed following delivery to acquire medical and outcomes data to be included in analysis.

24.12 Describe the potential benefits to science and/or society expected from this research.

Our study is a preliminary exploratory step evaluating whether placental QUS and uPDI imaging may be applied to evaluate pregnancies affected by FGR. It is anticipated that multi-modal, multi-scale imaging techniques may be able to provide insight into placental microvascular development and function. QUS and uPDI can be implemented on the same ultrasound scanner, which will facilitate eventual clinical adoption. The potential benefits would include improved management with decreased resource utilization for patients diagnosed with fetal growth restriction. There is also potential benefits for improved identification of patients at risk for serious adverse outcomes related to fetal growth restriction such as stillbirth and neonatal morbidity due to impaired in utero development.

24.13 Are individual subjects expected to directly benefit from participating in this research?

Note: Compensation is not considered a benefit.

○ Yes ◉ No

25.0 Costs and Compensation

25.1 Will the subject, or the subject's insurance, be responsible for any medical costs incurred as a result of participation in the research?

Take into account medical costs associated with study procedures, drugs, or devices.

○ Yes ◉ No

25.3 Will subjects be reimbursed for any expenses related to their research participation, including medical costs, travel, parking, or transportation?

○ Yes ◉ No

25.4 Will subjects receive any monetary compensation (cash, check, or giftcard) or non-monetary gifts, incentives, or tokens of appreciation for participating in this research?

Note: Reimbursement for costs is not considered compensation. Use of raffles or lotteries are discouraged at Carilion Clinic since the compensation is not being equitably dispersed to participants. Raffles and lotteries may be permitted on a case-by-case basis with appropriate justification.

◉ Yes ○ No

Please ensure the following language is in the consent document:

Include if payment for the study will be less than $100 in the next calendar year: Payments made to you as compensation for your participation will be tracked by the research team. This information will be submitted to Carilion's financial department for central tracking. If you receive greater than $600 from Carilion in a calendar year, this is considered taxable compensation and will be reported to the Internal Revenue Service (IRS). You will be issued a 1099 tax form by Carilion if you meet this reporting threshold.

Include if payment for the study will be $100 or more in the next calendar year: In order to receive compensation for your participation, you will be asked to complete an Internal Revenue Service (IRS) W-9 form. Your social security number will be required to complete the IRS form. Compensation to study subjects greater than $600 in a calendar year is considered taxable compensation and is reportable to the Internal Revenue Service (IRS). Carilion will be required to provide your name, social security number, address, and amount of payment to the IRS. You will be issued a 1099 tax form by Carilion if you meet this reporting threshold. This information and your payment amount will be kept secure and confidential in our research financial records and Carilion's financial office. This information will not be associated with the study name or the research data you provide as a participant

25.5 Please describe the compensation.

Include the amount and method of payment, and the distribution plan for the payment (payment received at each visit, payment at end of study, completion bonus, etc.). If a non-monetary item will be provided, state the approximate retail value of the item, when subjects will receive the item, any conditions or requirements that must be fulfilled for subjects to receive the item(s), and a picture of or link to the item online, if possible.

Each study participant will receive $5 payment at each visit and then receive a completion bonus in the form of Amazon giftcard following their delivery if all study research ultrasounds were completed. The total compensation will not exceed $50.
For example:
Study participant 1 has 2 research ultrasounds and received $5 each visit for a total of $10 compensation. No further research ultrasounds were planned prior to patient delivery. The patient receives a $40 Amazon gift card following delivery, sent as an eGift Card to the subject's electronic mail address ('email').
All compensation will be sent as Amazon eGift cards via the listed email on Epic. Should the subject not have an email listed on their Epic electronic health record (EHR), IRB-approved study team members will add one to their Epic chart at the first visit, following signature of the Informed Consent Form. Emails that are listed on Epic will be verified with the subject to ensure they are current and accessible by the subject, again after the ICF is signed.

25.6 If the research involves children or adults unable to consent to participation, explain who will receive the monetary compensation or non-monetary item(s).

☑ N/A

26.0 Application Questions Complete

26.1 You have now completed the IRB Application. Please click Save & Continue to proceed to the Initial Submission Packet.

Date Completing Form:

05/15/2026

The Initial Submission Packet is a short form filled out after the IRB application has been completed and is where you will attach protocol-related documents, such as consent forms and recruitment materials. You will also be able to conduct a final review of the IRB application.

The PI will be required to sign off on the final Initial Submission Packet. The study may then proceed to the Department Signoff, if necessary based on the application type selected, and may require COI review before proceeding to the IRB.

You can view the Submission History of the study at any time to determine the status.