EPA 600/R-05/009

Overall Procedures Protocol and Patient Enrollment Protocol

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Images

Prepared for:

Pauline Mendola, Ph.D.
U.S. Environmental Protection Agency
National Health and Environmental Effects Research Laboratory

Prepared by RTI International under contract 68-D-02-069:
Jodie Weiner, MSN

RTI Work Assignment Leader: Jodie M. Weiner, MSN
RTI International
3040 Cornwallis Road
Research Triangle Park, NC 27709-2194
Telephone: (919) 316-3890
Fax: (919) 541-3866
E-mail: weiner@rti.org

Disclaimer:

The information in this document has been funded wholly or in part by the U.S. Environmental Protection Agency under contract 68-D-02-069 to RTI International. It has been subjected to review by the National Health and Environmental Effects Research Laboratory and approved for publication. Approval does not signify that the contents reflect the views of the Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

Contract No. 68-D-02-069 **August 25, 2004**

Deliverable

Overall Procedures Protocol and Patient Enrollment Protocol

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Images

Work Assignment Number: 02-03

RTI Project No. 08601.001.003

Prepared for:
EPA Work Assignment Manager: Pauline Mendola, Ph.D.
Attn: Mr. James Kempf
U.S. Environmental Protection Agency
RTP - Procurement Operations Division
Mail Code E105-02
Research Triangle Park, NC 27711

Prepared by:
RTI Work Assignment Leader: Jodie M. Weiner, MSN
RTI International
3040 Cornwallis Road
Research Triangle Park, NC 27709-2194
Telephone: (919) 316-3890
Fax: (919) 541-3866
E-mail: weiner@rti.org

RTI Contracting Officer: Kelly Koeller-Anna
Office of Research Contracts
RTI International
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 316-3746
Fax: (919) 541-6624
E-mail: kellyk@rti.org

Overall Procedures Protocol

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Data Sets and Images

A. Abstract

The purpose of this study is to examine the feasibility of collecting, transmitting, and analyzing 3-D ultrasound data in the context of a multi-center study of pregnant women. The study will also examine the reliability of measurements obtained from 3-D images that have been stored and retrieved. In particular, measurements from stored 3-D scans will be compared to those from 2-D scans obtained at the time of ultrasound examination.

B. Background and Rationale

The National Children's Study (NCS) is a federally-coordinated longitudinal study of environmental influences on child health and development. The study will enroll a cohort of approximately 100,000 children before birth. The measurement of growth of the fetus is a primary requirement for the NCS, both as a pregnancy outcome and, perhaps more importantly, in relation to potential influences on health later in life. For instance, a causal association between sub-optimal fetal growth and later risk of abnormal glucose metabolism has been postulated and therefore is likely to be evaluated within the context of the NCS.

A Fetal Growth Workshop was held as part of the December 2002 NCS Assembly (planning) meeting. The workshop included a thorough discussion of the optimal methods to evaluate fetal growth and integrity. At that workshop the current research effort, a pilot study to evaluate the feasibility of three-dimensional (3-D) ultrasound data acquisition and the reliability of data retrieval from stored 3-D images, was identified as a central action item.

3-D ultrasound has several potential advantages over 2-D imaging. 3-D images contain a wealth of volumetric and morphologic information on organs and structural elements of the fetus and the fetal-placental unit, many of which cannot be obtained with 2-D ultrasound. This information can be used to more precisely evaluate overall fetal growth, using algorithms that require upper fetal arm or thigh volume, and can also be used to evaluate the growth, development and morphologic abnormalities of critical structures and organs such as the skeleton, brain, heart, kidneys, or adrenal glands. The ability to use 3-D datasets and images to make measurements and evaluate morphology after the scan allows for a rich dataset for future analyses. This capability also minimizes the patient burden in that the scans do not have to be analyzed during the patient visit, and thus requires less patient time.

The technology supporting 3-D, as well as 4-D, is advancing rapidly. However, whether it is feasible within the parameters of the proposed NCS - whether 3-D ultrasound datasets and images can be uniformly collected from multiple centers, transmitted to a central location, and then used to reliably assess fetal growth and development - is unknown.

C. Questions to be Answered

This study will examine the feasibility of collecting, transmitting, and analyzing 3-D datasets and images in the context of a multi-center study of pregnant women. This will include assessing any technical problems associated with 3-D scanning, and resolution, problems saving data for transmission from sites to a central facility, and problems associated with transmittal of data and resolution. The study will examine the reliability of measurements obtained from the 3-D data sets and images that have been stored and retrieved. Measurements from stored 3-D scans will be compared to those from 2-D scans obtained at the time of ultrasound examination. Inter-observer variability in measurements made with stored 3-D images will also be examined.

In addition, the study team is interested in obtaining specific information regarding burden for the site and the patients. Therefore, sites will record the amount of time necessary to perform the 2-D and 3-D exams and any technical or other difficulties encountered. In addition to the time necessary to perform the 3-D exam, the reasons patients refuse to participate and their reactions or comments made during or after the 3-D exam will be recorded to assess patient burden.

D. Study Design

With the U.S. Environmental Protection Agency's (EPA) concurrence, RTI[1] has selected three institutions within the U.S. to participate as sites in this feasibility study. Each of the three sites is experienced in performing 2-D and 3-D obstetrical exams and has at least one 3-D ultrasound machine.

Protocols have been developed to guide the site when enrolling study subjects (Attachment A), obtaining 2-D measurements, obtaining 3-D volume acquisitions and, once the patient has left determining organ volume measurements, and later transmitting data and images to the central facility. The technical protocols, which are not included in this document, follow standard operating procedures regarding the collection of this type of imaging data in patients in a clinical setting.

Each site is responsible for enrolling 20 women in each trimester of pregnancy for a total of 60 pregnant women per site over a 1-2 month enrollment period in the fall of 2004. For this feasibility study, 1st trimester is limited to 10-13 weeks gestation, 2nd trimester is defined as 14-26 weeks gestation, and 3rd trimester is defined as 27 weeks to

[1] RTI is the tradename for RTI International

term. For each enrollee, 2-D ultrasound measurements are obtained and then 3-D volume dataset and images are obtained. Once the patient has left organ volume measurements are determined from the 3-D volume dataset.

It is imperative that approval has been obtained from EPA, RTI, and site Institutional Review Boards (IRB) before any data is collected. Only after all approvals are obtained can appropriate training of personnel from each site be initiated, including on line training on research ethics and associated documentation. Only after training is completed can study procedures commence including enrollment of patients, performance of ultrasound examinations, data storage and transfer.

E. Study Procedures

As outlined in the **Patient Enrollment Protocol** (Attachment A), the site coordinator consults the patient charts and/or the ultrasound requests to identify all women who are to be seen in the clinic on a "study" day who are eligible for this study. The study coordinator enters this information onto the **Log of Eligible Patients** (Attachment B). The **Log of Eligible Patients** allows the collection of information on each eligible patient, including trimester of pregnancy, name, age, ultrasound appointment date; whether she was asked to participate in the study, and if not the reason(s); whether she consented to the study, and if not the reason(s) for refusal; and her study case identification number. The site coordinator is able to enter the trimester of pregnancy, name, age, and ultrasound appointment date before the clinic day begins, while the remaining information is entered at the end of the day. The information on the log will assist the site as it lists the women who have already been asked to participate. A woman will only be asked once if she wishes to participate in the study.

For each eligible patient being seen, the coordinator attaches a **Patient Packet** to the usual paperwork that is given to the sonographer. The patient packet includes the **Screening and Enrollment** form (Attachment C), 3-part NCR **Participant Informed Consent** form (Attachment D), 3-part NCR **Authorization for Use or Disclosure of Health Information** form (Attachment E), and a **2-D and 3-D Data** form (Attachment F). This alerts the sonographer that a patient is eligible for the study and should be asked to participate. In some ultrasound clinics, there are a large number of ultrasounds performed for routine purposes on an unscheduled basis. When these women present at the clinic, the site coordinator will determine if they are eligible, and if eligible, a **Patient Packet** is attached to the usual paperwork that is given to the sonographer.

Before the start of a 2-D ultrasound exam, the sonographer, using the **Screening and Enrollment** form, reviews the chart/ultrasound request to verify that the patient is eligible for study participation. If confirmed, he/she explains the nature of the study to the patient and discusses the procedures involved. If the patient is interested in participating, her signature is written on the **Participant Informed Consent** form (consent form) and the **Authorization for Use or Disclosure of Health Information** form.

The sonographer then signs the **Participant Informed Consent** form and gives a copy of both signed forms to the patient, keeps a copy for the site's study records, and places a copy in the **Patient Packet** to be returned to RTI. The sonographer then indicates on the **Screening and Enrollment** form that the **Participant Informed Consent** form and the **Authorization for Use or Disclosure of Health Information** form were signed and copies given to the patient. This **Screening and Enrollment** form also captures reasons for non-enrollment if the patient does not choose to participate in the study or if the patient was not asked to participate. The site coordinator reviews all **Patient Packets** at the end of each clinic day, including the **Screening and Enrollment** form, and completes the entry for each patient on the **Log of Eligible Patients**. The **Log of Eligible Patients** is the mechanism for a site to track who was eligible to be in the study, who was asked to be in the study, who agreed to participate, and reasons for declining to participate. The **Log of Eligible Patients** is retained at the site and is not sent to RTI.

The sonographer can complete the **2-D and 3-D Data** form as he/she proceeds through the 2-D and 3-D ultrasound scans or afterwards. If data are recorded later, the sonographer must take great care to ensure that the information can be located and entered on the **2-D and 3-D Data** form.

One of the objectives of this feasibility study is to investigate patient and site burden. Therefore, the sonographer records the start and end times for the 2-D and 3-D scans. This information will be entered on the **2-D and 3-D Data** form.

The sonographer records information from the 2-D and 3-D ultrasound (see Section G – Study Variables). If an intrauterine pregnancy (IUP) with cardiac activity is not visualized or a fetal anomaly is noted during the 2-D ultrasound, the patient's participation in this study is ended; however, medical care continues as outlined in the **Procedure to Follow After Detection of Fetal Anomaly Protocol** (Attachment G).

The 3-D exam consists of obtaining volume acquisitions, and after the patient leaves determining organ volume measurements of the fetal heart, kidneys, adrenal glands, lungs, pancreas, liver, upper arms, and thighs from the volume dataset. The 3-D volumes will be saved onto a CD/DVD so the volume of images can be reviewed at the central facility to determine organ volume measurements of the fetal heart, kidneys, adrenal glands, lungs, pancreas, liver, upper arms, and thighs as well as traditional 2-D measurements including crown-rump length (CRL), biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL).

The **2-D and 3-D Data** form provides a comment field where the sonographer enters information regarding the patient's response to the 3-D exam. Comments the patient makes about the additional time for the exam, the comfort of the exam, and being able to view the fetus in 3-D are recorded. Also, information from the sonographer's point of view, including the time, poor imaging or other technical challenges of the 3-D volume acquisitions or organ volume determinations are recorded. This information is important in the assessment of patient and site burden.

The scanning and organ volume measurement procedures to follow are found in the **2-D Ultrasound Protocol** and the **3-D Ultrasound and Organ Volume Measurements Protocols** (Attachments H and I).

A summary list of the necessary forms, and responsible person for the form completion, is listed in Exhibit 1:

Exhibit 1
Forms Completed at Local Site and Responsible Person

Name of Form	Attachment Designation	Staff Completing Form
Log of Eligible Patients	B	Site Coordinator
Screening and Enrollment	C	Sonographer
Participant Informed Consent	D	Sonographer
Authorization for Use or Disclosure of Health Information	E	Sonographer
2-D and 3-D Data	F	Sonographer
Weekly Shipping Inventory	K	Site Coordinator

After each ultrasound examination and organ volume measurements, ultrasound data including the 3-D volume dataset and images will be transmitted to RTI according to the **Data Storage, Transmission, and Retrieval Protocol** (see Attachment J).

The number of forms completed and shipped varies depending on whether the patient agreed to the study or declined participation. If the patient declined participation, only the **Screening and Enrollment Form** is returned. If the patient agreed to participate, the **Screening and Enrollment Form,** copies of the signed **Participant Informed Consent** and the **Authorization for Use or Disclosure of Health Information** form, the **2-D and 3-D Data Form**, and the CD/DVD with the 3-D volume dataset are returned. Each patient's forms and CD/DVD are kept in their respective **Patient Packets** in a locked cabinet until they are sent to RTI. The preaddressed overnight courier labels and bags should be used for shipping purposes. The supplied labels have been properly marked so billing is routed to RTI and sites are not responsible for the cost of shipping.

The site coordinator must complete a **Weekly Shipping Inventory** form (Attachment K) for each shipment of **Patient Packets**. The site coordinator indicates the forms included by case ID number. This form also provides a place to record the overnight shipment tracking number. The site needs to keep copies of all completed Weekly Shipping Inventory forms for their records.

Great care is taken in storing forms prior to shipment. All completed forms must be housed in a locked file cabinet that is only accessible to study staff. The **Log of Eligible Patients** must be placed in a locked drawer for overnight storage. When this log

is in use during the day, staff must be careful in how and where this log is displayed as it contains confidential patient information. The log is never placed in an area that is visible to patients.

The transmission method for the study data is outlined in the **Data Storage, Transmission, and Retrieval Protocol**. The Patient Packets, containing the CD/DVD and paper forms will be sent via overnight courier on the designated day of the week.

A copy of each patient's consent and HIPAA authorization will be kept at the local site in a study file.

As detailed in the **Data Storage, Transmission, and Retrieval Protocol**, 3-D volume datasets are sent to the two sonographers at the Central Facility. Both sonographers, following the **Central Facility Evaluation of 3-D Volume Dataset Protocol**, will manipulate the 3-D datasets and images to obtain volume measurements of the fetal heart, kidneys, adrenal glands, lungs, pancreas, liver, upper arms, and thighs as well as "2-D measurements" (see Attachment L). The Central Facility sonographers will record their organ volume measurements, traditional 2-D measurements, and comments on the **Central Facility 3-D Evaluation Form** (see Attachment M).

Once all patient data are received by RTI the data will be cleaned, compiled, and all patients' names and other identifying information will be separated from the data to be analyzed. The data will be analyzed by RTI statisticians following the **Analysis of Stored 3-D Ultrasound Exam Data and Creation of a Final Dataset without Identifiers Protocol** (see Attachment N). Preliminary analyses will include the following:

- Comparative analyses of traditional 2-D measurements, such as femur length and abdominal circumference, and those same measurements obtained from stored 3-D datasets and images.
- Comparative analyses of organ volume measurements obtained by the site and those obtained by a sonographer at a central facility using stored 3-D datasets and images.
- Inter-observer variability of measurements made by sonographers at the central facility.
- Assessment of respondent burden and acceptance.

At the study's end, RTI will deliver **Participant Informed Consent** and **Authorization for Use or Disclosure of Health Information** forms, de-identified datasets, and CD/DVDs with 3-D volume datasets to EPA. EPA is required to keep the consent and HIPAA authorization forms but will ensure that the consent forms, containing patients' names and study IDs, and the datasets are kept separate and never used to associate data with an individual. These datasets will be prepared according to the **Analysis of Stored 3-D Ultrasound Exam Data and Creation of a Final Dataset without Identifiers** Protocol.

The final report submitted to EPA by RTI will evaluate the overall feasibility of using 3-D ultrasound in the NCS including any recommendations or findings from this pilot study that would suggest optimal operations to enhance data reliability and patient acceptance.

The timeline for this feasibility study is very tight and breaks down as follows:

Activity	Target Date
Development of Protocols	August, 2004
Site Selection	August, 2004
IRB Submissions & Approvals	September - October, 2004
Conduct Study	November - December, 2004
Analysis of Data and Report to EPA	January 2005

F. Study Participants

The target number to be enrolled into the study is 180 pregnant women, 60 from each participating site. Each clinical site will recruit and enroll 20 patients per trimester as defined in the study design section of this protocol.

Study-eligible patients presenting for a routine, versus suspected abnormality, ultrasound should be asked to participate in this feasibility study. A woman is considered eligible for study participation if she meets the inclusion criteria.

Inclusion criteria:

- Patient is at least 18 years old.
- The obstetric ultrasound ordered must be for routine (versus suspected abnormality) indications only.
- One or more fetuses must be present.

A woman is considered ineligible for this study if either of the following exclusion criteria applies.

Exclusion criteria:

- Obstetric ultrasound is ordered for any other indication, including suspected fetal or fetal-placental abnormality, or on an emergency basis.
- Patient has previously participated in this study.

The preponderance of clinical information on obstetrical ultrasound indicates that the procedure is safe for the mother and fetus. In the 30+ years that ultrasound has been used to assist in the clinical care of pregnant women and their fetuses, there has not been a maternal health consequence or fetal anomaly that can be definitively linked to

ultrasound exposure. While ultrasound in a clinical setting allows evaluation of the placenta, uterus, and fetal structures and organs, it does not appear to have any risks.

The benefits to the participant include the ability to see the fetus in 3-D, which for many patients promotes bonding. Also, the sonographer will provide pictures of the exam for the patient to take home, including a 3-D image of the fetus if possible. The benefit to the research study is that combined with other patient's data, the study data will allow an objective decision on the feasibility of collecting, transmitting, and analyzing 3-D ultrasound data in the context of a large multi-center study of pregnant women in the U.S.

The exposure for 3-D is the same as 2-D, i.e., there is no known additional risk. 3-D ultrasound exposure is the same as 2-D except that more data is recorded from different directions and analyzed differently. Said another way, the 3-D probe is a 2-D probe with a motor which scans over very close planes, one after the other. These 2-D planes are fed into the computer and the computer transforms them into in 3-D image.

G. Study Variables

Data to be collected includes data entered by local site sonographers on the **Screening and Enrollment** form (Attachment B) and the **2-D and 3-D Data** form (Attachment E), and data entered by the two Central Facility sonographers on the **Central Facility 3-D Evaluation** form (Attachment I).

The **Screening and Enrollment** form contains the reason(s) a patient refused to participate. The reasons for study refusal must be documented clearly and concisely. This information will be used to inform research staff about areas of concern that can be immediately addressed and/or may help estimate the level of interest of pregnant women for participation in this assessment in the larger, NCS, study if 3-D is included.

The **2-D and 3-D Data** form allows collection of the following information:

- Date of ultrasound
- Patient's date of birth
- Patient's weight
- Date of patient's LMP (taken from the ultrasound request)
- Trimester indication
- Fetal age in weeks (taken from the ultrasound request)
- Indication for ultrasound exam
- Start time of 2-D scan
- Abdominal or transvaginal scan method
- Presence of IUP
- Presence of cardiac activity
- Number of fetuses

- Fetal presentation
- Presence of any fetal anomalies
- CRL or reason if not measured
- BPD or reason if not measured
- HC or reason if not measured
- AC or reason if not measured
- FL or reason if not measured
- End time of 2-D scan
- Start time of 3-D scan
- Volume acquisitions of fetus - to be able to later perform volume measurements of:
  -heart or reason if not obtained
  -right kidney or reason if not obtained
  -left kidney or reason if not obtained
  -right adrenal gland or reason if not obtained
  -left adrenal gland or reason if not obtained
  -right lung or reason if not obtained
  -left lung or reason if not obtained
  -pancreas or reason if not obtained
  -liver or reason if not obtained
  -right upper arm or reason if not obtained
  -left upper arm or reason if not obtained
  -right thigh or reason if not obtained
  -left thigh or reason if not obtained
- Stop time of 3-D scan
- Sonographer's name
- Sonographer comments on patient's response to 3-D exam
- Sonographer comments on the 3-D exam, including any time or technical challenges

The measurements obtained during the 2-D exam for this study will be a valuable reference for comparing the measurements obtained from stored 3-D volume datasets and images. Indicating whether 3-D volume acquisitions were obtained that can be stored and later evaluated to determine organ volume measurements is crucial to answer the question about feasibility of collecting such information during each trimester of pregnancy. The number of fetuses, fetal position, presence of any gross abnormalities, and placental location may be useful information to collect in the larger NCS. Therefore, the ability to uniformly collect these data will be explored. To be able to make generalizations based on fetal age, the fetal age in weeks and the patient's LMP will be collected also. Lastly, the sonographer comments on the 3-D exam will provide insight into the technical problems associated with 3-D scanning, and resolution, problems saving data for transmission from sites to central facility, and problems associated with transmittal of data and resolution. In addition to the time necessary to perform the 3-D exam, the reactions or comments made during or after the 3-D exam will be recorded to assess patient burden.

The **2-D and 3-D Data Form** is also the location where the organ volume measurements, which are determined after the patient leaves, are recorded. The sonographer who performed the 2-D and 3-D exam will record the following information on the 2-D and 3-D Data Form:

-heart or reason if not determined
-right kidney or reason if not determined
-left kidney or reason if not determined
-right adrenal gland or reason if not determined
-left adrenal gland or reason if not determined
-right lung or reason if not determined
-left lung or reason if not determined
-pancreas or reason if not determined
-liver or reason if not determined
-right upper arm or reason if not determined
-left upper arm or reason if not determined
-right thigh or reason if not determined
-left thigh or reason if not determined

- Sonographer comments regarding locating and determining organ volume measurements from the 3-D volume dataset, including any time or technical challenges

The data will be transmitted to the Central Facility as described in the **Data Storage, Transmission, and Retrieval Protocol**.

Each 3-D dataset will be reviewed by two 3-D expert sonographers at the Central Facility. The sonographers will utilize the appropriate software to view and manipulate the datasets to determine organ volume measurements as well as traditional 2-D measurements. Sonographers at the central facility will perform the evaluation and measurements from stored 3-D datasets and images and provide written feedback on any 3-D dataset and images that are less than adequate. The issues anticipated are problems with resolution or areas of interest not obtained. This information will be included in the narrative portion of the final report. Inter-observer variability in measurements made with stored 3-D will also be examined.

Once compiled and cleaned the data will be analyzed as detailed in the **Analysis of Stored 3-D Ultrasound Exam Data and Creation of a Final Dataset without Identifiers Protocol**.

H. Reports and Dissemination of Results

Final datasets shall be prepared according to the **Analysis of Stored 3-D Ultrasound Exam Data and Creation of a Final Dataset without Identifiers Protocol**. Preliminary analyses shall include the following:

- Comparative analyses of the "traditional" 2-D measurements obtained during the 2-D exam and derived from stored 3-D volume datasets.
- Comparative analyses of organ volume measurements done by sites from 3-D volume datasets and those done by the central facility using stored 3-D volume datasets.
- Inter-observer variability in measurements made by sonographers at the central facility using stored 3-D volume datasets.
- Assessment of respondent and site burden and acceptance.

Data will be grouped by site, by trimester, or by both site and trimester, but not by individual patient data.

The final report to EPA will evaluate the overall feasibility of using 3-D ultrasound in the NCS including any recommendations or findings from this pilot study that would suggest optimal operations to enhance data reliability and patient acceptance.

I. Consent and Confidentiality Procedures

Each research site must receive IRB approval from their institution for the study protocol as well as for the consent form to be used in this study. Patients cannot be approached as potential participants until approvals have been received from RTI, EPA, and the site's local IRB. Only the local IRB's approved consent form can be used. Before conducting the ultrasound, the patient must provide written consent. The patient may read the consent form or clinic study staff may read it to her. Clinic study staff must use their judgment about whether the patient is able to comprehend the full document. If there is any doubt about the patient's understanding, the consent form will be read in full to her. If the patient wishes to read the consent form, clinic study staff must still review the main points of the consent form. Each patient must be been given all the information necessary to make a completely informed and knowledgeable decision about participation. Clinic study staff will answer any questions that the patient has about the study. It is important that patients know that choosing to participate or refusing to participate in this study has no effect on their medical care.

Although this study involves women who are already having 2-D scans for standard indications as determined by their providers, it is still considered research on pregnant women and human fetuses. Therefore, special regulatory requirements apply as outlined in 45CFR46 Subpart B. Project staff will be prepared to demonstrate to their local IRB that this study involving pregnant women and fetuses meet those outlined requirements.

An additional important factor to recognize and understand in the conduct of this research study is the Health Insurance Portability and Accountability Act (HIPAA) that became effective in April 2003. This Federal regulation protects individuals' rights to control access to and release of health information about them. It also controls the means by which entities can keep health information confidential. Under HIPAA, either individual authorization must be obtained from each patient to access his/her Protected

Health Information (PHI) for a research study, or the research must qualify for an exception to this requirement. The data that this feasibility study is collecting is considered to be PHI and the participating clinics are covered entities; therefore, each site must comply with HIPAA regulations. For this study, each patient will be asked to sign an **Authorization for Use or Disclosure of Health Information** that will allow the participating clinic to release her health information to study staff at RTI International. An eligible patient cannot participate in this study unless she has signed both the **Participant Informed Consent** form and the **Authorization for Use or Disclosure of Health Information** form. Copies of both signed forms are retained by the study participant, filed at the site, and sent to RTI within each participant's **Patient Packet**.

J. Training

It is critical that study site staff follow all documented procedures as outlined in the various study protocols. These protocols provide guidance for patient enrollment, data collection, and data transfer to RTI. Also, all persons involved in the study will need documentation that they have completed the online human subjects tutorial.

After all regulatory approvals are obtained and human subject tutorials have been completed, an RTI project staff member will review the protocols with the site coordinator and sonographer(s) to ensure all protocols are understood. The RTI staff person will role play the consent process with the site staff to ensure the staff understand how to explain the study, the patient's rights and responsibilities, contacts for IRB or project concerns, and confidentiality of study data. Training will also include a 4-hour session covering the procedure for obtaining 3-D volumes and determining organ volume measurements from the 3-D volume datasets. After all aspects of training are successfully completed the site will be approved to begin enrolling patients.

Appendix A

Patient Enrollment Protocol

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Data Sets and Images

A. Screening and Tracking Participants

All eligible patients presenting for a routine, versus suspected abnormality, ultrasound will be asked to participate in the study. The target enrollment number is 60 pregnant women from each site. A woman is considered eligible for study participation if she meets the inclusion criteria.

Inclusion criteria:

- Patient must be at least 18 years old.
- The obstetric ultrasound ordered must be for routine, versus suspected abnormality, purposes only.
- One or more fetuses must be present.

A woman is considered ineligible for this study if either of the following exclusion criteria applies.

Exclusion criteria:

- Obstetric ultrasound is ordered for any other indication, including suspected fetal or fetal-placental abnormality, or on an emergency basis.
- Patient has previously participated in this study.

Each clinical site will recruit and enroll 20 patients per trimester. To increase the chance of being able to obtain organ volumes during the first trimester, for this study the "first trimester" is defined as 10-13 weeks. The second trimester is defined as 14-26 weeks and the third trimester is defined as 27 weeks to term. It is important that each site track the number of enrolled patients in each trimester to reach the target enrollment numbers.

Each site's study coordinator will review the scheduled ultrasounds prior to the start of daily clinic operations. Each woman who meets the study enrollment criteria will be listed on the **Log of Eligible Patients** (see Attachment B). The site coordinator will enter the trimester indication, the patient's name, the patient's age, the date of the appointment, and the case ID number for each eligible woman. (Sites will use the clinical estimate of the fetal age that is recorded on the ultrasound request to determine the trimester classification.) The site coordinator will then attach a **Patient Packet** containing a **Participant Informed Consent** form (see Attachment D), an **Authorization for Use of Disclosure of Health Information** form (see Attachment E), a

2-D and 3-D Data form (see Attachment F), and a **Screening and Enrollment** form (see Attachment C) to each eligible patient's chart. The attachment of the **Patient Packet** indicates to the sonographer that the patient is thought to be eligible for study participation. Each form in a **Patient Packet** has the same unique case ID number printed on it to ensure each eligible patient is associated with a unique identifier. On occasions when a woman is added to the ultrasound schedule after the coordinator's morning review, the site coordinator will assess the patient's eligibility. If the woman is eligible, the coordinator will add her information to the **Log of Eligible Patients** and attach a **Patient Packet** to her medical chart.

When a patient arrives for her ultrasound exam, the sonographer reviews the **Patient Packet** and begins the screening and enrollment process. The sonographer will use the **Screening and Enrollment** form that is included in the **Patient Packet** to screen and enroll the patient. The **Screening and Enrollment** form documents eligibility, whether the patient was asked to participate and if not the reason, whether the patient agreed to participate and if not the reason(s) (in the patient's own words when possible,) whether consent and HIPAA authorization were signed and whether the patient was given a copy of each. Once completed, the **Screening and Enrollment** form will be returned to the **Patient Packet**.

First, the sonographer uses the **Screening and Enrollment** form to verify eligibility and, if eligible, discusses participation with the patient. If the sonographer is unable to ask the patient to participate, an indication that the patient was not asked and the reason is written on the **Screening and Enrollment** form. If after discussing the study the patient is interested in participating, the sonographer asks the patient to read and sign both the **Participant Informed Consent** form and the **Authorization for Use of Disclosure of Health Information** form (see section B - Participant Consent and HIPAA Authorization.) After the patient signs both forms and copies of each are provided to the patient, the sonographer indicates on the **Screening and Enrollment** form that these forms were signed and copies provided to the patient.

As indicated on the **Screening and Enrollment** form, after eligibility is established, and the **Participant Informed Consent** form and **Authorization for Use of Disclosure of Health Information** form are signed, the exam can be started by following the procedures outlined in the **2-D Ultrasound Protocol** and **3-D Ultrasound and Organ Volume Measurements Protocol** (see Attachments H and I). All completed forms are returned to the **Patient Packet** and all packets are submitted to the site coordinator at the designated time near the end of each day.

At the end of each day, the site coordinator opens and reviews all **Patient Packets**. The coordinator will use the completed **Screening and Enrollment** forms to complete the **Log of Eligible Patients**, including whether a patient was asked to participate, consented to the study, and if not, the reason(s) for refusal. The **Log of Eligible Patients** is the site's primary source of data used to track who was asked to be in the study, who agreed to be in the study, and the reasons for declining study participation. RTI will not receive a copy of the **Log of Eligible Patients**.

B. Patient Consent and HIPAA Authorization

As described above, once the sonographer determines a patient is eligible, he/she explains the nature of the study to the patient and discusses the procedures involved. If the patient is interested in participating, her signature is written on the 3-part NCR **Participant Informed Consent** form and the 3-part NCR **Authorization for Use or Disclosure of Health Information** form prior to the conduct of any other study procedures.

The patient may read the consent form or clinic study staff may read it to her. The sonographer must use judgment about whether the patient is able to comprehend the full document. If there is any doubt about the patient's understanding, the consent form is read in full to her. If the patient wishes to read the consent form, the sonographer should still review the main points of the consent form. The sonographer must be sure that each patient has been given all the information necessary to make a completely informed and knowledgeable decision about participation and therefore must answer any questions that the patient has about the study. It is important that patients know that choosing to participate or refusing to participate in this study has no effect on their medical care. If the patient decides to participate and therefore signs the **Participant Informed Consent** a copy is given to the patient.

If a woman declines participation and does not sign the consent form, she will be thanked for considering participation and the sonographer will document the patient's reason(s) for refusing on the **Screening and Enrollment** form. The reasons for study refusal are extremely important to document for this feasibility study. The reasons may inform research staff of areas of concern that should be addressed now and for future studies. It is important that the sonographer be clear and concise in the explanation, and when possible, includes the woman's own words.

Once a patient has signed the consent form, the sonographer will give the patient a copy of the **Authorization for Use or Disclosure of Health Information** form to review and sign. This form allows the participating clinic to release her health information to study staff at RTI. An eligible patient cannot participate in this study unless she has signed both the study consent form and the **Authorization for Use or Disclosure of Health Information** form. Copies of both signed forms are provided to the study participant. The site also retains copies of each signed form for the site study files and sends the originals to RTI via overnight courier at the end of every week.

C. Data Collection

The sonographer can complete the **2-D and 3-D Data** form as he/she proceeds through the 2-D and 3-D ultrasound or record the data afterwards. If data is recorded later, the sonographer must take great care to ensure that the information can be located and entered on the **2-D and 3-D Data** form.

Information will be recorded from the 2-D and 3-D ultrasound as described in Section F, Study Variables, of the **Overall Procedures Protocol**. Note: If an intrauterine pregnancy (IUP) with cardiac activity is not visualized during the 2-D ultrasound, or a fetal anomaly is noted, the patient's participation in this study will be terminated; however, the ultrasound and appropriate medical support continues as outlined in the **Procedure to Follow After Detection of Fetal Anomaly Protocol** (see Attachment G).

Data is collected on patient and site burden in accordance with the study objectives. One assessment of patient burden is through patient comments about the exam. Therefore, it is important to inform the patient when the switch is made between the 2-D and 3-D exam and that she will be asked to provide her impressions of the 3-D exam when it is completed. Another way burden is being assessed is the time necessary to perform the 2-D and 3-D scans. To that end, the start and end times of the 2-D scan and 3-D scans should be recorded on the **2-D and 3-D Data** form.

The **2-D and 3-D Data** form also provides a comment field where the sonographer enters information regarding the patient's response to the 3-D exam. Any comments made by the patient are recorded (e.g., additional time for the exam, the comfort of the exam, being able to view the fetus in 3-D, etc.). Information from the sonographer's point of view is also very important, (e.g., time requirements, imaging or other technical challenges of the 3-D scan, etc.) and should be recorded as well. The scanning procedures that must be followed are in the **2-D Ultrasound Protocol** and the **3-D Ultrasound and Organ Volume Measurements Protocol**.

At any point in the study the patient can decide she no longer wishes to participate. A note indicating her withdrawal, and reason for withdrawal, will be recorded on the **2-D and 3-D Data** form as well as on the **Screening and Enrollment** form. At the end of the day, the site coordinator will add this information to the **Log of Eligible Patients**. The ultrasound exam and any appropriate medical care should continue.

Appendix B

Log of Eligible* Patients
(Destroy After Completion of Recruitment)
Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Data Sets and Images

Week Starting Monday _____ _____, 2004

Trimester** (Circle)	Name	Age	Date Of Appt	Asked to Participate	Consent to Participate	Patient Case ID	Reason Not Asked, or Declined, to Participate
1 2 3	_____	_____	_____	Y N	Y N	_____	_____
1 2 3	_____	_____	_____	Y N	Y N	_____	_____
1 2 3	_____	_____	_____	Y N	Y N	_____	_____
1 2 3	_____	_____	_____	Y N	Y N	_____	_____
1 2 3	_____	_____	_____	Y N	Y N	_____	_____
1 2 3	_____	_____	_____	Y N	Y N	_____	_____
1 2 3	_____	_____	_____	Y N	Y N	_____	_____

*Eligible patients: ≥18 y/o, IUP, routine or dating ultrasound
** 1st trimester is 10-13 weeks; 2nd trimester is 14-26 weeks; 3rd trimester is 27-term

Appendix C

Case ID Number: ___ ___ ___ ___ ___

Screening and Enrollment Form

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Images

1. Verify patient is eligible for study:
   a. Patient is 18 years old or older YES NO→Stop Enrollment
   b. OB ultrasound for routine or dating purposes YES NO→Stop Enrollment
   c. This is patient's first time being asked to participate YES NO→Stop Enrollment

2. Patient asked to participate? YES NO→2.a. then Stop Enrollment

   2.a. Indicate reason(s) patient was not asked to participate

   _____

   _____

3. Patient agreed to participate? YES NO→3.a. then Stop Enrollment

   3.a. Indicate reason(s) patient did not agree to participate. Use the patient's exact words when possible:

   _____

   _____

   _____

4. Patient signed consent form and was given a copy YES NO→Stop Enrollment

5. Patient signed HIPAA authorization and was given a copy YES NO→Stop Enrollment

If the answers to all questions are "YES", patient has been successfully enrolled into the study.

Appendix D

Case ID Number: ___ ___ ___ ___ ___

United States Environmental Protection Agency
Epidemiology and Biomarkers Branch, Human Studies Division
Conducted by RTI International and (Name of Clinical Site)
Consent to Participate in a Research Study

Medical IRB Study #_____
Consent Form Version Date: May 6, 2004
Title of Study: Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Images
Principal Investigator: Pauline Mendola, Ph.D.
Phone number: (919) 966-6953
Co-Investigators: Mark Klebanoff, M.D. M.P.H.; Kenneth Schoendorf, M.D. M.P.H.; Catherine Spong, M.D.

You are being asked to take part in a research study. The investigators listed above are in charge of the study; other professional persons may help them or act for them.

What are some general things you should know about research studies?
Research studies are designed to gain scientific knowledge that may help other people in the future. You may not receive any direct benefit from participating. There may also be risks associated with participating in research studies.

Your participation is voluntary. You may refuse to participate, or may withdraw your consent to participate in any study at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your doctor. If you are a patient with an illness, you do not have to participate in research in order to receive treatment.

Details about this particular study are discussed below. It is important that you understand this information so that you can decide in a free and informed manner whether you want to participate. You will be given a copy of this consent form. You are urged to ask the investigators named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
The purpose of this research study is test the feasibility of using 3-D ultrasound at multiple clinic centers in a research study. This is a pilot study, which is a small research study that will try out things that might be used in a bigger study. We want to know if it is possible to save and later read the images from the 3-D ultrasound accurately because we want to do a large study in the near future that will look at how the environment may affect children's health and would like to include 3-D ultrasound as one of the tests.

What will happen if you take part in the study?
In this pilot, we are taking images (you can think of these as "pictures"), saving them, sending them to a central medical office, and later looking at the pictures to measure

body parts of the fetus. "Fetus" is the word we use for the unborn baby. This study will investigate the possibility of saving and later reading these images accurately. This will help with plans for a larger study in the near future that will look at how the environment affects children's health. We are asking you to be in this study because you are having a regular 2-D ultrasound. This study will compare the 3-D ultrasound to the regular 2-D ultrasound.

If you choose to take part in this research study, we will do your regular 2-D ultrasound in which we measure body parts of the fetus and record the results. Then we will adjust the machine to do the 3-D ultrasound scan. You will not feel any difference with the switch to 3-D, but you may notice better pictures of the fetus. We will then record images of the fetus so that the researchers can later compare the results with your regular ultrasound.

How many subjects will participate in this study?

A total of approximately 180 participants at three institutions will take part in this study, including approximately 60 participants from this institution.

How long will your participation last?

The 3-D scan may take only a few minutes or it could be up to 15 minutes longer than your current appointment. One of the reasons we are doing this pilot study is to see how long the 3-D scan takes.

What are the possible risks or discomforts?

There are no known risks to you or your fetus. It has been over 40 years since ultrasound was first used on pregnant women. No research studies have shown a risk to the fetus. The 3-D ultrasound is the same as the 2-D except that more data are recorded from different directions and analyzed differently. During the ultrasound exam, you will be lying down and will be able to move around on the table to be as comfortable as possible. It is possible that we will not be able to complete the 3-D part of the exam (the research part of the exam) because we are unable to see the structures and/or the organs of the fetus well enough. It is also possible that during the exam we may find that your fetus is not growing well or has a problem that is not related to this study. If we find this, your participation in the study will end but your ultrasound exam and discussion about the exam will still take place. If a problem is noticed, only the research will be stopped. The care you receive from your doctor will be the same including a discussion about the possible problem with your fetus.

What are the possible benefits?

The benefits of being in this study are that you will be able to see your fetus in a 3-D way. You will be given copies of some pictures to keep from this visit.

How will your privacy be protected?

All data will be kept private to the extent allowed by law. No participants will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law

requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, we will take all steps allowable by law to protect the privacy of personal information.

To protect your privacy, we will keep the records and images under a code number rather than by name. Any link between your name and coded records and images will be kept in locked files in a locked room where only study staff will have access to them.

Will it cost you anything to participate?
You will not incur any extra costs associated with the 3-D scan. You will receive some pictures from this visit.

Who is sponsoring this study?
This research is funded by U.S. Environmental Protection Agency. This means that the research team (RTI, International and (Name of clinical site)) is being compensated by the sponsor for conducting the study. The researchers do not, however, hold a direct financial interest in the sponsor or in the outcome of the study.

What if you want to stop before your part in the study is complete?
You are free to be part of the study or not. Also, you are free to ask to stop the ultrasound at any time, for any reason. If you say you do not want to be part of the study or if you ask to stop the study, you will still get the same health care service, without penalty. The investigators also have the right to stop your participation at any time.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have any questions about this study now, please ask. If you have further questions, you should call Dr. Pauline Mendola of the U.S. Environmental Protection Agency at 919-966-6953. You can also call Jodie Weiner, RN, MSN of RTI at 1-800 334-8571, extension 3890 or (clinical site study coordinator) of (name of clinical site) at (telephone number of clinical site study coordinator).

What if you have questions about your rights as a subject?
This research has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects (Medical IRB) at the University of North Carolina at Chapel Hill. If you have any questions or concerns regarding your rights as a research subject, you may contact the Chairman of the Committee at (919) 966-1344. You may also call Dr. William McDonnell of the U.S. Environmental Protection Agency, who is the Director of the National Health and Environmental Effects Research Laboratory Human Research Protocol Office at (919) 966-6220.

- -

Case ID Number: ___ ___ ___ ___ ___

Subject's Agreement:

I have read the information provided above. I voluntarily agree to participate in this study.

_____ _____
Signature of Research Subject Date

_____
Printed Name of Research Subject

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent

Appendix E

Case ID Number: ___ ___ ___ ___ ___

Authorization for Use or Disclosure of Health Information

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Images

Patient Name: _____
First Middle Last

Patient's Date of Birth: _____/_____/_____
Month Day Year

I, the undersigned, authorize the disclosure of individually identifiable health information about me for research, as described below.

Description of information to be disclosed, including dates of service related to such information: Patient name, patient date of birth, date of first day of last period, date of ultrasound appointment, measurements of the fetus, images of the fetus, and an indication if any problems noted during the ultrasound.
Provider authorized to disclose my health information (provider name and address):

Persons or class of persons to whom my health information may be disclosed: Research staff at RTI International, Research Triangle Park, NC, and the U.S. Environmental Protection Agency (EPA).
Purpose for this disclosure of my health information: The Federal government is planning to conduct a research study in the near future that will look at the environment's impact on children's health and development (National Children's Study). The measurement of growth of the fetus is a primary requirement for this future study as a way to predict the health of the pregnancy, newborn, and possibly the child's health later in life. One way to measure the growth of the fetus is an ultrasound exam. The Environmental Protection Agency (EPA) has asked RTI International to conduct a pilot study now that will help them decide if images of a fetus from a 3-D ultrasound exam can be obtained, stored, and later read. Researchers are also interested in obtaining specific information about reasons women choose not to take part in the study and what women think of the having the 3-D ultrasound examination. This pilot study cannot be conducted without obtaining the participating patient's ultrasound information.

Case ID Number: ___ ___ ___ ___ ___

This authorization expires (specific date, time period after signature, or "not applicable"):

I understand that I may revoke this authorization at any time by notifying _____ [NAME OF PROVIDER] in writing.

I also understand that I may refuse to sign this authorization and that my refusal will in no way affect my treatment, payment, enrollment in a health plan, or eligibility for benefits.

By signing below, I give permission to the provider named above to release information about this ultrasound exam to staff at RTI International and the EPA.

Signature of Patient or Patient's Personal Representative:

_____

Date: _____/_____/_____
Month Day Year

For Personal Representative (if applicable):

Printed Name of Personal Representative: _____
First Middle Last

Nature of Personal Representative Relationship/Authority to Act for the Patient

(parent, guardian, etc.): _____

Disposition: Original to patient; Copy kept by site; Copy sent to RTI

08601.001.003
Version 12-10-02

Appendix F

Case ID Number: ___ ___ ___ ___ ___

2-D and 3-D Data Form

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Images

1. Date of Ultrasound: _____/_____/_____
   Month Day Year

2. Patient's Date of Birth: _____/_____/_____
   Month Day Year

3. Patient's Weight: _____
   Pounds

4. Date of last menstrual period: _____/_____/_____
   Month Day Year

5. Indicate trimester:

   First □
   Second □
   Third □

6. Indicate Fetal Age: _____weeks

7. Indication for ultrasound exam:
   Routine
   Suspected Abnormality □ → END STUDY PARTICIPATION (Patient does not meet inclusion criteria)

8. Start time of 2-D ultrasound: _____:____ AM or PM (circle one)

9. Indicate scan method(s):
   Abdominal
   Transvaginal □

10. Is there an IUP? YES NO → END STUDY PARTICIPATION following steps in Fetal Anomaly Protocol

11. Is there visible cardiac activity? YES NO → END STUDY PARTICIPATION following steps in Fetal Anomaly Protocol

Case ID Number: ___ ___ ___ ___ ___

12. Number of fetuses? _____ (If > 1 fetus, complete and attach a separate 2-D and 3-D Data Form for each fetus)

13. Fetal presentation:
Cephalic
Transverse
Breech

14. Is there ≥ fetal anomalies? NO YES →END STUDY PARTICIPATION following steps in Fetal Anomaly Protocol

15. Record the 2-D Measurements (check box if not measured)

a. Crown-Rump Length (CRL):	_____mm	not measured
b. Biparietal Diameter (BPD):	_____mm	not measured
c. Head Circumference (HC):	_____mm	not measured
d. Abdominal Circumference (AC):	_____mm	not measured
e. Femur Length (FL):	_____mm	not measured

16. PLEASE STATE REASONS FOR ANY "NOT MEASURED" IN QUESTION 15:

_____

_____

_____

17. Stop time of 2-D scan: ____:_____ AM or PM (circle)

18. Start time of 3-D scan: ____:_____AM or PM (circle)

Tell patient that the 3-D exam is beginning

Case ID Number: ___ ___ ___ ___ ___

19. Acquire Volume Datasets to ensure later measurement of:

a. Head	obtained	not obtained
b. Heart	obtained	not obtained
c. Right kidney	obtained	not obtained
d. Left kidney	obtained	not obtained
e. Right adrenal gland	obtained	not obtained
f. Left adrenal gland	obtained	not obtained
g. Right lung	obtained	not obtained
h. Left lung	obtained	not obtained
i. Pancreas	obtained	not obtained
j. Liver	obtained	not obtained
k. Right upper arm	obtained	not obtained
l. Left upper arm	obtained	not obtained
m. Right thigh	obtained	not obtained
n. Left thigh	obtained	not obtained

20. PLEASE STATE REASONS FOR ANY "NOT OBTAINED" IN QUESTION 19:

_____

_____

_____

_____

_____

21. Stop time of 3-D scan: _____:_____ AM or PM (circle)

22. Sonographer's name: _____
First Last

23. SONOGRAPHER COMMENTS:

a. Patient's response to 3-D exam: (time, comfort, views of fetus, etc): _____

_____

_____

_____

_____

Case ID Number: ___ ___ ___ ___ ___

b. Sonographer response to 3-D exam: (time, technical challenges, etc): _____

_____

_____

_____

_____

Patient portion of study is complete. After patient has left, determine and record organ volume measurements.

24. Determine the organ volume measurements from the 3-D volume datasets (check box if unable to determine volume)

a.	Head	_____	unable to determine
b.	Heart	_____	unable to determine
c.	Right kidney	_____	unable to determine
d.	Left kidney	_____	unable to determine
e.	Right adrenal gland	_____	unable to determine
f.	Left adrenal gland	_____	unable to determine
g.	Right lung	_____	unable to determine
h.	Left lung	_____	unable to determine
i.	Pancreas	_____	unable to determine
j.	Liver	_____	unable to determine
k.	Right upper arm	_____	unable to determine
l.	Left upper arm	_____	unable to determine
m.	Right thigh	_____	unable to determine
n.	Left thigh	_____	unable to determine

25. STATE REASONS FOR ANY "UNABLE TO DETERIME" IN QUESTION 24:

_____

_____

_____

_____

_____

Case ID Number: ___ ___ ___ ___ ___

26. SONOGRAPHER COMMENTS REGARDING LOCATING AND DETERMINING ORGAN VOLUME MEASUREMENTS FROM 3-D VOLUME DATASET (TIME, TECHNICAL CHALLENGES, ETC): _____

_____

_____

_____

_____

_____

_____

_____

Appendix G

Procedure to Follow After Detection of Fetal Anomaly Protocol

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Data Sets and Images

Each site must consider their usual routine for handling the detection of a fetal anomaly during an obstetrical ultrasound in order to decide which of the following guidelines will be followed for patients enrolled in the study. Once a set of guidelines are chosen they must be followed for all patients enrolled in the study.

Option 1:

When a sonographer is unable to detect cardiac activity or detects a fetal anomaly, the sonographer will stop the exam and tell the patient "I am having difficulty seeing what I need to see and therefore need to contact a physician to assist me. I will contact the physician right away." Then the sonographer will contact the physician by beeper, or in person if a physician is within the ultrasound suite, to ensure a physician is with the patient within 15 minutes of the exam being stopped. The physician will talk to the patient regarding the exam and the reason their participation in the study was stopped. If the woman is a patient of the institution, the physician will continue with the evaluation and counseling appropriate for the anomaly. If the patient was referred by an outside physician, the physician will let the patient know that there may be an issue with the fetus and that the physician will contact the referring physician to decide on a next step. The referring physician will then decide to follow up with patient or request that the patient be evaluated by a physician at that institution.

The sonographer will complete as much as possible of the patient's **2-D and 3-D Data** form including the reason some measurements or volumes not obtained.

Option 2:

When a sonographer is unable to detect cardiac activity or detects a fetal anomaly the sonographer will complete the routine exam as much as possible but not attempt to obtain 3-D volumes. The sonographer will tell the patient "I had difficulty seeing what I needed to see so was unable to do the 3-D scan." The sonographer will tell the patient that the procedure at their clinic is to provide the information to a physician (images and notes) and then the physician provides feedback. The physician will review the exam notes and images and then meet with the patient within 15-30 minutes of the exam completion.

The physician will talk to the patient regarding the exam and the reason their participation in the study was stopped. If the woman is a patient of the institution, the physician will continue with the evaluation and counseling appropriate for the anomaly. If the patient was referred by an outside physician, the physician will let the patient know that there may be an issue with the fetus and that the physician will contact the referring

physician to decide on a next step. The referring physician will then decide to follow up with patient or request that the patient be evaluated by a physician at that institution.

The sonographer will complete as much as possible of the patient's **2-D and 3-D Data** form including the reason some measurements or volumes not obtained.

Appendix H

DRAFT - 2-D Ultrasound Protocol

DRAFT

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Data Sets and Images

A. Abstract

This protocol specifies the steps to follow to obtain and record the 2-D exam data. The protocol follows the guidelines specified in the American Institute of Ultrasound in Medicine (AIUM) Practice Guideline for the Performance of an Antepartum Obstetric Ultrasound Examination, which was published in conjunction with the American College of Obstetricians and Gynecologists (ACOG) and the American College of Radiology (ACR) (http://www.aium.org/provider/standards/obstetrical.pdf).

B. Preparation Before the Exam

This protocol assumes the following steps have been completed:

- The Study Coordinator has reviewed the patient's chart and determined that the patient is eligible and has therefore entered the patient's information on the **Log of Eligible Patients**.
- The Sonographer has completed the **Screening and Enrollment** form.
- The **Participant Informed Consent** form and **Authorization for Use or Disclosure of Health Information** form has been signed and a copy of each given to the patient.

For this feasibility study, a patient is only asked to participate if she is already scheduled for a routine exam at an ultrasound clinic that meets the standards and guidelines for accreditation by the AIUM (see ***Appendix A***). AIUM accreditation must be current and the standards and guidelines adhered to including the responsibilities of the physician director and sonographers. In addition, the AIUM policies and procedures safeguarding patients, ultrasound personnel, and equipment, incident reporting, patient confidentiality, policies on prevention of infectious disease, and the ALARA Principle must be followed throughout the study period.

It is imperative that the ALARA principle, as low as reasonably achievable, is followed for both the 2-D and 3-D exams. The Voluson 730 has a "safety guard" called I-Limiter ("Intensity Limiter"). The I-Limiter limits the maximum power settings of the US machine to safe acoustic output levels of intensity and surface temperature of the probe. This setting cannot be tampered with or in any way altered to allow for greater power settings. Sites must follow the standards and guidelines on equipment and personnel performance quality assurance that are set out by the AIUM for accredited practices during the study period.

C. Equipment Preparation

Both the Transabdominal Transducers and the Transvaginal Ultrasound Transducers should be cleaned and available for use for each patient. AIUM states "Transducers used on the skin's surface should be cleaned according to guidelines already established for endocavitary transducers. Although endocavitary ultrasound probes might be considered even less critical instruments because they are routinely protected by single use disposable probe covers, leakage rates of 0.9% - 2% for condoms and 8%-81% for commercial probe covers have been observed in recent studies. For maximum safety, one should therefore perform high-level disinfection of the probe between each use and use a probe cover or condom as an aid to keeping the probe clean. (See ***Appendix B*** for full details)

Scanning in the first trimester may be performed either transabdominally or transvaginally. If a transabdominal examination is not definitive, a transvaginal scan or transperineal scan should be performed whenever possible.

D. Patient Scan

A standard exam, following the site's standard exam protocol should be followed. This protocol only addresses those assessments and measurements that are to be used for the study. For women in their first, 2nd, or 3rd trimester the following should be determined and recorded on the 2-D Measurements and 3-D Volume Acquisitions form (see ***Appendix C***).

1. The date of the ultrasound
2. Patient's date of birth
3. Patient's weight
4. Patient's date of last menstrual period
5. Trimester indicated
6. Fetal age (as listed on ultrasound request form)
7. Indication for ultrasound (routine or suspected pathology) - if the ultrasound is ordered to confirm or rule out suspected pathology the patient is not eligible for inclusion in the study and her involvement in the study should end immediately.
8. Start time for the 2-D ultrasound
9. Indication of scan method used (abdominal or transvaginal)
10. Whether there is an intrauterine pregnancy (IUP)
11. Whether this is cardiac activity
12. Number of fetuses
13. Fetal presentation (cephalic, transverse, and breech)
14. Fetal anomalies - if an anomaly is noted, the patient's involvement in the study is ended, and the sonographer should follow the Fetal Anomaly Protocol.

It may be difficult to visualize different structures due to fetal size, position, movement, abdominal scars, and increased maternal wall thickness. A second- or third-trimester scan may pose technical limitations for an anatomic evaluation due to imaging

artifacts from acoustic shadowing. When this occurs, the report of the sonographic examination should document the nature of this technical limitation.

15. Crown-Rump Length
16. Biparietal Diameter (BPD)
    Biparietal diameter is measured at the level of the thalami and cavum septi pellucidi. The cerebellar hemispheres should not be visible in this scanning plane. The measurement is taken from the outer edge of the proximal skull to the inner edge of the distal skull.
17. Head Circumference (HC)
    Head circumference is measured at the same level as the biparietal diameter, around the outer perimeter of the calvarium.
18. Abdominal Circumference (AC)
    Abdominal circumference should be determined at the skin line on a true transverse view at the level of the junction of the umbilical vein, portal sinus, and fetal stomach, when visible.
19. Femur Length (FL)
    Femoral diaphysis length can be reliably used after 14 weeks' gestational age. The long axis of the femur shaft is most accurately measured with the beam of insonation being perpendicular to the shaft, excluding the distal femoral epiphysis.

If one or more of the measurements could not be obtained the sonographer should indicate this on the data entry form and indicate the suspected reason for this omission.

When all measurements that are able to be obtained are recorded the sonographer should note and record the time on the data form.

Appendix A

Standards and Guidelines for the Accreditation of Ultrasound Practices

Approved March 13, 2002, November 10, 2002

These *Standards and Guidelines for the Accreditation of Ultrasound Practices* provide license and educational requirements for medical staff and personnel who perform and interpret ultrasound. Furthermore, these *Standards* specify the requirements for personnel performance, scientific interpretations, quality assurance of equipment, staff performance, record keeping, and space management for the clinical practices where studies are performed.

Purpose
Ultrasound makes important contributions to patient care and may be used in a variety of settings. Ultrasound practices that meet the standards and guidelines described below will be eligible for ultrasound practice accreditation.

Accreditation
Accreditation may be obtained in

- Abdominal/General Ultrasound
- Breast Ultrasound (Diagnostic or Interventional)
- Gynecologic Ultrasound
- Obstetric or Trimester-Specific Obstetric Ultrasound

The completed application and supporting documents are reviewed by the AIUM's Ultrasound Practice Accreditation Program's peer reviewers. Reaccreditation is required every 3 years. However, an update report is required for significant changes in personnel, physical facility, policies and procedures, instrumentation, or quality assurance. In case of major changes in personnel or the practice, the AIUM's Ultrasound Practice Accreditation Department must be notified immediately.

Personnel
Responsibilities, Licensing, and Educational Requirements

Physician Director of Ultrasound
A qualified physician director of ultrasound is responsible for ensuring that all clinical services are provided; for ensuring that support services are appropriate, and for determining the quality and appropriateness of patient care. The physician director of ultrasound may supervise the entire operation of the facility or may delegate specific operations to associates and sonographers. The physician director of ultrasound is responsible for certifying that the practice continues to meet the *Standards and Guidelines for the Accreditation of Ultrasound Practices.* The physician director of ultrasound must meet all additional requirements for physicians who perform or interpret ultrasound examinations.

Physicians

Qualified medical staff will interpret and/or perform clinical studies in accordance with privileges approved by the physician director of ultrasound. All interpreting physicians must meet the following requirements:

- Must be a physician with a current state license
- Must meet the AIUM's *Training Guidelines for Physicians Who Evaluate and Interpret Diagnostic Ultrasound Examinations*
- Must maintain documentation of appropriate continuing education:
    - If the practice is applying for accreditation in any category other than breast ultrasound, must obtain a minimum of 30 hours of AMA PRA category 1 CME credits in ultrasound, every 3 years
    - If the practice is applying for accreditation in breast ultrasound, must obtain a minimum of 10 hours of AMA PRA category 1 CME credits in breast ultrasound, every 3 years
- If the practice is applying for breast ultrasound accreditation, must be an accredited (MQSA) interpreter of mammograms, or must have an accredited (MQSA) mammography practitioner available
- If the practice is applying for breast ultrasound accreditation, must meet the following requirements:
    - For Diagnostic Breast Ultrasound-The physician must attest that he/she has participated in 60 nonscreening breast ultrasound cases in the year prior to the application.
    - For Interventional Breast Ultrasound-The physician must have performed 25 ultrasound-guided interventional procedures. The first five of these cases must have been supervised by another physician experienced in interventional sonography of the breast. At least three of the first five must be core biopsies. A physician documenting that he/she has safely performed 75 interventional cases in the 3 years prior to the application can also satisfy the requirement.
- Must meet the following procedure volume requirements depending on the type(s) of accreditation for which the practice is applying:
    - For gynecologic ultrasound accreditation, each participating physician must meet a minimum of 170 gynecologic ultrasound procedures annually.
    - For obstetric ultrasound accreditation, each participating physician must meet a minimum of 170 obstetric ultrasound procedures annually.
    - For obstetric/gynecologic ultrasound accreditation, each participating physician must meet a minimum of 170 obstetric/gynecologic ultrasound procedures

annually. They must have no fewer than 50 cases per year in either obstetric or gynecologic ultrasound.

- For abdominal/general ultrasound accreditation, each participating physician must meet a minimum of 300 abdominal/general ultrasound procedures annually.
- For diagnostic breast ultrasound accreditation, each participating physician must meet a minimum of 60 diagnostic ultrasound procedures annually.
- For interventional breast ultrasound accreditation, each participating physician must meet a minimum of 12 interventional ultrasound procedures annually.
- For physicians who do not meet these annual volume requirements, they should see the *Quality Assurance for Case Volume Requirements* described below.

Chief Sonographer

A qualified chief sonographer may be designated for the facility. The chief sonographer will report to the physician director of ultrasound, and will be responsible for those tasks specified by the physician director of ultrasound for the day-to-day operation of the facility, and for the maintenance and operation of the equipment. The chief sonographer must meet all additional requirements for sonographers and other nonphysicians who perform ultrasound examinations.

Sonographers

Qualified sonographers will be responsible for those tasks specified by the physician director of ultrasound and chief sonographer. Sonographers will perform sonographic examinations. Furthermore, sonographers will have appropriate training for the performance of those sonographic examinations. Requirements for sonographers and other nonphysicians who perform ultrasound exams are as follows:

- Must be certified by the ARDMS (American Registry of Diagnostic Medical Sonographers) or must become ARDMS-certified prior to reaccreditation
- Must be certified in each area of ultrasound the sonographer performs and for which the practice seeks accreditation. A sonographer required to become ARDMS-certified in multiple specialties, must obtain a minimum of 1 additional specialty per accreditation cycle
- If the practice is applying for accreditation in any area(s) other than breast ultrasound, must obtain a minimum of 30 hours of continuing medical education (CME) credits in ultrasound every 3 years
- If the practice is applying for breast ultrasound accreditation, must acquire 10 CME credit hours in breast ultrasound over 3 years. If the practice is applying for accreditation in other ultrasound modalities as well as breast, the 10 CME credits apply toward the requirement of 30 CME credits over 3 years; and
- Must maintain documentation of appropriate continuing education. With the exception of sonographers in practices seeking accreditation in breast ultrasound, a copy of the sonographer's current ARDMS card will serve as adequate documentation of appropriate continuing medical education.

Nursing and Ancillary Support Staff
Nursing services support must be sufficiently trained and available, when necessary, to ensure appropriate care and emergency support for patients.

Clerical and Administrative Support Staff
Clerical and administrative support must be sufficient to ensure an efficient operation and accurate record keeping.

Quality Assurance for Case Volume Requirements
Physicians who interpret and evaluate ultrasound examinations are expected to meet the minimum annual volume requirements. Physicians who do not meet the minimum volume of ultrasound procedures on an annual basis can participate in a quality assurance program designed to increase their exposure to ultrasound examinations and ensure quality ultrasound care. Physicians who do not meet the minimum annual ultrasound volume requirements can meet the case study requirements in any one of the following ways:

- They can double read ultrasound studies for quality assurance purposes.
- They can have their ultrasound studies re-read by a physician who does meet the minimum volume requirements.
- They can participate in a monthly case study review seminar developed and conducted by physicians in the practice who do meet the minimum annual ultrasound volume requirements.

Document Storage and Record-Keeping Guidelines and Requirements
There must be provisions for the retrieval and storage of examination records of all studies performed.

- Appropriate documentation of every study must include permanent ultrasound images stored on suitable recording media, as well as a report that indicates the findings obtained by examination.
- The report must contain image information; see the *AIUM Standard for Documentation of an Ultrasound Examination* (Appendix C). For the purposes of accreditation, all case studies and reports will be evaluated and must be properly labeled as outlined in the *Instructions for Completing the Application for Ultrasound Practice Accreditation.*
- Ultrasound images, and a report from the interpreting physician, must be maintained in a readily accessible fashion for comparison and consultation.
- Recording media must have a shelf life compatible with the minimum number of years, required by law, for the maintenance of patient records. In most states this will be for at least 7 years after the patient's last examination was performed; however, these requirements vary from state to state.

Preliminary and Final Reports
A preliminary report is a written or verbal report released prior to being signed by the physician responsible for giving the final interpretation. Preliminary reports for fetal biometry, biophysical profiles, and viability can be given by a sonographer who is ARDMS-registered in that specialty,

as long as the results are normal and the final report is complete within 2 hours; this preliminary report would be equivalent to a worksheet and would not include recommendations or an impression. All other reports must be reviewed by a physician prior to being released.

- If preliminary reports are issued, the reports must be labeled "Preliminary Report."
- A written policy for communicating the potential differences and changes that may arise between the interpretation of the final report and the preliminary report must be in place for any practice that generates preliminary reports.
- Verified final reports must be available within 24 hours of completion of the exam or, for nonemergency cases, by the next business day; exceptions to this time frame must be clarified.

Policies and Procedures Safeguarding Patients, Ultrasound Personnel, and Equipment

Policies on Patients

Incident Reporting
A policy/procedure must exist for responding to and reporting any accidents or complications that occur in the facility.

Patient Confidentiality
All practice personnel must adhere to professional ethics and behavior ensuring patient confidentiality.

Policies on Prevention of Infectious Disease
The practice must have procedures and policies on the control of infectious diseases, equipment cleaning/disinfection, and protection of practice personnel from the transmission of infectious disease.

ALARA Principle
Personnel must be familiar with and show evidence of practicing the ALARA (as low as reasonably achievable) principle.

Instrumentation and Quality Assurance

Policies on Equipment

The ultrasound equipment must meet all state and federal guidelines.

Studies must be conducted with real-time equipment, and transducers must be available with a frequency range that will optimize beam penetration and resolution.

Instrumentation used for diagnostic testing must be maintained in good operating condition and undergo routine calibration at least once a year.

All equipment must be serviced at least annually, according to the manufacturers' specifications

or, more frequently, if problems arise.

There must be routine inspection and testing for electrical safety of all existing equipment.

Policies on Physician Interpretation and Examination Performance

The practice must show ongoing monitoring of the clinical practice's personnel performance, including all physicians and sonographers.

- Ultrasound studies must be supervised and interpreted by a physician with training and experience in the specific area of sonography.
- Findings must be recorded and results communicated in a timely fashion to the physician responsible for care. Although a sonographer may play a critical role in extracting the information essential to deriving a diagnosis, the rendering of a final diagnosis of ultrasound studies represents the practice of medicine and, therefore, is the responsibility of the supervising physician.
- Findings of diagnostic studies must be interpreted and reported by the qualified physicians approved by the physician director of ultrasound.
- Reports must specifically address the indication for the study and findings.
- The practice must demonstrate regular peer-review; the diagnostic interpretations and technical merit of images generated by the practice must be independently evaluated for image clarity and diagnostic accuracy.
- The practice must show ongoing monitoring of the clinical practice's personnel performance, including all physicians and sonographers.
- The practice must obtain regular correlation of ultrasound diagnosis of normal and abnormal studies with clinical, radiographic, laboratory, surgical, and pathology findings; a record of this must be maintained and kept current. Information obtained should be disseminated to both physician and sonographer personnel of the ultrasound practice in a timely fashion.
- Physician interpretation and reports of studies should be performed within 24 hours; the responsible physician must be available for timely consultation.
- If physicians are not immediately available for the patient at the time of the sonogram, the sonographer must be registered in the specialty area; a mechanism must be in place to address unexpected or emergency findings; sonograms must be finally read within 24 hours, and if the patient is not kept until the physician reviews the images, a call-back mechanism must be described.
- If the practice is applying for breast ultrasound accreditation, the following information - at a minimum - should be kept in a database to allow proper analysis of examinations for accuracy and appropriateness:

    1. Individual interpreting the case

2. Lesion classification category (similar to the BIRAD codes or 5 levels of concern)*
3. Recommendations made as part of the report or verbally
4. Indications for the examination
5. Pathologic diagnosis
6. Clinical follow-up results when available
7. Mammography correlation

Optionally, the individual sonographic findings for each examination may be recorded if a more detailed analysis is desired.

*Breast Ultrasound Lesion Classification Category

1	Negative	Negative
2	0%	Benign
3	2%	Probably benign
4a	3%-49%	Suspicious
4b	50%-89%	Suspicious
5	> 90%	Highly suggestive of malignancy

It is usually not possible to obtain complete data for all or even most of the examinations performed. Given the difficulties of obtaining follow-up and the labor required, practices should set reasonable goals for obtaining clinical-pathologic correlations. For patients not going to biopsy, attempting to get follow-up in 10% of cases is reasonable. For patients going to biopsy, sonographic-pathologic correlations should be obtained in at least 90% of cases.

American Institute of Ultrasound in Medicine (AIUM) web site, http://www.aium.org/provider/statements/_statementSelected.asp?statement=26, downloaded on August 11, 2004.

Appendix B

Guidelines for Cleaning and Preparing Endocavitary Ultrasound Transducers Between Patients

Approved June 4, 2003

The purpose of this document is to provide guidance regarding the cleaning and disinfection of transvaginal and transrectal ultrasound probes.

All sterilization/disinfection represents a statistical reduction in the number of microbes present on a surface. Meticulous cleaning of the instrument is the essential key to an initial reduction of the microbial/organic load by at least 99%. This cleaning is followed by a disinfecting procedure to ensure a high degree of protection from infectious disease transmission, even if a disposable barrier covers the instrument during use.

Medical instruments fall into different categories with respect to potential for infection transmission. The most critical level of instruments are those that are intended to penetrate skin or mucous membranes. These require sterilization. Less critical instruments (often called "semi-critical" instruments) that simply come into contact with mucous membranes such as fiber optic endoscopes require high-level disinfection rather than sterilization.
Although endocavitary ultrasound probes might be considered even less critical instruments because they are routinely protected by single use disposable probe covers, leakage rates of 0.9% - 2% for condoms and 8%-81% for commercial probe covers have been observed in recent studies. For maximum safety one should therefore perform **high-level disinfection** of the probe between each use and use a probe cover or condom as an aid to keeping the probe clean.

There are four generally recognized categories of disinfection and sterilization. **Sterilization** is the complete elimination of all forms or microbial life including spores and viruses.
Disinfection, the selective removal of microbial life, is divided into three classes:
High-Level Disinfection - Destruction/removal of all microorganisms except bacterial spores
Mid-Level Disinfection - Inactivation of Mycobacterium Tuberculosis, bacteria, most viruses and most fungi and some bacterial spores.
Low-Level Disinfection - Destruction of most bacteria, some viruses and some fungi. Low-level disinfection will not necessarily inactivate Mycobacterium Tuberculosis or bacterial spores.

The following specific recommendations are made for the use of endocavitary ultrasound transducers. Users should also review the Centers for Disease Control and Prevention document on sterilization and disinfection of medical devices to be certain that their procedures conform to the CDC principles for disinfection of patient care equipment.

1. CLEANING - After removal of the probe cover, use running water to remove any residual gel or debris from the probe. Use a damp gauze pad or other soft cloth and a small amount of mild non-abrasive liquid soap (household dishwashing liquid is ideal) to thoroughly cleanse the transducer. Consider the use of a small brush especially for crevices and areas of angulation depending on the design of your particular transducer. Rinse the transducer thoroughly with

running water, and then dry the transducer with a soft cloth or paper towel.

2. DISINFECTION - Cleaning with a detergent/water solution as described above is important as the first step in proper disinfection since chemical disinfectants act more rapidly on clean surfaces. However, the additional use of a high level liquid disinfectant will ensure further statistical reduction in microbial load. Because of the potential disruption of the barrier sheath, additional high level disinfection with chemical agents is necessary. Examples of such high level disinfectants include but are not limited to

- 2.4-3.2% glutaraldehyde products (a variety of available proprietary products including "Cidex," "Metricide," or "Procide").

- Non-glutaraldehyde agents including Cidex OPA (o-phthalaldehyde), Cidex PA (hydrogen peroxide & peroxyacetic acid)

- 7.5% Hydrogen Peroxide solution

- Common household bleach (5.25% sodium hypochlorite) diluted to yield 500 parts per million chlorine (10 cc in one liter of tap water). This agent is effective but generally not recommended by probe manufacturers because it can damage metal and plastic parts.

Other agents such as quaternary ammonium compounds are not considered high level disinfectants and should not be used. Isopropanol is not a high level disinfectant when used as a wipe and probe manufacturers do generally not recommend soaking probes in the liquid.

The FDA has published a list of approved sterilants and high level disinfectants for use in processing reusable medical and dental devices. That list can be consulted to find agents that may be useful for probe disinfection.

Practitioners should consult the labels of proprietary products for specific instructions. They should also consult instrument manufacturers regarding compatibility of these agents with probes. Many of the chemical disinfectants are potentially toxic and many require adequate precautions such as proper ventilation, personal protective devices (gloves, face/eye protection, etc.) and thorough rinsing before reuse of the probe.

3. PROBE COVERS - The transducer should be covered with a barrier. If the barriers used are condoms, these should be nonlubricated and nonmedicated. Practitioners should be aware that condoms have been shown to be less prone to leakage than commercial probe covers, have a six-fold enhanced AQL (acceptable quality level) when compared to standard examination gloves. They have an AQL equal to that of surgical gloves. Users should be aware of latex-sensitivity issues and have available nonlatex-containing barriers.

4. ASEPTIC TECHNIQUE - For the protection of the patient and the health care worker, all endocavitary examinations should be performed with the operator properly gloved throughout the procedure. Gloves should be used to remove the condom or other barrier from the transducer and to wash the transducer as outlined above. As the barrier (condom) is removed, care should be

taken not to contaminate the probe with secretions from the patient. At the completion of the procedure, hands should be thoroughly washed with soap and water.

Note: Obvious disruption in condom integrity does NOT require modification of this protocol. These guidelines take into account possible probe contamination due to a disruption in the barrier sheath.

In summary, routine high-level disinfection of the endocavitary probe between patients, plus the use of a probe cover or condom during each examination is required to properly protect patients from infection during endocavitary examinations. For all chemical disinfectants, precautions must be taken to protect workers and patients from the toxicity of the disinfectant.

Amis S, Ruddy M, Kibbler CC, Economides DL, MacLean AB. Assessment of condoms as probe covers for transvaginal sonography. J Clin Ultrasound 2000;28:295-8.

Rooks VJ, Yancey MK, Elg SA, Brueske L. Comparison of probe sheaths for endovaginal sonography. Obstet. Gynecol 1996;87:27-9.

Milki AA, Fisch JD. Vaginal ultrasound probe cover leakage: implications for patient care. Fertil Steril 1998;69:409-11.

Hignett M, Claman P. High rates of perforation are found in endovaginal ultrasound probe covers before and after oocyte retrieval for in vitro fertilization-embryo transfer. J Assist Reprod Genet 1995;12:606-9.

Sterilization and Disinfection of Medical Devices: General Principles. Centers for Disease Control, Division of Healthcare Quality Promotion.
http://www.cdc.gov/ncidod/hip/sterile/sterilgp.htm (5-2003).

ODE Device Evaluation Information--FDA Cleared Sterilants and High Level Disinfectants with General Claims for Processing Reusable Medical and Dental Devices, March 2003.
http://www.fda.gov/cdrh/ode/germlab.html (5-2003).

American Institute of Ultrasound in Medicine (AIUM) web site, http://www.aium.org/provider/statements/_statementSelected.asp?statement=27, downloaded on August 11, 2004.

Appendix C

2-D and 3-D Data Form

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Images

1. Date of Ultrasound: _____/_____/_____
   Month Day Year

2. Patient's Date of Birth: _____/_____/_____
   Month Day Year

3. Patient's Weight: _____
   Pounds

4. Date of last menstrual period: _____/_____/_____
   Month Day Year

5. Indicate trimester:

   First □
   Second □
   Third □

6. Indicate Fetal Age: _____weeks

7. Indication for ultrasound exam:
   Routine
   Suspected Abnormality □ → END STUDY PARTICIPATION (Patient does not meet inclusion criteria)

8. Start time of 2-D ultrasound: _____:____ AM or PM (circle one)

9. Indicate scan method(s):
   Abdominal
   Transvaginal □

10. Is there an IUP? YES NO → END STUDY PARTICIPATION following steps in Fetal Anomaly Protocol

11. Is there visible cardiac activity? YES NO → END STUDY PARTICIPATION following steps in Fetal Anomaly Protocol

12. Number of fetuses? _____ (If > 1 fetus, complete and attach a separate 2-D and 3-D Data Form for each fetus)

13. Fetal presentation:
Cephalic
Transverse
Breech

14. Is there ≥1 fetal anomaly? NO YES →END STUDY PARTICIPATION following steps in Fetal Anomaly Protocol

15. Record the 2-D Measurements (check box if not measured)

a. Crown-Rump Length (CRL):	_____mm	not measured
b. Biparietal Diameter (BPD):	_____mm	not measured
c. Head Circumference (HC):	_____mm	not measured
d. Abdominal Circumference (AC):	_____mm	not measured
e. Femur Length (FL):	_____mm	not measured

16. PLEASE STATE REASONS FOR ANY "NOT MEASURED" IN QUESTION 15:

_____

_____

_____

17. Stop time of 2-D scan: ____:_____ AM or PM (circle)

18. Start time of 3-D scan: ____:_____AM or PM (circle)

Tell patient that the 3-D exam is beginning

19. Acquire Volume Datasets to ensure later measurement of:

a. Head	obtained	not obtained
b. Heart	obtained	not obtained
c. Right kidney	obtained	not obtained
d. Left kidney	obtained	not obtained
e. Right adrenal gland	obtained	not obtained
f. Left adrenal gland	obtained	not obtained
g. Right lung	obtained	not obtained
h. Left lung	obtained	not obtained
i. Pancreas	obtained	not obtained
j. Liver	obtained	not obtained
k. Right upper arm	obtained	not obtained
l. Left upper arm	obtained	not obtained
m. Right thigh	obtained	not obtained
n. Left thigh	obtained	not obtained

20. PLEASE STATE REASONS FOR ANY "NOT OBTAINED" IN QUESTION 19:

_____

_____

_____

_____

_____

21. Stop time of 3-D scan: _____:_____ AM or PM (circle)

22. Sonographer's name: _____
First Last

23. SONOGRAPHER COMMENTS:

a. Patient's response to 3-D exam: (time, comfort, views of fetus, etc): _____

_____

_____

_____

b. Sonographer response to 3-D exam: (time, technical challenges, etc): _____

_____

_____

_____

_____

Patient portion of study is complete. After patient has left, determine and record organ volume measurements.

24. Determine the organ volume measurements from the 3-D volume datasets (check box if unable to determine volume)

a.	Head	_____	unable to determine
b.	Heart	_____	unable to determine
c.	Right kidney	_____	unable to determine
d.	Left kidney	_____	unable to determine
e.	Right adrenal gland	_____	unable to determine
f.	Left adrenal gland	_____	unable to determine
g.	Right lung	_____	unable to determine
h.	Left lung	_____	unable to determine
i.	Pancreas	_____	unable to determine
j.	Liver	_____	unable to determine
k.	Right upper arm	_____	unable to determine
l.	Left upper arm	_____	unable to determine
m.	Right thigh	_____	unable to determine
n.	Left thigh	_____	unable to determine

25. STATE REASONS FOR ANY “UNABLE TO DETERIME” IN QUESTION 24:

_____

_____

_____

_____

_____

26. SONOGRAPHER COMMENTS REGARDING LOCATING AND DETERMINING ORGAN VOLUME MEASUREMENTS FROM 3-D VOLUME DATASET (TIME, TECHNICAL CHALLENGES, ETC): _____

_____

_____

_____

_____

_____

_____

_____

Appendix I

3-D Ultrasound and Organ Volume Measurements Protocol

DRAFT

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Data Sets and Images

1.0 Abstract

This protocol specifies the steps to follow to obtain 3-D volumes that will allow the sonographer, after the exam has been completed and the patient has left the exam area, to determine organ volume measurements for the fetal head, heart, kidneys, adrenal glands, lungs, pancreas, liver, upper arms, and thighs. While there are practice guidelines for the performance of a 2-D exam which are published by AIUM (American Institute of Ultrasound Medicine) in conjunction with the American College of Obstetricians and Gynecologists (ACOG) and the American College of Radiology (ACR) (http://www.aium.org/provider/standards/obstetrical.pdf), standard guidelines for obtaining 3-D volumes and determining organ volume measurements from these datasets do not exist. Under consultation with RTI, Dr. Linda Chan, a maternal-fetal medicine specialist (perinatologist), reviewed the published literature on fetal organ volume measurement, and created the guidelines contained in this and the **Central Facility Evaluation of 3-D Volume Dataset Protocol**. Dr. Chan, and nationally recognized leaders in the 3-D fetal ultrasound field including Dr. Delores Pretorius and Dr. Wesley Lee agree that the most reliable method for obtaining organ volumes and determining organ volume measurements must be agreed upon before the feasibility study can be started. RTI therefore recommends that a panel of 3-D experts evaluate the existing published literature and unpublished data and then revise as necessary the procedures detailed in this draft protocol.

2.0 Background

Three-dimensional (3D) ultrasonography (US) provides the simultaneous display of the 3 orthogonal planes of the VOI (volume of interest). This multiplanar display (sagittal, transverse, and coronal views) of the fetal images allows the examiner to perform quantitative and semi-quantitative evaluation of the VOI via interactive serial slice-reconstruction with appropriate computer software and interface. With the advent of 3DUS, measurements of both regular and irregular shaped organ volumes are now possible.

Assessment of fetal anatomy and fetal weight estimation are important aspects of prenatal care. Two-dimensional (2D) ultrasound (US) has been the main diagnostic tool used in the estimation of fetal weight using 2D fetal biometric measurements in standard mathematical models. Recent efforts have been made to improve the predictive value of fetal weight estimation formulas by the addition of fetal soft tissue mass volumes, which is made possible only with the advent of 3DUS.

The most common technique to obtain fetal volume measurement with 3DUS is from serial measurements of the cross-sectional contour of the VOI using the multiplanar view. A standardized transverse 2D fetal image is typically placed on the A plane (upper left). The B plane (upper right) will be the corresponding standardized 2D sagittal view. The reference point is usually placed along the long axis and at the beginning of the VOI to be measured. In this example, it is the sagittal view located on the B plane. Serial tracings of the contour (perimeter) of the VOI are made on the A plane in a stepwise fashion, either at fixed distance intervals or by arbitrary intervals determined manually by the examiner, until the whole length of the VOI is measured. The length of the VOI (distance between each serial tracing measurement) is automatically tracked by the 3DUS measurement software and is incorporated into the calculation of the final volume measurement. The C plane (bottom left) is the coronal view and is generally not used to obtain volumetric measurements. Depending on the VOI to be measured, at times it is advantageous to put the sagittal or coronal fetal image on the A plane.

The conventional volume measurement using the multiplanar method is time-consuming. Depending on the complexity of the shape and size of the VOI to be measured, it takes anywhere from 2 to 20 minutes to complete a volume measurement, with an average of 10 to 15 minutes. Investigators have attempted to streamline the time necessary to obtain the volume measurement by cutting down the number of perimeter tracings (Song et al., 2000) or via the use of sonographic measurement such as the fractional limb measurement (Lee et al., 2001). The fractional limb measurement takes advantage of the software, 3DView version 4.4. This software automatically defines a cylindrical limb volume that is based on 50% of the total long bone diaphysis length. The resulting partial limb volume is divided into 5 subsections of equal length to allow manual tracing of surface contours from an axial view. Each fractional limb volume measurement takes only a few minutes to determine. Currently, the lead investigator in this study has an additional 250 patients being evaluated to validate the precision of using fractional limb volume with standard 2D fetal biometric measurements in the estimation of fetal weight.

More recently, the VOCAL volume calculation software program utilizes a manual tracing of the contour of structures and subsequently calculates the volume (VOCAL – Virtual Organ Computer-Aided AnaLysis). The VOCAL mode allows for rotational measurement of the VOI along an axis in predefined rotation of 3, 9, 15, or 30 degrees angle. This new modality improves the accuracy of the volume measurement process by allowing the examiner to have visual control and correction abilities in the multiplanar display mode. In one study, it took about 5 to 10 minutes to measure each of the fetal lungs either by the multiplanar or by the VOCAL mode. The VOCAL measurement in this study was taken with the use of the non-conventional longitudinal view of the lungs and had an increased inter-observer error (Kalache et al., 2003). However, when VOCAL volumetric measurement was used with the standard transverse view of the fetal lungs, the VOCAL method was as accurate as the conventional multiplanar serial measurements (Ruano et al., 2004). Volume measurement using the VOCAL technique has the advantage of predetermined fixed rotational angle to measure the VOI, and theoretically may lead to more reproducible data among different examiners, and perhaps a decrease in the time necessary to measure the VOI. Further evaluation of the VOCAL technique in the assessment of volumetric measurements using 3DUS is warranted.

3.0 Preparation Before the Exam

This protocol assumes that the 2-D exam has been completed following the **2-D Ultrasound Protocol** by the same sonographer who will follow this protocol. AIUM policies and procedures which are discussed in the **2-D Ultrasound Protocol** must continue to be followed for the 3-D exam.

Even though there are no known risks associated with ultrasound exposure, there remains the theoretical risk and therefore the sonographer needs to ensure that the 3-D scan not exceed 30 minutes regardless of whether all 3-D volumes have been obtained.

4.0 Equipment Preparation

The same equipment preparation as described in the **2-D Ultrasound Protocol** is required

5.0 3-D Volume Acquisitions and Organ Volume Measurements

Using the same **2-D and 3-D Data Form** with the patient's 2-D exam data, record the time that the scan began. Tell the patient that the 3-D scan is beginning and that she will be asked her impressions of the 3-D scan when it is completed.

Obtain 3-D volumes as detailed below. It may be difficult to visualize different structures due to fetal age, size, position, movement, abdominal scars, and increased maternal wall thickness. A second- or third-trimester scan may pose technical limitations for an anatomic evaluation due to imaging artifacts from acoustic shadowing. Indicate whether a volume was obtained that will enable organ volume measurement after the patient departs or that an adequate volume was not obtained. If a volume is not obtained for one or more organs the sonographer should indicate this on the data entry form and indicate the suspected reason for this omission.

6.0 First trimester 3-D Ultrasound scans (10-13 weeks gestation):

Either a transvaginal or abdominal transducer can be used for the 2-D ultrasound exam. The same scan method should be used for the 3-D volume acquisitions. A 3D volume should be acquired that includes the entire fetus and the uterus, and the dataset is then saved in the SonoView for later analysis.

While it is postulated that organ size may prohibit organ volume measurement in the first trimester, for this pilot study the sonographer should attempt organ volume measurements as is described in the following section.

7.0 Second trimester (14-26 weeks) and third trimester (27 weeks to term) 3DUS scans:

Second and third trimester 3DUS should be performed using either a 2-5 MHz or a 4-8 MHz transabdominal curved array transducer with an internal motor control for volumetric acquisition. These probes have the ability to acquire up to 16 volumes per second. All fetal

images will be optimized using either the Compound Resolution Imaging (CRI) mode or with the Tissue Harmonic Imaging mode prior to 3D volume acquisition. If Volume Contrast Imaging (VCI) is available, it should be used to visualize the fetal adrenals, liver, and the Pancreas. If Spatio-Temporal Image Correlation (STIC) is available, it should be used for the volumetric evaluation of the fetal heart.

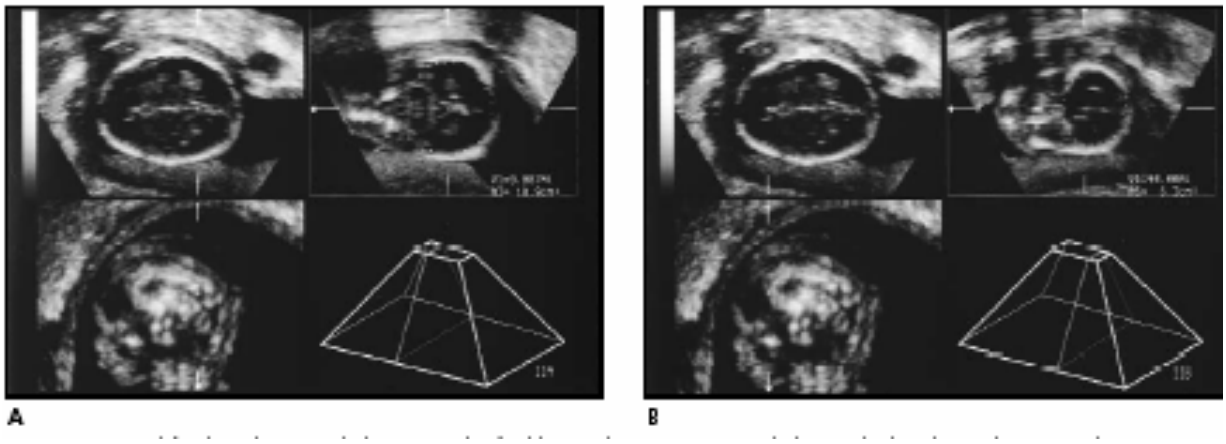
All VOI are initially identified with standardized landmarks in the 2DUS mode. Once all the landmarks in the VOI are in view, the 3D function of the probe is activated. The sector angle, penetration depth, frame rate, lateral resolution, axial resolution, and magnifications are then optimized to the VOI. The VOI is then acquired after adjusting the volume box to include the VOI in its entirety. As much as possible, the 3DUS volume acquisition should be made when the fetus is at rest or with no movement. The following are methodologies for the acquisition of the 3DUS dataset for each of the fetal organ of interest.

The volume acquisitions will take place while the patient is still on the examination table, while the organ volume measurement will take place after the exam is completed and the patient has left. For the sake of clarity, both volume acquisition and organ volume measurement are described below.

7.1 Head:

The total fetal brain volume can be measured from 20 to 40 weeks gestation. The fetal brain is identified in the axial position at the level of the BPD (biparietal diameter), with the thalamic nuclei, cavum septum pellucidum, and the midline falx cerebri clearly visible. A 3D volume is then acquired and stored to SonoView for later analysis (Endres and Cohen, 2001; Chang et al., 2003).

In order to measure the 3D brain volume, the axial plane is fixed as the anchor with the cursor dot on the midline falx cerebri in the A Plane (upper left). The volumes were determined by scrolling through the fetal head from posterior to anterior and measuring the areas of 8 to 10 serial coronal cuts in the B plane (upper right). The areas were calculated at the inner edge of the fetal skull bone by manual tracing. The 3DUS measured the distance the cursor was moved between the coronal cuts and automatically added a series of vertical cylindrical slices to calculate the fetal brain volume. The figures below is taken from Endres and Cohen, 2001, showing representative coronal areas at the levels of the fetal cerebellum (Fig. A) and orbits (Fig. B).



7.2 Heart

The calculation of the cardiac volume only applies to gestations between 20 to 30 weeks since there is no published nomogram outside of this gestational age range . The fetal heart is identified in the transverse axis in the chest with the four chambers of the heart (4CH) visualized. The fetal spine should be located posteriorly at close to the 6 o'clock position as much as possible in order to avoid acoustic shadowing from the rib cage. Once the four-chamber view of the heart is focused, a 3DUS volume is acquired for later analysis.

To measure the cardiac volume, first the 4CH view in the transverse axis is place in the A plane (upper left). The focal point is then fixed along the axis of the heart at the apex, and the corresponding heart area is measured in the B plane (upper right) along the entire length of the heart at 1 mm intervals (Chang et al., 1997).

Note: The measurement of total fetal cardiac volume is not clinically useful or relevant.

7.3 Kidney

Renal volume can be measured between 15 to 40 weeks gestations. The transverse fetal trunk containing both kidneys with fetal spine preferably at the 12 o'clock position, or with minimal acoustic shadowing is scanned with 3DUS probe.

To measure the renal volume, first the plane of the longest axis of the kidney is fixed in the A plane (upper left). The contour of the transverse kidney is then measured in 10 mm slice on the B plane (upper right) along the entire length of the kidney.

Note: The 10 mm slice measurement is different than what's published where 2 authors measured the kidneys in 1 mm slice. In view that the fetal kidney is a symmetrical cylindrical structure, this change should not affect the final volume measurement and should save some time in data analysis.

No difference in renal volume was reported between the right and the left kidney.

(Hsieh et al., 2000; Yu et al., 2000)

7.4 Adrenal Gland

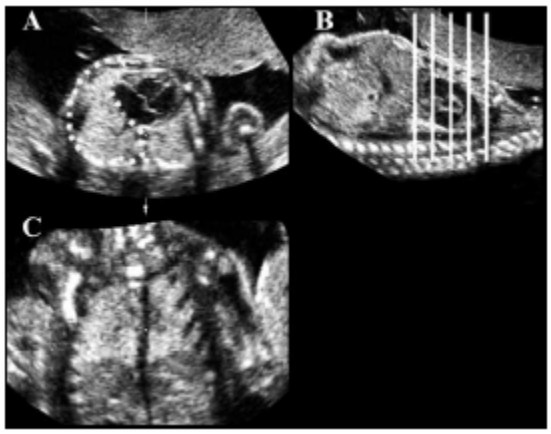
The fetal adrenal gland volume can be measured between 21 to 40 weeks gestations. The transverse fetal trunk containing the fetal adrenal glands with fetal spine preferably at the 12 o'clock position, or with minimal acoustic shadowing is scanned with 3DUS probe.

The fetal adrenal gland volume measurement is performed with the long axis of the adrenal gland fixed in the A plane. Subsequent serial measurement of the perimeter of the adrenal gland in 1 mm slice is performed on the B plane until the entire length of the adrenal gland is measured. (Chang et al., 2002)

7.5 Lung

3D volume is acquired whenever possible from the anterior fetal chest wall at the level of the 4CH (four chamber heart) view in the transverse axis.

To measure the fetal lungs, the transverse 4CH view is placed on the A plane (upper left) and the midline sagittal chest is placed on the B plane (upper right). The perimeter of each transverse section of the lung is traced serially in 10 mm slice from the dome of the diaphragm to the clavicle in the A plane.



(Sabogal et al., 2004; Kalache et al., 2003; Pohl and Rempen, 1998; Osada et al., 2002; Ruano et al., 2004; Chang et al., 2003; Laudy et al., 1998; Lee et al., 1996.)

7.6 Pancreas

There is no published nomogram for fetal pancreatic volume. The fetal pancreas is first identified in the anterior fetal abdomen in the transverse axis at the level of the fetal stomach.

The fetal pancreas volume measurement is performed with the long axis of the pancreas fixed in the A plane. Subsequent serial measurement of the perimeter of the pancreas in 3 mm slice is performed on the B plane until the entire length of the pancreas is measured.

7.7 Liver

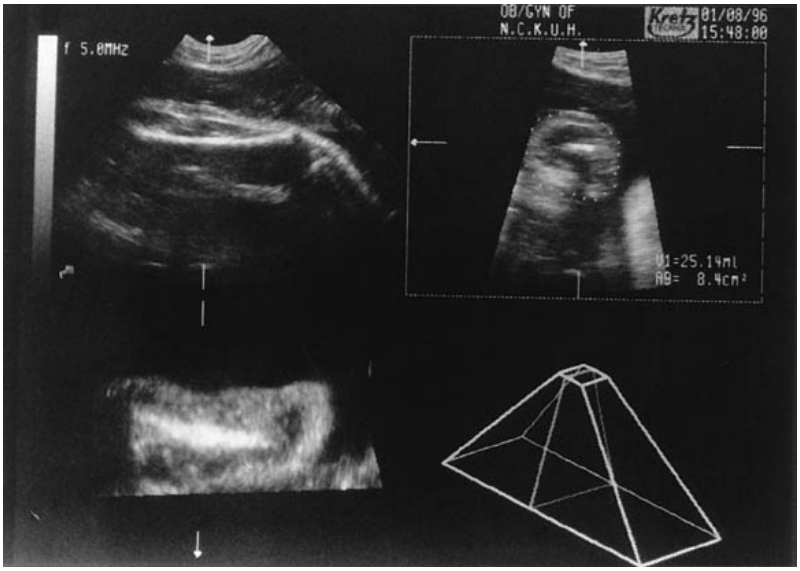
The traditional transverse plane for the fetal abdominal circumference (AC) is identified (the presence of the transverse vertebral body, presence of fetal stomach and the umbilical portion of the left portal vein deep in the liver). A 3D volume is obtained at the level of the AC for later analysis.

For the volumetric measurement of the fetal liver, the frontal view of the liver anterior to the fetal stomach is visualized and is measured as described by Boito et al. In a simultaneous demonstrated sagittal cross section, the outline of the liver is traced manually in approximately 10 sagittal sections between the most lateral left and right points of the diaphragm in the frontal plane. The liver is measured from its upper limit at the diaphragm to its distal rim as the lower limit. (Boito et al., 2003; Boito et al., 2002; Kuno et al., 2002; Chang et al., 2003; Chang et al., 1997.)

7.8 Upper Arm

The fetal humerus is visualized in its entirety perpendicular to the ultrasound beams and a 3D volume is acquired taking care to include all of the soft tissues of the upper arm.

The volume calculation is performed with the length of the humerus fixed in the A plane. The upper arm volume is then measured by serial tracing of the contour of the upper arm in the B plane in 3 mm slice until the entire length of the upper arm is measured from diaphysis to diaphysis. (Liang et al, 1997; Chang et al., 2002 and 2003.)

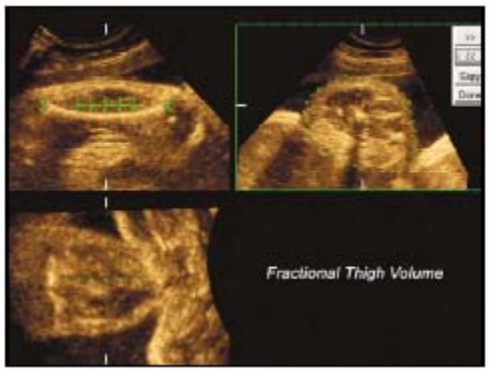


7.9 Thigh

The fetal femur is visualized in its entirety perpendicular to the ultrasound beams and a 3D volume is acquired taking care to include all of the soft tissues of the thigh.

The volume calculation is performed with the length of the femur fixed in the A plane. The thigh volume is then measured by serial tracing of the contour of the thigh in the B plane in 3 mm slice until the entire length of the thigh is measured from diaphysis to diaphysis.

Note: If Lee et al. publish their latest report on fractional thigh volume and can confirm good correlation of his fetal EFW formula to the birth weight, then his method of calculation of limb volumes should replace the above 3DUS measurements of the upper arm and the thigh. The following is an example of fractional thigh volume taken from his publication in Journal of Ultrasound Medicine 2001.)



(Chang et al., 2003;, Chang et al. 1997; Lee et al., 2001; Song et al., 2000; Schild et al., 2000; Lee et al., 1997; Comstock et al., 1997)

8.0 Storing 3-D Volume Acquisitions

When the organ volume measurements are completed, the sonographer saves the 3-D volume dataset to a CD/DVD. The volumes, without being compressed, are saved to a CD/DVD. Only one patient's data should be each CD/DVD. Once saved, place the CD/DVD should be placed in the patient's **Patient Packet** and placed in a locked cabinet until sent to RTI.

References

Boito SM, Struijk PC, Ursem NT, Stijnen T, Wladimiroff JW. Assessment of fetal liver volume and umbilical venous volume flow in pregnancies complicated by insulin-dependent diabetes mellitus. BJOG 2003 Nov;110(11):1007-13.

Boito SM, Laudy JA, Struijk PC, Stijnen T, Wladimiroff JW. Three-dimensional US assessment of hepatic volume, head circumference, and abdominal circumference in healthy and growth-restricted fetuses. Radiology 2002 Jun;223(3):661-5.

Chang CH, Yu CH, Chang FM, Ko HC, Chen HY. The assessment of normal fetal brain volume by 3-D ultrasound. Ultrasound in Med Biol 2003;29:1267-72.

Chang CH, Yu CH, Chang FM, Ko HC, Chen HY. The assessment of normal fetal liver volume by three-dimensional ultrasound. Ultrasound Med Biol 2003;29(8):1123-29.

Chang CH, Yu CH, Chang FM, Ko HC, Chen HY. Assessment of fetal adrenal gland volume using three-dimensional ultrasound. Ultrasound Med Biol 2002;28:1383-87.

Chang CH, Yu CH, Chang FM, Ko HC, Chen HY. Three-dimensional ultrasound in the assessment of normal fetal thigh volume. Ultrasound Med Biol 2003;29:361-6.

Chang CH, Yu CH, Chang FM, Ko HC, Chen HY. Assessment of normal fetal upper arm volume by three-dimensional ultrasound. Ultrasound in Medicine and Biology 2002;28(7):859-863.

Chang CH, Yu CH, Ko HC, Chang FM, Chen HY. Prenatal assessment of normal fetal humerus volume by three-dimensional ultrasound. Ultrasound Med Biol 2003;29:1675-80.

Chang FM, Hsu KF, Ko HC, Yao BL, Chang CH, Yu CH, Chen HY. Three-dimensional ultrasound assessment of fetal liver volume in normal pregnancy: a comparison of reproducibility with two-dimensional ultrasound and a search for a volume constant. Ultrasound in Med Biol 1997;23(3):381-89.

Chang FM, Hsu KF, Ko HC, Yao BL, Chang CH, Yu CH, Liang RI, Chen HY. Fetal heart volume assessment by three-dimensional ultrasound. Ultrasound Obstet Gynecol 1997;9:42-8.

Chang FM, Liang RI, Ko HC, Yao BL, Chang CH, Yu CH. Three-dimensional ultrasound-assessed fetal thigh volumetry in predicting birth weight. Obstet Gynecol 1997c;90:331-39.

Endres LK, Cohen L. Reliability and validity of three-dimensional fetal brain volumes. Journal of Ultrasound Medicine 2001;20;1265-69.

Kalache KD, Espinoza J, Chaiworapongsa T, Londono J, Schoen ML, Treadwell MC, Lee W, Romero R. Three-dimensional ultrasound fetal lung volume measurement: a systematic study comparing the multiplanar method with the rotational (VOCAL) technique. Ultrasound Obstet Gynecol 2003; 21:111-18.

Kuno A, Hayashi Y, Akiyama M. Three-dimensional sonographic measurement of liver volume in the small for gestational age fetus. Journal of Ultrasound Medicine 2002;21:361-66.

Laudy JA, Janssen MM, Struyk PC, Stijnen T, Wladimiroff JW. Three-dimensional ultrasonography of normal fetal lung volume: a preliminary study. Ultrasound Obstet Gynecol. 1998 Jan;11(1):13-6.

Lee W, Comstock CH, Kirk JS, Smith RS, Monck JW, Deenadayalu R, Bendick PJ. Birthweight prediction by three-dimensional ultrasonographic volumes of the fetal thigh and abdomen. J Ultrasound Med. 1997 Dec;16(12):799-805.

Lee W., Deter RL, Ebersole JD, Huang R, Blanckaert K, Romero R. Birth weight prediction by three-dimensional ultrasonography. J Ultrasound Med 2001;20:1283-92.

Lee A, Kratochwill A, Stumpflen I, Deutinger J, Bernaschek G. Fetal lung volume determination by three-dimensional ultrasonography American Journal of Obstetrics and Gynecology 1996;175:588-92.

Liang RI, Chang FM, Yao BL, Chang CH, Yu CH, Ko HC. Predicting birth weight by fetal upper-arm volume with use of three-dimensional ultrasonography. Am J Obstet Gynecol 1997;177:632-8.

Laudy JA, Janssen MM, Struyk PC, Stijnen T, Wallenburg HC, Wladimiroff JW. Fetal liver volume measurement by three-dimensional ultrasonography: a preliminary study. Ultrasound Obstet Gynecol 1998;12:93-6.

Lee W., Deter RL, Ebersole JD, Huang R, Blanckaert K, Romero R. Birth weight prediction by three-dimensional ultrasonography. J Ultrasound Med 2001;20:1283-92.

Osada H, Iitsuka Y, Masuda K et al. Application of lung volume measurement by three-dimensional ultrasononography for clinical assessment of fetal lung development. J Ultrasound Med 2002;21:841-847.

Pohls UG, Rempen A. Fetal lung volumetry by three-dimensional ultrasound. Ultrasound Obstet Gynecol 1998;11:6-12.

Ruano R, Joubin L, Sonigo P, Benachi A, Aubry MC, Thalabard JC, Brunelle F, Dumez Y, Dommergues M. Fetal lung volume estimated by 3-dimensional ultrasonography and magnetic resonance imaging in cases with isolated congenital diaphragmatic hernia. J Ultrasound Med 2004 Mar;23(3):353-8.

Sabogal JC, Becker E, Bega G, Komwilaisak R, Berghella V, Weiner S, Tolosa J. Reproducibility of fetal lung volume measurements with 3-dimensional ultrasonography. J Ultrasound Med 2004; 23(3):347-52.

Schild RL, Fimmers R, Hansmann M. Fetal weight estimation by three-dimensional ultrasound. Ultrasound Obstet Gynecol 2000;16:445-52.

Song TB, Moore TR, Lee JY, Kim YH, Kim EK. Fetal weight prediction by thigh volume measurement with three-dimensional ultrasonography. Obstetrics and Gynecology 2000;96:157-61.

Yu CH, Chang CH, Chang FM, Ko HC, Chen HY. Fetal renal volume in normal gestation: a three-dimensional ultrasound study. Ultrasound in Medicine and Biology 2000; 26:1253-6.

Appendix A

2-D and 3-D Data Form

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Images

1. Date of Ultrasound: _____/_____/_____
   Month Day Year

2. Patient's Date of Birth: _____/_____/_____
   Month Day Year

3. Patient's Weight: _____
   Pounds

4. Date of last menstrual period: _____/_____/_____
   Month Day Year

5. Indicate trimester:

   First □
   Second □
   Third □

6. Indicate Fetal Age: _____weeks

7. Indication for ultrasound exam:
   Routine
   Suspected Abnormality □ → END STUDY PARTICIPATION (Patient does not meet inclusion criteria)

8. Start time of 2-D ultrasound: _____:____ AM or PM (circle one)

9. Indicate scan method(s):
   Abdominal
   Transvaginal □

10. Is there an IUP? YES NO → END STUDY PARTICIPATION following steps in Fetal Anomaly Protocol

11. Is there visible cardiac activity? YES NO → END STUDY PARTICIPATION following steps in Fetal Anomaly Protocol

12. Number of fetuses? _____ (If > 1 fetus, complete and attach a separate 2-D and 3-D Data Form for each fetus)

13. Fetal presentation:
Cephalic
Transverse
Breech

14. Is there ≥1 fetal anomaly? NO YES →END STUDY PARTICIPATION following steps in Fetal Anomaly Protocol

15. Record the 2-D Measurements (check box if not measured)

a. Crown-Rump Length (CRL):	_____mm	not measured
b. Biparietal Diameter (BPD):	_____mm	not measured
c. Head Circumference (HC):	_____mm	not measured
d. Abdominal Circumference (AC):	_____mm	not measured
e. Femur Length (FL):	_____mm	not measured

16. PLEASE STATE REASONS FOR ANY "NOT MEASURED" IN QUESTION 15:

_____

_____

_____

17. Stop time of 2-D scan: ____:_____ AM or PM (circle)

18. Start time of 3-D scan: ____:_____AM or PM (circle)

Tell patient that the 3-D exam is beginning

19. Acquire Volume Datasets to ensure later measurement of:

o. Head	obtained	not obtained
p. Heart	obtained	not obtained
q. Right kidney	obtained	not obtained
r. Left kidney	obtained	not obtained
s. Right adrenal gland	obtained	not obtained
t. Left adrenal gland	obtained	not obtained
u. Right lung	obtained	not obtained
v. Left lung	obtained	not obtained
w. Pancreas	obtained	not obtained
x. Liver	obtained	not obtained
y. Right upper arm	obtained	not obtained
z. Left upper arm	obtained	not obtained
aa. Right thigh	obtained	not obtained
bb. Left thigh	obtained	not obtained

20. PLEASE STATE REASONS FOR ANY "NOT OBTAINED" IN QUESTION 19:

_____

_____

_____

_____

_____

21. Stop time of 3-D scan: _____:_____ AM or PM (circle)

22. Sonographer's name: _____
First Last

23. SONOGRAPHER COMMENTS:

a. Patient's response to 3-D exam: (time, comfort, views of fetus, etc): _____

_____

_____

_____

b. Sonographer response to 3-D exam: (time, technical challenges, etc): _____

_____

_____

_____

_____

Patient portion of study is complete. After patient has left, determine and record organ volume measurements.

24. Determine the organ volume measurements from the 3-D volume datasets (check box if unable to determine volume)

o. Head	_____	unable to determine
p. Heart	_____	unable to determine
q. Right kidney	_____	unable to determine
r. Left kidney	_____	unable to determine
s. Right adrenal gland	_____	unable to determine
t. Left adrenal gland	_____	unable to determine
u. Right lung	_____	unable to determine
v. Left lung	_____	unable to determine
w. Pancreas	_____	unable to determine
x. Liver	_____	unable to determine
y. Right upper arm	_____	unable to determine
z. Left upper arm	_____	unable to determine
aa. Right thigh	_____	unable to determine
bb. Left thigh	_____	unable to determine

25. STATE REASONS FOR ANY "UNABLE TO DETERIME" IN QUESTION 24:

_____

_____

_____

_____

_____

26. SONOGRAPHER COMMENTS REGARDING LOCATING AND DETERMINING ORGAN VOLUME MEASUREMENTS FROM 3-D VOLUME DATASET (TIME, TECHNICAL CHALLENGES, ETC): _____

_____

_____

_____

_____

_____

_____

Appendix J

Data Storage, Transmission, and Retrieval Protocol

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Images

A. Abstract

This protocol includes the procedure for transmitting data from the local sites to the Central Facility (RTI and expert sonographers). This protocol also includes the procedures for the storage and retrieval methods that will be utilized by the expert sonographers at the Central Facility.

B. Introduction

Several methods have been considered for transmitting the 3-D volume datasets and these options have been discussed in another deliverable (Interim Report) under this work assignment. The work completed to date indicates that the methods for transmitting the 3-D volume datasets are limited. There is a potential option that is worth exploring further that may allow the files to be transmitted, stored, and retrieved electronically. This protocol, based on a transmission method that entails CD/DVDs, is being submitted as a deliverable under this work assignment until other transmission options can be fully vetted.

C. Transmitting Data from a Local Site to the Central Facility

This protocol assumes the 2-D exam, 3-D volume acquisitions, and the organ volume measurements were performed according to the **2-D Ultrasound Protocol** and the **3-D Ultrasound and Organ Volume Measurements Protocol.** These protocols detail how to complete the **Screening and Enrollment Form** and the **2-D and 3-D Data Form.** This protocol assumes these forms were accurately completed. As discussed in the **3-D Ultrasound and Organ Volume Measurements Protocol**, the 3-D volume dataset is saved by the local sonographer, without applying any type of compression, to a CD/DVD.

The **Patient Packets**, each containing a patient's CD/DVD, **Screening and Enrollment Form**, **2-D and 3-D Data Form**, **Participant Informed Consent**, and **Authorization for Use or Disclosure of Health Information** are stored in a locked cabinet until they are sent to RTI. At the end of each week, during the data collection period, each site's study coordinator will send all **Patient Packets** from the week to RTI via overnight courier.

D. Storage of Data at the Central Facility

For this study, RTI is the Central Facility for data storage and study data analysis. A medical institution, yet to be determined, will act as the Central Facility for clinical issues and will evaluate the images and determine organ volume measurements from stored 3-D volume datasets.

Once a **Patient Packet** is received by RTI, it will be checked to ensure that all forms are present, complete, and legible and that the CD/DVD containing the 3-D volume dataset is present. An incomplete **Patient Packet** will trigger contact with the site to request the missing materials. Only patients with complete data, including signed **Participant Informed Consent** and **Authorization for Use or Disclosure of Health Information**, will be included in the data database. After the materials have been checked in, the patient's CD/DVD will be copied. The original CD/DVD and two **Central Facility 3-D Evaluation Forms** will be placed in an envelope. This envelope, referred to as a **Patient Evaluation Packet**, will be kept in a locked cabinet until it is sent, via overnight courier, to the sonographers at the Central Facility.

E. Retrieving the Data at the Central Facility

Both sonographers at the Central Facility will use the proprietary software that corresponds to the 3-D ultrasound machine on which the 3-D volume dataset was created. This is necessary because, at the present time, static images generated by ultrasound machines can be read by other computers but manipulation of the images can only be done using the proprietary software.

Each sonographer at the Central Facility will complete a **Central Facility 3-D Evaluation Form**. Once completed, both forms, and the patient's CD/DVD will be returned to the **Patient Evaluation Packet** and kept in a locked cabinet until sent to RTI via overnight courier. Once a packet is received by RTI, it will be checked to ensure that both forms are present, complete, and legible and that the CD/DVD containing the 3-D volume dataset is present. An incomplete packet will trigger contact with the sonographers at the Central Facility to request the missing materials.

Appendix K

Weekly Shipment Form

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Images

Site Name: ____________________________ Date of Shipment: _____/_____/______
Month Day Year

FedEx Tracking # ______________________

Materials included in this shipment:

For each Case ID included in this mailing, please place an "X" in the appropriate box for each form you are submitting. Please be sure to double check your work before mailing.

Case ID		
__ __ __ __ __	Consent Form 3-D Dataset CD/DVD	☐ Authorization for Use or Disclosure of Info Form ☐ 2-D and 3-D Data Form
__ __ __ __ __	Consent Form 3-D Dataset CD/DVD	☐ Authorization for Use or Disclosure of Info Form ☐ 2-D and 3-D Data Form
__ __ __ __ __	Consent Form 3-D Dataset CD/DVD	☐ Authorization for Use or Disclosure of Info Form ☐ 2-D and 3-D Data Form
__ __ __ __ __	Consent Form 3-D Dataset CD/DVD	☐ Authorization for Use or Disclosure of Info Form ☐ 2-D and 3-D Data Form
__ __ __ __ __	Consent Form 3-D Dataset CD/DVD	☐ Authorization for Use or Disclosure of Info Form ☐ 2-D and 3-D Data Form
__ __ __ __ __	Consent Form 3-D Dataset CD/DVD	☐ Authorization for Use or Disclosure of Info Form ☐ 2-D and 3-D Data Form
__ __ __ __ __	Consent Form 3-D Dataset CD/DVD	☐ Authorization for Use or Disclosure of Info Form ☐ 2-D and 3-D Data Form
__ __ __ __ __	Consent Form 3-D Dataset CD/DVD	☐ Authorization for Use or Disclosure of Info Form ☐ 2-D and 3-D Data Form
__ __ __ __ __	Consent Form 3-D Dataset CD/DVD	☐ Authorization for Use or Disclosure of Info Form ☐ 2-D and 3-D Data Form
__ __ __ __ __	Consent Form 3-D Dataset CD/DVD	☐ Authorization for Use or Disclosure of Info Form ☐ 2-D and 3-D Data Form
__ __ __ __ __	Consent Form 3-D Dataset CD/DVD	☐ Authorization for Use or Disclosure of Info Form ☐ 2-D and 3-D Data Form
__ __ __ __ __	Consent Form 3-D Dataset CD/DVD	☐ Authorization for Use or Disclosure of Info Form ☐ 2-D and 3-D Data Form

Distribution: Send original to RTI (with case materials), retain copy for your records.

Appendix L

Central Facility Evaluation of 3-D Volume Dataset Protocol

DRAFT

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Data Sets and Images

A. Abstract

This protocol specifies the steps the sonographers at the Central Facility will follow to determine organ volume measurements for the fetal head, heart, kidneys, adrenal glands, lungs, pancreas, liver, upper arms, and thighs and traditional 2-D measurements from stored 3-D volume datasets.

B. Introduction

This protocol assumes that the 3-D exam and organ volume measurements were completed following the **3-D Ultrasound and Organ Volume Measurements Protocol.** It is also assumes that the Central Facility, and the study sonographers at the Central Facility, adhere to AIUM policies and procedures, which were discussed in the **2-D Ultrasound Protocol**.

C. Preparation for Evaluation

Each of the sonographers will perform the same evaluation of each patient's 3-D volume datasets. Therefore, in each **Patient Packet** there are two copies of the **Central Facility 3-D Evaluation Form** (see Attachment A) as well as the patient's CD/DVD containing the 3-D volume dataset.

D. Evaluate the 3-D Volume Acquisitions

Evaluation of the images and determination of organ volume measurements can be done on the same type of machine that the images were obtained on or on a personal computer by using the proprietary software that corresponds to the machine from which the images were created.

Using the 3-D volume dataset contained on the patient's CD/DVD, the sonographer takes "traditional" 2-D measurements (crown-rump length, biparietal diameter, head circumference, abdominal circumference, and femur length). The sonographer records these measurements and the reasons for measurements that could not be obtained on the **Central Facility 3-D Evaluation Form.**

Then, following the procedures for determining organ volume measurements found in the **3-D Ultrasound and Organ Volume Measurements Protocol,** the sonographer determines organ volume measurements. The main distinction between the Central Facility evaluation and that done by the local site sonographer is that the Central Facility sonographers are asked to record the image quality for each organ and an overall rating of the 3-D image quality.

Attachment A

Central Facility 3-D Evaluation Form

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Images

Patient and Fetal Information Collected by Local Site (completed by RTI):

Patient's date of last menstrual period: _____/_____/_____
Month Day Year

Trimester:
- First
- Second
- Third

Fetal Age: _____weeks

Scan method(s):
- Abdominal
- Transvaginal

Number of fetuses _____ (If > 1 fetus, a separate 2-D and 3-D Data Form should have been completed)

Fetal presentation:
- Cephalic
- Transverse
- Breech

To be Completed by Central Facility Sonographer:

1. Date of Evaluation: _____/_____/_____
Month Day Year

2. Record the 2-D Measurements (check box if not measured)

a. Crown-Rump Length (CRL):	_____mm	not measured
b. Biparietal Diameter (BPD):	_____mm	not measured
c. Head Circumference (HC):	_____mm	not measured
d. Abdominal Circumference (AC):	_____mm	not measured
e. Femur Length (FL):	_____mm	not measured

3. PLEASE STATE REASONS FOR ANY "NOT MEASURED" IN QUESTION 2:

_____

_____

_____

4. Sonographer's name: _____
First Last

5. Determine the organ volume measurements from the 3-D volume datasets (check box if unable to determine volume). Indicate the image quality (4=Excellent, 3=Adequate, 2=Poor, 1=Inadequate)

a. Head	_____	unable to determine	Image quality _____
b. Heart	_____	unable to determine	Image quality _____
c. Right kidney	_____	unable to determine	Image quality _____
d. Left kidney	_____	unable to determine	Image quality _____
e. Right adrenal gland	_____	unable to determine	Image quality _____
f. Left adrenal gland	_____	unable to determine	Image quality _____
g. Right lung	_____	unable to determine	Image quality _____
h. Left lung	_____	unable to determine	Image quality _____
i. Pancreas	_____	unable to determine	Image quality _____
j. Liver	_____	unable to determine	Image quality _____
k. Right upper arm	_____	unable to determine	Image quality _____
l. Left upper arm	_____	unable to determine	Image quality _____
m. Right thigh	_____	unable to determine	Image quality _____
n. Left thigh	_____	unable to determine	Image quality _____

6. STATE REASONS FOR ANY "UNABLE TO DETERIME" IN QUESTION 5:

_____

_____

_____

_____

_____

7. SONOGRAPHER COMMENTS REGARDING LOCATING AND DETERMINING ORGAN VOLUME MEASUREMENTS FROM 3-D VOLUME DATASET (TIME, TECHNICAL CHALLENGES, ETC):

_____

_____

_____

_____

_____

_____

_____

8. SONOGRAPHER OVERALL RATING OF 3-D IMAGES QUALITY

Excellent □
Adequate □
Poor □
Inadequate □

Appendix M

Central Facility 3-D Evaluation Form

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Images

Patient and Fetal Information Collected by Local Site (completed by RTI):

Patient's date of last menstrual period: _____/_____/_____
Month Day Year

Trimester:
- First
- Second
- Third

Fetal Age: _____weeks

Scan method(s):
- Abdominal
- Transvaginal

Number of fetuses _____ (If > 1 fetus, a separate 2-D and 3-D Data Form should have been completed)

Fetal presentation:
- Cephalic
- Transverse
- Breech

To be Completed by Central Facility Sonographer:

1. Date of Evaluation: _____/_____/_____
Month Day Year

2. Record the 2-D Measurements (check box if not measured)

a. Crown-Rump Length (CRL):	_____mm	not measured
b. Biparietal Diameter (BPD):	_____mm	not measured
c. Head Circumference (HC):	_____mm	not measured
d. Abdominal Circumference (AC):	_____mm	not measured
e. Femur Length (FL):	_____mm	not measured

3. PLEASE STATE REASONS FOR ANY "NOT MEASURED" IN QUESTION 2:

_____

_____

_____

4. Sonographer's name: _____
First Last

5. Determine the organ volume measurements from the 3-D volume datasets (check box if unable to determine volume). Indicate the image quality (4=Excellent, 3=Adequate, 2=Poor, 1=Inadequate)

o. Head	_____	unable to determine	Image quality _____
p. Heart	_____	unable to determine	Image quality _____
q. Right kidney	_____	unable to determine	Image quality _____
r. Left kidney	_____	unable to determine	Image quality _____
s. Right adrenal gland	_____	unable to determine	Image quality _____
t. Left adrenal gland	_____	unable to determine	Image quality _____
u. Right lung	_____	unable to determine	Image quality _____
v. Left lung	_____	unable to determine	Image quality _____
w. Pancreas	_____	unable to determine	Image quality _____
x. Liver	_____	unable to determine	Image quality _____
y. Right upper arm	_____	unable to determine	Image quality _____
z. Left upper arm	_____	unable to determine	Image quality _____
aa. Right thigh	_____	unable to determine	Image quality _____
bb. Left thigh	_____	unable to determine	Image quality _____

6. STATE REASONS FOR ANY "UNABLE TO DETERIME" IN QUESTION 5:

_____

_____

_____

_____

_____

7. SONOGRAPHER COMMENTS REGARDING LOCATING AND DETERMINING ORGAN VOLUME MEASUREMENTS FROM 3-D VOLUME DATASET (TIME, TECHNICAL CHALLENGES, ETC):

_____

_____

_____

_____

_____

_____

_____

8. SONOGRAPHER OVERALL RATING OF 3-D IMAGES QUALITY

Excellent □
Adequate □
Poor □
Inadequate □

Appendix N

Analysis of Stored 3-D Ultrasound Exam Data and Creation of a Final Dataset without Identifiers Protocol

DRAFT

Testing Feasibility of 3-D Ultrasound Data Acquisition and Reliability of Data Retrieval from Stored 3-D Images

1.0 Abstract

This protocol has been developed to describe the methods for treating the data collected in the 3-D pilot study and includes cleaning the data, merging the two sets of measurement data, analyzing data according to the guidelines in the Work Assignment, and producing a final dataset without identifiers that will be delivered to EPA. This protocol assumes the steps outlined in the **Protocol for Data Transmission** have been followed.

2.0 Cleaning and Compiling Data

We will review the hardcopy documents to ensure the data recorded on them can be entered, (i.e., the data are legible) and to code text responses.

We will develop an application using Entrypoint Plus to enter the measurements data under program control. We will re-key 100% of the data to ensure keying accuracy.

After the data are entered and verified, we will convert the database to a SAS dataset and perform range checks, skip pattern checks, and consistency checks to ensure the data are accurate and consistent. Frequencies of each item will be generated to identify outliers and unexpected values.

While the patient consent forms and HIPAA authorizations will be returned to RTI, the only data entry associated with these documents will be an indication of their receipt. A variable will be added to each patient's record in the database for HIPAA authorization and patient consent so only data for persons for whom RTI received completed consent and HIPAA authorization will be included in the analysis.

RTI will merge site derived and central facility derived sets of measurements for each patient and then create recoded and derived variables that are needed for analysis. This compiled dataset will be used to perform the analyses.

3.0 Analysis of the Data

As detailed in the work assignment, the analysis will include:

- Comparative analyses of the "traditional" 2-D measurements obtained during the 2-D exam and derived from stored 3-D volume datasets.
- Comparative analyses of organ volume measurements done by sites from 3-D volume datasets and those done by the central facility using stored 3-D volume datasets.
- Inter-observer variability in measurements made by sonographers at the central facility using stored 3-D volume datasets.
- Assessment of respondent, and site, burden and acceptance.

3.1 Comparative analyses of the "traditional" 2-D measurements obtained during the 2-D exam and derived from stored 3-D volume datasets

The measurements to be compared from 2-D and 3-D data are already in the same format at this point, such as femur length in millimeters. Several measurements are of interest, including crown-rump length, biparietal diameter, head circumference, abdominal circumference and femur length. Due to sonographer effect and other factors that are not controlled in the study, these measurements are expected to be correlated. Multivariate Analysis Of Variance (MANOVA) is a statistical method to evaluate the difference in correlated measurements and to estimate the variance components from various factors that influence the accuracy of the measurements. This method will be used to test the equality of the 2-D and 3-D measurements and estimate the difference if any. Each pair of the 2-D and 3-D measurements are taken from the same fetus, thus the observation is the difference of the pair and the test of the equality of the measurements from 2-D and 3-D data becomes the test to see if the mean of the difference is zero. We will build a random effect into the model to reflect the variation induced by the sonographers and model the observational error as a function of the image quality. It is expected that when the image quality is good, the observational error will be small, while when the image quality is poor, the observational error will be large.

3.2 Comparative analyses of organ volume measurements done by sites from 3-D volume datasets and those done by the central facility using stored 3-D volume datasets

We assume that data quality is not reduced due to transmission and storage of the data, because the data is transmitted and stored in digital form throughout the process. Thus, the major source of variation between the sites and the central facility would be human factors. MANOVA will also be used for this part of the analysis.

The model will be used to:

- Evaluate any systematic difference in organ volume measurements determined by sites and by the central facility.
- Estimate and compare the variances from various sites and the central facility.

Again, the image quality will be reflected in the error structure by modeling the variance of the error as a function of the image quality.

3.3 Inter-observer variability in measurements made by sonographers at the central facility using stored 3-D volume datasets

Two sonographers at the central facility will evaluate each 3-D volume dataset. Therefore, we will be able to estimate the variability due to sonographers at the central facility. Since only one local site sonographer will evaluate the 3-D volume dataset for organ volume measurements, data from all sites will be considered collectively to estimate the variability among the sites. We will test the equality of the variances at the central facility and at the sites. Various assumptions used in the model will be carefully examined by residual analysis to make sure all assumptions are reasonable.

We will be using Multivariate Analysis Of Variance model to evaluate:

- Any systematic difference in organ volume measurements, and
- Variance components due to various factors, such as observer and image quality.

Based on the results of the study, we will suggest a calibration procedure to correct any systematic difference.

3.4 Assessment of respondent, and site, burden and acceptance

We will produce descriptive statistics on the respondent burden and acceptance and reasons for not agreeing to participate in the study (3-D exam). In addition, we will produce descriptive statistics on the site burden. The assessment will include tables showing:

- The number and percentage of patients who are asked and refuse to participate in the study by their reason(s) for refusal
- The number and percentage of patients by their concerns and views about the 3-D exam
- The mean and variance of the time required to perform the 3-D volume acquisitions
- The mean and variance of the time to determine the organ volume measurements from 3-D volume datasets at the site and the central facility

4.0 Protocol for Creation of Data Set (without identifiers)

RTI will create a dataset that includes all variables, excluding identifying variables, for delivery to EPA. RTI will prepare a codebook for the data file and deliver it along with the data in either a fixed-format text file, SAS dataset, SPSS dataset, or other agreed upon format via CDs. The 3-D volume datasets, which will be identified by a study case identification number and not a patient name or other identifying information, will be delivered to EPA at the conclusion of the project. RTI will not maintain study data.