

Is transabdominal sonography comparable to transvaginal sonography for eligibility assessment prior to medical abortion?

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Project summary

Ultrasound use in the assessment of medical abortion eligibility varies by practice site. The National Abortion Federation (NAF), the Society of Family Planning (SFP), and the World Health Organization (WHO) guidelines do not recommend the routine use of ultrasonography; however, many institutions and practices still require this as part of clinic protocol. Furthermore, many clinicians routinely perform transvaginal sonography (TVS), a more invasive assessment than transabdominal ultrasound (TAS). Reliance on ultrasound in general, and TVS specifically, decreases access to medical abortion by requiring facilities to purchase and maintain an ultrasound machine, employ trained staff, and perform high-level disinfection (HLD) between examinations. Studies have investigated ways to improve access to medical abortion through a variety of approaches to simplifying care and removing barriers in a variety of practice settings.

Our project takes a health services research approach to simplifying medical abortion. We will perform a multicenter, randomized controlled trial in practices that routinely use TVS to compare how often clinicians order additional testing prior to medical abortion after the use of either TVS or TAS to assess medical abortion eligibility. We plan to study providers of different clinical backgrounds and in different clinical settings. We anticipate enrolling approximately 800 patients receiving care from about 30 providers over 6-8 months. Clinicians who routinely provide medical abortion with TVS at Columbia University Medical Center (CUMC) and Planned Parenthood of Central and Greater Northern New Jersey (PPCGNNJ) will participate.

Women who present for medical abortion will be eligible for this study, and will undergo a routine evaluation including relevant history, abdominal examination, and randomization to receive either TVS or TAS. Following evaluation, providers will make a clinical decision regarding the patient's eligibility for medical abortion, and will proceed with usual care. We will evaluate the proportion of women in the TVS and TAS groups for whom providers ordered additional testing or additional visits prior to making a decision regarding eligibility.

Our primary study outcome will be the proportion of women whose clinician orders additional evaluation after sonography and prior to determination of medical abortion eligibility. We hypothesize this proportion will be greater among those randomized to TAS (non-inferiority boundary of 80%). That is, if clinicians order additional testing in less than 20% of women undergoing TAS, we will consider TAS to be non-inferior to TVS.

Our second major outcome will be patient satisfaction after ultrasound examination. We hypothesize satisfaction will be greater among those randomized to TAS. Following study activities, each participant will complete a satisfaction questionnaire regarding the type of ultrasound she received (TVS or TAS) using a visual analog scale (VAS) and be asked, if she were to require an ultrasound in the future, which she would prefer.

The results from this study could demonstrate that when TAS is used, clinicians order additional testing in a greater proportion of patients than when TVS is used. However, we hypothesize this difference in proportions will fall within a non-inferiority boundary of 80%. Although we expect a difference, we anticipate that this difference in proportions will not be so large that using TAS instead of TVS will be burdensome to providers, clinics, or patients. Many providers in the US already have TVS capabilities and HLD, and may desire to continue using this tool. For such providers, however, switching from TVS to TAS for most patients could reduce costs and increase patient satisfaction. For potential providers who do not have TVS capabilities, our results will help to estimate how often TAS would be sufficient to provide care versus how often patients might need a referral for additional testing.

1. Description of the project

1.1 Rationale and objectives of the study

1.1.1 Rationale

Medical abortion accounts for an increasing proportion of abortions performed in the United States; as of 2012, 20.8% of all abortions were medical abortions.¹ Medical abortion use, however, lags behind the large increase in access some, including Finer and colleagues, anticipated when mifepristone was first introduced in the United States; most medical abortions are still performed by physicians and at facilities where surgical abortion is also offered.^{2,3,4} Many barriers to access remain, including the routine reliance on ultrasound for pregnancy dating, supported by legislative requirements as well as specific clinic protocols and provider preferences.^{5,6} Routine use of ultrasonography and particularly TVS may be a holdover secondary to its use in early clinical trials of medical abortion efficacy - its use has remained a part of many providers' clinical practice despite evidence that it is not always necessary. Proposals to improve access include simplification of the medical abortion process by eliminating routine sonography, eliminating the initial in-person visit,⁷ home use of mifepristone,^{8,9,10} involving more non-physician clinicians in care,^{11,12,13,14,15} increasing services offered in the primary care setting,^{16,17,18,19} allowing for remote forms of follow-up,^{20,21,22,23,24} and numerous other proposed strategies.^{25,26,27} Many of the approaches under investigation are either directly or indirectly related to telemedicine, which is increasingly being used in clinical settings to increase access to care, both in the rural United States, and around the world, and is acceptable to both patients and providers.^{28,29,30,31,32,33,34,35}

Many U.S. abortion providers will not prescribe mifepristone (Mifeprex) for first trimester medical abortion without confirming early intrauterine pregnancy (IUP) by ultrasound, and these early dating ultrasounds are commonly performed transvaginally. Without ultrasound, providers are concerned about underestimating gestational age or missing a miscarriage or ectopic pregnancy. Although ectopic pregnancy is rare among women seeking abortion,^{36,37,38} serious morbidity could occur due to delayed diagnosis. Organizations including NAF,^{39,40,41} WHO,⁴² the American College of Obstetricians and Gynecologists (ACOG),⁴³ and others^{44,45} recommend ultrasonography at the physician's discretion. The Mifeprex prescribing information also supports ultrasound only as needed,⁴⁶ yet many sites still require this as part of standard clinic protocol.

The routine use of TVS or TAS requires facilities providing medical abortion to purchase and maintain an ultrasound machine and employ trained and certified staff. TVS (but not TAS) additionally requires the use of HLD between examinations.⁴⁷ These factors can be burdensome or even prohibitive in many clinic settings. HLD requirements are particularly cumbersome; HLD requires expensive equipment up front, expensive supplies (including the proprietary disinfection solution) on an on-going basis, and costly replacement of probes which degrade with repeated transfers and disinfection. Furthermore, the time required for disinfection between patients interferes with clinic flow and operations. For example, the Trophon EPR high level disinfection system has a 7.5 minute disinfection cycle. In addition, providers or staff must detach the probe from the US machine, wipe off the ultrasound gel, run the disinfection cycle, wipe off the chemical solution, and replace the probe, a process that can easily take 15 minutes. Less expensive HLD systems take even longer, with some disinfection cycles lasting up to 45 minutes, and also may require clinics to have negative pressure ventilation systems to avoid toxicity from the disinfectant. The Centers for Disease Control and Prevention (CDC) has stringent guidelines on both instrument maintenance and healthcare facility auditing.^{48,49} Hospitals are generally in compliance secondary to Joint Commission requirements; however, few practices and clinics are in compliance given these onerous requirements and related costs.

Studies have examined outcomes of medical abortion provided in settings without routine use of ultrasound (such as many locations outside the United States), discussed below in section 1.2. In the proposed study, we will quantify the proportion of women whose providers order additional testing to determine medical abortion eligibility and will compare this proportion between those who received TVS and those who received TAS. We will assess patient satisfaction with each method of ultrasound and compare these results. Our literature review yielded no prior studies examining outcomes of TVS compared with TAS, nor are there any randomized controlled trials including acceptability as an outcome. We will collect data from a range of providers who currently routinely rely on TVS.

This study, specifically, would be of value for the many clinicians who currently use TVS for all medical abortion patients and could support using TAS rather than TVS in a majority of these patients. The results could also provide guidance on how often practice settings without TVS and HLD would be able to provide medical abortion, and for which patients. Such settings could include primary care or rural clinics, any low volume clinics, or those where the costs and time associated with the HLD required for use of TVS prohibit or limit the provision of medical abortion. In addition, even high-volume specialty family planning clinics would benefit from a reduction in use of TVS. One of our collaborators anticipates the cost of implementing HLD in their clinical setting would be at least \$100,000 in capital costs alone. If TVS is used infrequently, a busy clinic could make do with one HLD system. However, if every patient receives TVS, the costs associated with such frequent HLD use will be much higher. If our results show routine use of TAS only requires a small increase in the proportion of patients who receive additional testing prior to medical abortion, it could be both cost-effective and possibly more satisfactory to women to provide TAS for most patients. Cost savings could come from decreased use of HLD itself, increased lifespan of transvaginal probes, decreased time spent for patients to undress and dress for exams, and overall streamlined patient flow. We therefore propose a randomized controlled trial aimed at improving the health care processes around provision of medical abortion and provider assessment of eligibility.

In the US, many providers have sonography available and use it routinely. However, even in the US, many clinics may seek to offer medical abortion without sonography, and other researchers are studying this type of approach. This proposed study will evaluate a more intermediate change in practice, primarily geared towards the large number of providers who routinely provide transvaginal ultrasound. For those providers, moving from TVS to TAS could be both cost effective and acceptable to patients.

1.1.2 Objectives and hypotheses

We hypothesize that for the majority of patients seeking medical abortion, history plus TAS will be comparable (non-inferior) to history plus TVS in the assessment of medical abortion eligibility. In our own recent clinical experience, approximately 5.1% (standard error 2.0%) of patients required further clinical testing after TVS before determination of eligibility. Conversely, 94.9% of patients did not require additional testing. Our objectives include:

Primary Outcomes:

1. **Hypothesis 1:** We hypothesize that history and TAS will be sufficient to determine eligibility in more than 80% of patients (thus our non-inferiority boundary is 80%).
 - a. Evaluate how often the provider orders additional tests (see table 1, in Appendix) prior to providing medical abortion, but after:
 - i. History plus TAS or,
 - ii. History plus TVS
 - b. Evaluate whether the results for TAS exceed the non-inferiority boundary of 80%

2. Hypothesis 2: We hypothesize that patient satisfaction and acceptability will be greater for TAS compared to TVS, based on visual analog scale rating performed by patients following visit. We found no direct data to inform us about the likely size of the difference in acceptability of TVS compared to TAS, as this has not previously been studied (see Section 1.2).
 - a. Assess which ultrasound modality is preferable (“In the future, if you had the choice to receive either TVS or TAS, which would you prefer?”)
 - b. Evaluate if acceptability varies according to patient characteristics including:
 - i. Gestational age
 - ii. Ultrasound experience
 - iii. Abortion or other obstetric experience
 - iv. Additional factors (e.g. age)

Secondary Outcomes: Identify patient and provider characteristics associated with ordering additional tests:

- a. Gestational age (GA) by LMP (≤ 35 days vs. 35-49 days vs. > 49 days, vs. uncertain GA)
- b. Body mass index (BMI) and history of Cesarean delivery
- c. Provider type or experience (physician, APC)
- d. Site (CUMC, PPCGNNJ)
- e. Secular trends within the study (first third of patients seen by providers vs. last third of patients)
- f. Early pregnancy failure

Note: The use of sonography or other strategies for follow-up and cost-effectiveness analyses are also important, but are beyond the scope of this project.

1.2 Previous related studies

As noted in section 1.1.1, related studies include those comparing various methods of pregnancy dating to one another, as well as those that more specifically consider outcomes of medical abortion when ultrasound is only used “as indicated,” and not routinely. Some of these have examined the overall effectiveness and safety of medical abortion outside of the United States, often in places without access to ultrasound, or where it is not used on a routine basis, revealing few complications or adverse events.^{50,51,52,53,54} Multiple studies have evaluated the use of any ultrasound prior to medical abortion,^{55,56,57,58,59,60,61} including two review articles suggesting that in most cases clinicians can use LMP to estimate gestational age and routine sonography is unnecessary.^{62,63}

None of these studies compared TVS and TAS for determining gestational age or eligibility, need for further testing, or patient acceptability. In 2011, Kulier and Kapp⁶⁴ performed a review to determine whether the use of pre-abortion ultrasound had an effect on safety or efficacy, but found no published data addressing this question.

Despite the evidence provided by previous studies, the largest medical abortion provider in the US, Planned Parenthood Federation of America (PPFA), routinely uses TVS for most patients seeking medical abortion. CDC recommendations for HLD of all endoprobes, however, make continued routine TVS use unsustainable. Given the great scrutiny PPFA receives, the organization will only change its guidelines in this regard with high quality evidence supporting an alternative and reliable method of pregnancy dating.

While many providers continue to routinely use ultrasound, TAS may be a less costly, more widely available, and acceptable alternative to TVS. Lohr et al⁶⁵ compared TAS to TVS prior to medical abortion

and found that abdominal sonography was 100% sensitive for detecting a gestational sac but only 68% sensitive for detecting an embryonic pole; the sensitivity decreased further as BMI increased. This study did not address practice implications of switching to TAS. We have found no prior studies looking at whether women who receive TAS prior to medical abortion then undergo more additional testing compared to TVS. This question is particularly important because of the dramatic new expenses related to implementing HLD requirements.

Research on the acceptability of ultrasound modalities for patients is also limited. One study from 1997 considered acceptability of TVS in the first trimester, finding that it was overall acceptable and well-tolerated.⁶⁶ Others have assessed the acceptability of TVS for diagnostic purposes (such as assessing follicular development and ruling out pelvic pathology).⁶⁷ One small study evaluated acceptability of TVS in 107 women presenting with vaginal bleeding in the first trimester, finding that 99% would agree to have a TVS if needed in the future.⁶⁸ While women in these studies found TVS acceptable, no randomized trials evaluate acceptability of these ultrasound modalities in women presenting for abortion. We were unable to find prior studies using a VAS to quantify patient satisfaction for a diagnostic test such as ultrasound, as most similar studies use a Likert scale or other measurement tools.

1.3 Design and methodology

1.3.1 Research design and general methodological approach

This will be a randomized controlled trial comparing TAS to TVS in medical abortion eligibility assessment. With this trial, we aim to improve healthcare processes under real-world conditions at specific clinics where providers now routinely use TVS prior to medical abortion. We will consult the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 guidelines^{69,70} and the CONSORT guidelines, specifically the Practihc (Pragmatic Randomized Controlled Trials in Health Care) reporting guidelines.^{71,72,73} Study protocols will closely match usual care at these sites to help ensure high generalizability of the results of this pragmatic trial.

To evaluate clinician practices at different sites, we plan to enroll women at a hospital-based clinic system (including sites serving Medicaid patients and a faculty practice serving commercially insured patients), and one Planned Parenthood affiliate. Sites will vary in location, ranging from urban clinics to large suburban practices. This will provide diverse study participants and providers. Please see Table 2 (in appendix) for further details on each potential site. Currently, these sites routinely perform TVS before medical abortion.

1.3.1.a: Sites

We will enroll participants at Columbia University Medical Center (CUMC) and Planned Parenthood of Central and Greater Northern New Jersey affiliate (PPCGNNJ). We met with Elizabeth Talmont, Vice President of Research Development at PPCGNNJ, to discuss our proposed study at length and visited these clinics. Clinics affiliated with CUMC and PPCGNNJ have relevant research experience, including randomized controlled trials and abortion research.

1.3.1.b: Participants

Study participants will include women with an estimated gestational age up to 70 days based on LMP, who desire medical abortion and present to any of our study sites for care. Study participants will complete a questionnaire regarding demographic information as well as experiences with abortion, including medical abortion specifically, delivery, miscarriage, TAS, and TVS. Further inclusion and

exclusion criteria are listed below in section 1.3.2. Study forms will not include any personal identifiers and all participants will be assigned study identification numbers to protect confidentiality.

1.3.1.c: Training, Study Coordinators

A study coordinator at each site will be on location during patient care sessions when medical abortion is provided. The study coordinator will obtain informed consent from all patients at time of enrollment. Study coordinators will also be responsible for ensuring completion of all study documents including: baseline patient and provider characteristics; information on history, physical exam, and imaging results via chart abstraction; and subsequent clinical outcomes for any individual who did not receive medical abortion on the date of study enrollment. As clinic charting and routine practice vary between sites (for example, PPCGNNJ uses paper charts while CUMC uses an electronic medical record system), study coordinators will receive standardized training on all study protocols and additional practice in chart abstraction based on study site.

Prior to study initiation, the investigators will practice chart abstraction for up to 100 charts from each clinical site to 1) improve abstraction tools and familiarize study staff with differing medical record systems, 2) ascertain a more precise estimate of the proportion of patients who need further testing, and 3) troubleshoot any potential problems. The investigators will then train the coordinators in chart abstraction prior to study initiation. Investigators will provide coordinators with 10 charts where further testing was ordered and 20 charts where no additional testing was ordered, to develop skills in relevant chart abstraction.

1.3.1.d: Training, Providers

Prior to participation, providers who routinely offer medical abortion at the study sites will complete a questionnaire regarding professional characteristics. Investigators will provide a training session for all providers at each site to review TAS (i.e. techniques and standardized reporting) as we assume some providers have less experience with this when compared to TVS in early pregnancy. This training session will help minimize differences in TVS and TAS related to provider experience or variability in current practice. In addition, prior to participant enrollment, each clinic site will have a one-week “run-in period,” during which providers will perform both TVS and TAS to accustom providers and clinic staff to study protocols. Study coordinators will abstract charts using study forms during this run-in period for all study endpoints.

1.3.1.e: Intervention

Using the appointment log, the attending physician will identify women scheduled for abortion services that match eligibility criteria and provide these names to the onsite study coordinator. The attending physician can delegate identifying eligible study participants to the onsite coordinator, depending on clinic flow and protocols. Coordinators will explain the study, enroll patients, obtain informed consent, and administer a baseline questionnaire.

All patients seeking medical abortion will undergo routine intake, history, and exam per regular clinic protocol. The study will not require additional testing outside of routine care, which can include a detailed menstrual and reproductive history, measurement of height and weight, or performance of a urine pregnancy test. Prior to ultrasound, study coordinators will provide the sonographer with a sealed, opaque, and sequentially numbered envelope indicating ultrasound assignment (TVS or TAS), and the appropriate test will be performed (see section 1.3.3 for additional details on randomization). After completion of the assigned ultrasound, the provider will use all available information to make a clinical

decision, and the woman will either proceed to receive a medical abortion or undergo further testing if required by the provider. We expect that some participants who do not require additional testing may decide to undergo surgical abortion, due to personal preference or due to gestation age and they will not be excluded from analysis.

Coordinators will abstract information from patient records regarding clinical characteristics (BMI), ultrasound results (including if a miscarriage was diagnosed), plan of care, and whether any further testing was ordered or performed (including type of testing). Coordinators will abstract this information within one week of the index visit. All study sites include this documentation in the clinical record.

1.3.1.f: Outcomes

After history and the assigned ultrasound examination, providers will make an assessment and clinical plan for that participant. That plan of care may include provision of medical abortion that day or additional testing (see Table 1). For example, if a provider is concerned about ectopic pregnancy, further testing could include a pelvic exam, transfer to the emergency department, or additional tests or interventions. Study coordinators will abstract the details of additional evaluation performed from patient charts.

While we will enroll only patients specifically presenting for medical abortion, we will collect data for women who are found to be at too advanced a gestational age to proceed with medical abortion, those who decide during the course of their evaluation that they would prefer an aspiration procedure, those who are diagnosed with miscarriage or ectopic pregnancy, and those who decide to continue the pregnancy.

At the end of their visit, study participants will complete a standardized questionnaire including a 100 mm visual analog scale (VAS) to assess the acceptability of the type of ultrasound they were randomized to receive. We will therefore be able to compare acceptability of ultrasound between women randomized to receive TVS or TAS. We will also ask whether these participants would prefer TVS or TAS in future gynecologic care.

In summary, the main outcomes of this study are: 1) how often the provider orders additional testing in each randomization group (TVS or TAS); and 2) patient acceptability scores for each US modality. Secondary outcomes will include subgroup analyses, including provider type, provider experience, site, and patient characteristics. However, we anticipate some limitations to such analyses based on sample size and will be focusing on the two primary outcomes.⁷⁴

1.3.1.g: Other

We will register our trial with ClinicalTrials.gov. Please see section 1.3.9 for more information regarding data management.

1.3.2 Criteria for selection of subjects

1.3.2.a: Inclusion criteria for providers and sites

Physicians (specializing in either Obstetrics/Gynecology or Family Medicine), nurse practitioners, and other advanced practice clinicians who provide medical abortion services and routinely use TVS prior to medical abortion are eligible for this study. All clinics selected for this study currently provide medical abortion up to 70 days from LMP. Our study will not require any change to current protocols used at these clinics when scheduling patients for medical abortion. All clinics use clinical charting (either EMR

or paper charts) which have pre-specified templates from which relevant data can be extracted, including all tests that have been ordered or performed.

1.3.2.b: Exclusion criteria for providers and sites

Providers who do not provide medical abortion services are not eligible.

1.3.2.c: Inclusion criteria for patients

Eligible patients include English- or Spanish-speaking women seeking medical abortion, 18 years or older. They will be at an estimated gestational age up to 70 days from LMP.

1.3.2.d: Exclusion criteria for patients

We will exclude women under 18 years old. Since parental consent is required for participation in research, inclusion of younger women could impair patient confidentiality. There are otherwise no study-specific exclusion criteria. If after enrollment, a woman proves to be at too advanced a gestational age for medical abortion (>70 days from LMP), elects aspiration abortion, has an ectopic pregnancy, or has an early pregnancy failure, she is still eligible for participation and will be included in the analysis.

1.3.3 Subject recruitment and allocation

Please see Table 2 for specific characteristics of proposed study locations, including details of each site's capacity and providers. These sites may change depending on workflow and patient volume. We plan to start enrollment at one CUMC site and one PPCGNNJ site; both sites are diverse in both patient and provider types. Once these sites are well-integrated, we will decide if we need to add more clinics to bolster participation and enrollment. We plan to include more sites as needed based on needed sample size and recruitment rate.

We will randomize patients to the type of ultrasound using a 1:1 ratio, stratified by site, with half of the participants at each site being randomized to receive TAS, and half to receive TVS. Block size will be created using simple randomization; block size will vary between 4 and 6. An investigator experienced with generating randomized sequences and not directly involved in this study will be responsible for creating the entire randomization schedule; first, by defining the sequence of block sizes and second, by defining the assignments within each block. Most of the fellows in the last decade in this division have carried out randomized trials as part of fellowship projects and thus division staff has substantial experience in generating the lists. The central research office at CUMC will prepare opaque, sealed envelopes containing cards indicating whether a given patient has been randomized to receive either TVS or TAS. These envelopes and cards will be sequentially numbered, corresponding to site, and sequentially numbered study enrollment logs. The allocation will remain concealed from the sonographer as well as the participant and provider until the coordinator provides the ultrasound randomization envelope to the sonographer, following the consent and enrollment process. The sonographer will open the sealed, opaque envelope immediately prior to the ultrasound examination, which will then be performed according to randomization assignment.

There will be no blinding. Even if the clinician providing care does not perform the ultrasound, by viewing the image and interpreting the results they would immediately be able to see if TVS or TAS was performed. It is also not feasible to blind study participants to the type of ultrasound being performed. A study in which participants undergo both types of US, but the clinician uses only one for clinical decision making would be possible, but would not improve on the planned study.

1.3.4 Description of the drugs and devices to be studied

All clinics participating in this study provide medical abortion using the evidence-based regimen of mifepristone and misoprostol. This includes mifepristone 200 mg orally on day 1 in the office, followed by misoprostol 800 mcg buccally 24-48 hours later, at home. Mifepristone, or Mifeprex, is manufactured by Danco Laboratories, LLC (P.O. Box 4816 New York, NY 10185). There are multiple manufacturers of misoprostol; at CUMC by Greenstone, LLC (100 Route 206 North Peapack, NJ 07977), and at Planned Parenthood of Greater and Central New Jersey by Novel Laboratories, Inc. (390 Campus Dr., Somerset, NJ 08873).

1.3.5 Admission procedure

The clinician in charge of clinic operations for a given patient care session will review their schedule and identify patients for potential enrollment, or they may delegate identification to an onsite study coordinator. The study coordinator will then approach all eligible patients and if the patient is interested and agrees to participate, obtain informed consent. Participants will undergo the assessment as described in section 1.3.1.e.

1.3.6 Follow-up procedure

This is a single-day study; follow-up evaluation of medical abortion is not a specific aim of this study and all participants will follow-up with their provider per each site's individual protocol. For example, at CUMC, enrolled participants will return for a repeat ultrasound and physical exam in 1-2 weeks to assess completion of medical abortion. For those patients who do not receive an abortion on the day of study enrollment, study coordinators will perform follow-up chart abstraction to ascertain eventual outcome (i.e. abortion performed at later date, surgical abortion performed, patient elected to continue pregnancy, ectopic pregnancy diagnosed, etc.). Study coordinators will also perform chart abstraction to record details about any additional testing ordered and final clinical outcome as available two weeks from the time of the enrollment visit.

1.3.7 Criteria for discontinuation

1.3.7.a: Provider component

Providers may choose to discontinue participation in this study at any point. We anticipate overall participation to last for at least four months and for at most eight months for each provider.

1.3.7.b: Patient component

Patients can withdraw from the study at any point. The duration of the study for each patient may vary; the patient may be present in the clinical environment for several hours from registration to discharge. However, study-specific activities for each participant will last no more than 1-2 hours.

1.3.8 Laboratory and other investigations

All women seeking abortion who are involved in this study will undergo a routine evaluation as part of routine care. This will begin with intake per clinic routine, followed by history, physical examination (vital signs, abdominal exam), and then either TVS or TAS depending on randomization. We will compensate clinical sites for the cost of additional testing beyond their usual practice in the group randomized to receive TAS, under the assumption that this group will undergo additional testing due to study participation, compared to those who receive TVS.

Ultrasound machines and HLD systems vary by site. At Planned Parenthood and CUMC, providers utilize the LOGIQ P5 ultrasound manufactured by GE Healthcare. Planned Parenthood will be utilizing the Trophon EPR HLD system manufactured by GE Healthcare and CUMC utilizes Cidex OPA, manufactured by ASP.

1.3.9 Data management

The CUMC Division of Family Planning and Preventive Services currently employs a research manager and five research coordinators who will be available to assist with this study. The research manager will assist the investigators with IRB preparation and submission, staff training manuals, and will carry out data monitoring. We will assign some study tasks to research coordinators depending on expertise and availability. If necessary, we will hire a new research coordinator to assist with data management.

We will collect all study data using paper forms. The central research office staff will obtain logs, distribute study forms to sites, and collect data for every 10-20 enrollments at each site, or at least on a twice monthly basis. Study coordinators will be responsible for abstracting data from all patient charts and using study forms to compile this information, as described in section 1.3.1.c. Investigators will review 10% of charts abstracted by study coordinators in order to assess adherence to standardized data collection and recording. Investigators will develop a study database in Research Electronic Data Capture (REDCap), a mature, secure, web-based application for building and managing surveys and databases. This system has been IRB-approved for use here at CUMC and research office staff is familiar with its use. Using single data entry, research staff will enter all data from research forms into this database. Following data entry, all forms will be stored in a locked file cabinet in the research office until study completion and manuscript publication.

All staff members involved with data management will be required to complete CUMC's Research Compliance and Administration System (RASCAL) and HIPAA trainings. Only research team members will be permitted access to study data. All data will be managed on CUMC-encrypted computing devices which are password-protected, fire-walled devices linked to a secure server located within the Department of Obstetrics and Gynecology.

1.3.10 Data analysis

First, we will evaluate baseline characteristics of all women entered into this study. We will also evaluate if randomization was successful in creating comparable groups. We will use a test of difference in proportions to compare outcomes in this study. We will compare the overall proportions with additional testing. We will also compare acceptability of TVS vs. TAS and assess satisfaction. For our secondary analyses, we will compare subgroups defined by provider and provider type, clinic site, and based on clinical characteristics including GA, BMI, and previous C/S. We will evaluate whether there is a difference in the proportion receiving additional tests in the TVS and TAS groups that is associated with any of these variables (physician provider compared to APC provider, Ob/Gyn physician compared to Family Medicine physician, obese participant compared to normal weight participant, etc.). We will use SAS to analyze our findings, as both fellows currently have access to SAS and use it routinely as part of graduate school studies.

1.3.11 Number of subjects and statistical power

This randomized study among women seeking medical abortion will compare the proportion of women who require additional testing after either TVS (usual care) or TAS (the intervention). The study also will

compare patient satisfaction with TVS compared to TAS. The first objective (comparing rate of additional testing) drives the sample size calculations. Table 3 provides the results; below we present our analysis.

Our estimate of additional testing ordered after TVS comes from our own clinic where a new fellow without previous medical abortion experience ordered additional tests (see table 1) in 9 out of 120 patients (7.5%, standard error $\pm 2.4\%$). On further analysis, 3 of these patients had previously been seen for possible miscarriage or pregnancy of unknown location. Therefore, 6 of 117 patients referred specifically for medical abortion received additional testing (5.1%, standard error $\pm 2.0\%$). The main reason for ordering additional tests was the inability to identify an intrauterine pregnancy by TVS. Most of these patients received a combination of serial quantitative hCG levels or repeat sonography; all were ultimately found to have very early intrauterine pregnancies identified upon follow-up. The rate of additional testing ordered might be lower in the hands of more experienced clinicians and sonographers; however, we are unaware of any other estimates. Performing additional chart abstraction in preparation for the study (described above) will permit a more precise estimate of further testing at these sites.

Our base assumption is that 5-7.5% of patients will need additional testing after TVS. We also expect to see the greatest variability between TVS and TAS findings between 35 and 49 days estimated gestational age, compared to those less than 35 days and greater than 49 days. Prior to 35 days, we expect neither TVS nor TAS to be able to identify a gestational sac for most women (thus resulting in additional testing in both groups), and after 49 days we expect both TVS and TAS to usually be able to identify a gestational sac with fetal pole (thus resulting in less additional testing in both groups). Between 35 and 49 days, however, we expect some proportion of patients to have a gestational sac with or without a yolk sac identifiable on TVS but not on TAS and in this range, the proportion of patients for whom clinicians order additional tests may be higher. We expect the proportion where providers encounter uncertainty, leading to additional testing, would be greater at earlier gestational ages and perhaps in those patients with an uncertain LMP or irregular cycle (questions we will be formally evaluating as described in Hypothesis #1, section 1.1.2).

Further, we expect clinicians to order more testing after TAS because TAS has lower resolution than TVS. The transabdominal probe is further from the uterus, and thus uses a lower frequency to achieve a longer focal length. TAS typically uses a 3-6 mHz probe while TVS uses a probe with 5-10 mHz frequency. TAS may have even less resolution in an obese patient as the distance to the uterus will be greater; obesity's effect of decreasing resolution was noted in a prior study by Lohr et al.⁶³

We expect additional testing after TVS to mainly include serial quantitative beta-hCG tests and additional visits for a repeat sonogram. We expect that additional testing after TAS would include the same, plus same-day use of TVS if TAS inadequate to confirm eligibility for medical abortion. At all study sites, immediate TVS will be available

We have no expectation that TAS would be equal or superior to TVS in identifying an early IUP, therefore, we will calculate the sample size for the planned study based on identifying a non-inferiority margin and using a one-sided alpha level. We will consider a large margin of inferiority to be acceptable in this comparison for two reasons. First, some additional testing following TAS use may be acceptable because the large reduction in the need for HLD (by decreasing use of TVS) would enhance clinic operations and thus ultimately benefit patients. Second, clinical anecdotes indicate that patients prefer TAS to TVS because they don't need to get undressed and because it is a less intrusive and uncomfortable examination. Thus, even if using TAS might require additional testing more often, we expect that this trade-off would be acceptable to patients and to clinic managers. The second primary objective of the proposed study will evaluate the existence and strength of the (possible) preference for TAS over TVS. If patients prefer TAS, clinicians will need to consider this a trade-off with additional testing.

The program for calculation of sample size for non-inferiority tests comes from GJ Stoddard.⁷⁵ We set alpha at 0.05, and are performing a one-sided test as we do not expect that TAS would be superior to TVS. We evaluated a number of alternative assumptions, including power of 80% and 90%, a p_1 (following TVS) of 5% and 10%, a p_2 (following TAS) of 10%, 15% and 20%, and a non-inferiority margin of 15% - 25%, and we show select results in Table 3. We will be basing our analysis on an inferiority boundary of 80%, as shown in row 1 of this table ($p_1=5\%$ and $p_2=10\%$).

Table 3: Non-inferiority measures for 1-sided hypothesis test (one-sided α of 5%, power of 80%)

p_1 (TVS)	p_2 (TAS)	Inferiority Margin	Inferiority Boundary	n (number of participants per arm)
5%	10%	-10%	80%	340
7.5%	15%	-10%	75%	394

1.3.12 Study limitations

Our project is a randomized controlled trial that will aid us in better answering the question of whether TAS provides sufficient information or changes the need for further testing to determine medical abortion eligibility, when compared to TVS. Providers' judgment still may have an important effect on our clinical outcomes, however, our endpoint is whether the provider orders a test or not.. Subjectivity is certainly possible, even likely, but our design replicates the real-world healthcare setting in which providers currently routinely use TVS. We are using the PractiHC extension to the CONSORT guidelines to assist us in designing this study in a way that will provide useful information for our health-services study question.

We anticipate possible differences in outcomes based on provider type and experience. For this reason, we are attempting to include a variety of providers and analyze these differences, as discussed above. We may have difficulty enrolling a sufficient number of patients for certain provider types (such as family physicians) to demonstrate any real differences in proportions between groups and are therefore not basing our power calculations on such planned analyses. We visited multiple family medicine clinics in preparation for this study, but ultimately excluded these study sites due to low medical abortion volume. Additional details regarding practice volume at proposed study sites within CUMC and PPCGNNJ are included in Table 1.

1.3.13 Duration of project

The anticipated duration of this project will include eight months for enrollment and an additional six months for data analysis.

1.4 Project management

The primary faculty mentor for this study is Dr. Carolyn Westhoff, with additional mentorship by Dr. Anne Davis. Planned Parenthood of Central and Greater Northern New Jersey is the only site outside of CUMC where we will be enrolling providers and patients. Annie Fu will be primarily responsible for analyzing data regarding the proportion of women who receive additional testing and Caitlin Weber will be focusing on analysis of the patient satisfaction data. Both fellows will share responsibility for preparation of study documents and protocols, and for training providers and coordinators on study protocols. Both fellows will also analyze data regarding secondary outcomes, following work on primary outcomes.

1.5 Links with other projects

Gynuity Health Projects is currently running a single-arm trial with approximately 300 participants evaluating “no-touch” medical abortion. While not directly linked, our study’s findings will complement their research and contribute to the body of literature on methods of determining medical abortion eligibility that could help improve access and decrease costs.

1.6 Main problems anticipated

We anticipate some challenges integrating study protocols with preexisting workflows at the research sites. Some locations use ancillary staff for portions of the patient evaluation, such as medical assistants collecting basic history information, or other staff members performing sonography. To assess any disruption in workflow and associated redundancies or delays, we interviewed multiple medical abortion providers, including those working at our proposed study sites, to clearly identify the range of clinic workflows, and consider approaches to integrating study protocols that would be less disruptive. We anticipate that the main potential disruption to workflow would be utilizing TAS instead of a routine TVS in these sites where it is not currently performed routinely, and have planned provider training and a run-in period to mitigate this issue (see Section 1.3.1.d.).

We are planning this project as a multicenter study, which we expect to introduce some additional challenges. While initially envisioned as a larger study at multiple sites outside of our own institution, in order to minimize challenges with IRB approval, we will enroll only providers at CUMC and PPCGNNJ and we will therefore only require CUMC and PPCGNNJ IRB approval. In addition, PPCGNNJ sites are easily accessible by public transportation and car.

This Planned Parenthood affiliate also has research experience including current participation in a large multicenter trial investigating self-administration of Depo Provera, being carried out by the Planned Parenthood Federation of America (PPFA) Research department. Dr. Westhoff is a co-investigator of that trial. This affiliate has excellent compliance with study protocols and has a skilled staff prepared to handle a randomized trial such as the one proposed in this study. PPFA’s study monitors have found these sites to have excellent adherence to research requirements.

1.7 Expected outcomes of the study and dissemination of findings

We anticipate that the difference in the proportion of patients receiving additional testing prior to medical abortion after TAS will fall within a non-inferiority boundary of 80% when compared to the proportion receiving additional testing after randomization to TVS, in sites where providers are currently routinely using TVS. As the proportion of women receiving TVS who need further testing is low, between 5-10%, we suspect the use of TAS instead will not change management for the majority of patients.

Some providers already forgo TVS in certain patients, but the results from this study could help demonstrate that even fewer patients require this step and help clinic administrators better anticipate costs, workflow, and staffing needs. By decreasing the use of routine TVS, many clinics could see a significant reduction in operational costs by avoiding the routine need for HLD after each patient. A switch to TAS could improve clinic workflow, help avoid a potentially unacceptable portion of the examination for patients, and increase access to care by allowing clinics without HLD capabilities to provide care for patients. Even if TAS results in 20% of patients requiring further testing, 80% of patients will not need additional evaluation. This is still an acceptable and desirable outcome as clinics can eliminate the need for HLD for 80% of patients.

Minimal research has examined patient acceptability during the medical abortion evaluation process and we identified no published data comparing acceptability with TVS and TAS. From prior research, TVS is an acceptable modality for the majority of patients, but some research has shown that use of TVS (in pregnant women) can carry “significant levels of psychological trauma.”⁷⁶ We suspect women may find TVS less acceptable than TAS due to its more invasive nature, but are interested to know if any particular patient characteristics are associated with differences in acceptability. We expect that eliminating routine use of TVS will lead to an improved, less invasive and more patient-centered clinical experience.

Following completion of this project, we intend to write manuscripts for publication, in addition to presenting findings in multiple venues including at our own institution and at the Fellowship in Family Planning Annual Meeting. We will also present these results to Medical Affairs at Planned Parenthood Federation of America and the National Medical Committee.

We see this project as a complement to other work attempting to simplify the medical abortion process, while still maintaining both high quality and patient-centered care. We hope that our work will contribute to the continually growing body of health services research.

2. Ethical considerations

2.1 Informed decision-making and confidentiality

Approval of the Institutional Review Board at CUMC and Planned Parenthood will occur prior to initiation of the study. All patient and provider information will be kept confidential, in accordance with Health Insurance Portability and Accountability Act (HIPAA) guidelines.

All participants will receive copies of consent forms following enrollment and provision of informed consent. Participants are able to withdraw from the study at any point during their visit. While this is a randomized study, we do not anticipate any significant risks to patients in either group.⁷⁷ For Spanish-speaking participants, all necessary forms and questionnaires will be translated into Spanish, and accuracy of translated materials verified and approved by CUMC Translation Center, in accordance with IRB requirements.

Study forms will not include any personal identifying information. All subjects will have a study identification number to protect patient confidentiality. A master file linking ID to the subject's name will be kept in the research office at CUMC as discussed in section 1.3.9.

Personnel

Annie Fu, MD (40% effort) and **Caitlin Weber, MD** (40% effort) are the primary investigators. Dr. Fu will predominantly be responsible for the Planned Parenthood clinical sites and Dr. Weber will assume responsibility over the CUMC clinical sites. They will develop the quantitative instruments for the study and will assume overall responsibility for research coordinator training, data collection, statistical analyses, and manuscript preparation. They will recruit all of the providers into the study and take the lead on separate parts of the analysis as provided in the detailed protocol. No salary support is requested from this application.

Carolyn Westhoff, MD, MSc, Co-Investigator (10% effort, in kind) will work closely with Drs. Fu and Weber and assist in the design and implementation of all study protocols. Additionally, she will collaborate with Drs. Fu and Weber on the statistical analysis and manuscript preparation.

Anne Davis, MD, MPH, Co-investigator (10% effort, support through fellowship funds) will work closely with Drs. Fu and Weber and assist in the design and implementation of all study protocols. Additionally, she will collaborate with Drs. Fu and Weber on the statistical analysis and manuscript preparation.

Yenny Villela, RDMS, Research Coordinator and certified sonographer (100% effort for 10 months) will facilitate implementation of the study. She will be at the CUMC clinics to recruit patients, provide them with informed consent, perform all intake procedures, and assist with training. She will also collect provider forms, perform data entry, and perform chart abstraction.

TBN, the data analyst (350 hours) will assist with managing data input.

Renee Peele, MPA, Administrator (10% effort) will manage all personnel and budget issues throughout the study. She will track supplies and process compensation for study participants.

Claudia Roca, MPH, Research Manager (20% effort) will track IRB approval, oversee the research coordinator, manage and maintain administrative study files, handle communication between the investigators, track IRB approval and monitor CUMC and Planned Parenthood Central and Greater Northern New Jersey sites.

Elizabeth Talmont, MSN, NP, Co-Investigator (5% effort, in kind) will work closely with Drs. Fu and Weber and will be responsible for the implementation of study procedures at the Planned Parenthood sites.

TBN, Research Coordinator (100% effort for 8 months) will be at the clinics to recruit patients, provide them with informed consent, perform all intake procedures and assist with chart abstraction.

Appendix:**Table 1: Potential additional testing ordered by providers**

<ul style="list-style-type: none"> • Additional visit (within 1 week) for reassessment • TVS (performed following TAS on the same day of service or at the additional visit) • Pelvic examination (bimanual) • Quantitative serum β-hCG levels • Urine pregnancy test • Diagnostic aspiration procedure • Referral for urgent evaluation (i.e. at an urgent care center or the emergency department) • Other methods not listed here

Table 2: Proposed Research Sites

Clinical Site		Clinic Type	Providers	Insurance	Setting	Average med ab volume/month
CUMC	VC10	Hospital-based	3 O/G 1 FM	M	Urban	30
	1790 Broadway	Private practice	4 O/G	C/S	Urban	8
	Farrell	Hospital-affiliated	2 FM	M	Urban	8
PPCGNNJ	Elizabeth	Free-standing clinic	3 O/G 1 FM 1 NP	M/C/S	Urban	80
	Hackensack		1-3 NP	M/C/S	Suburban	60
	Morristown		1 NP 3 O/G	M/C/S	Suburban	50
	Trenton		1-3 NP	M/C/S	Urban	30
Total	Up to 7 available sites ¹		21-25 (13 O/G, 4 FM, 4-8 NP)			266

Key: O/G = Obstetrician/Gynecologist physician, FM = Family Medicine physician, M = Medicaid insurance, C = Commercial insurance, NP = Nurse Practitioner, S = self-pay.

¹Not all sites will be used in the study unless otherwise indicated, e.g. for improved enrollment/recruitment.

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