Ultrasound to Enhance Treat-to-Target in Rheumatoid Arthritis: A Cross-Sectional Study

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Study Summary

Title	**Ultrasound to Enhance Treat-to-Target in Rheumatoid Arthritis: A Cross-sectional study**
Short Title	Ultrasound Efficacy in Moderate RA
Methodology	Single-arm pilot interventional study
Study Duration	Approximately 12 months
Study Center	Clinic sites for the University of Pennsylvania Division of Rheumatology: Perelman Center for Advanced Medicine (PCAM), Penn Medicine University City (PMUC), Radnor, Valley Forge, and Cherry Hill
Objectives	Primary: • To determine the frequency of low synovitis scores by ultrasound in patients with RA in moderate or high disease activity with a low number of swollen joints. Secondary: • To compare physician treatment recommendations for patients with RA in moderate disease activity before versus after receiving ultrasound results.
Number of Subjects	40
Main Inclusion and Exclusion Criteria	Inclusion: • Age ≥18 • Meet ACR 2010 Criteria for RA • Treatment with a DMARD • Clinical Disease Activity Index (CDAI) > 10 (Composite score: Swollen Joint Count (SJC) + Tender Joint Count + Patient Global Score + Physician Global Score) • SJC ≤2 Exclusion: • Evidence of significant large joint activity with warmth and swelling (knee, hip, shoulder, elbow) • Joint MRI or musculoskeletal ultrasound in the past 3 months
Statistical Methodology	Primary Endpoint Analysis: To assess patient characteristics associated with having low synovitis scores to inform inclusion criteria for a future interventional study. Fisher's exact tests will be used to compare the proportion of low synovitis scores in patients in certain prespecified subgroups. Secondary Endpoint Analysis: The frequency of changes in physician treatment recommendations and disease activity assessment, and provider

	confidence in disease activity assessment (5-point Likert scale) before and after ultrasound will be calculated using Fisher's exact tests and Wilcoxon Signed Rank test, respectively.
Data and Safety Monitoring Plan	The PI will be responsible for the data quality management and ongoing safety of the subjects throughout their participation.

Background and Study Rationale

This protocol details study procedures that will be conducted in compliance and in full accordance with the provisions set forth in the protocol as well as, Good Clinical Practice standards, all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations. All episodes of noncompliance will be documented and reported accordingly.

1. Introduction

A target-oriented, or "treat-to-target" (T2T), approach for the treatment of Rheumatoid Arthritis (RA) is recommended by the current guidelines. This approach uses more aggressive and expensive therapies. Given the high cost of treatment expenses and the prevalence of RA as a common autoimmune disease, the need for a cost-effective and low medication toxicity approach is needed in order to minimize costs and maximize patient outcomes. In addition to treatment options, routine composite disease activity scores typically do not account for the effect comorbid conditions can have on RA resulting in inaccurate, biased, or elevated scores leading to escalation of therapies such as T2T. Ultrasound has a validated scoring system to grade joint inflammation and might serve as an unbiased and more precise approach to tailoring treatments for patients with moderate disease activity while cutting costs, reducing adverse medication events, and maximizing patient outcomes. This study will recruit 40 eligible patients with RA with moderate or high disease activity to determine if a bilateral hand/wrist ultrasound can inform disease activity assessment.

1.1 Background and Relevant Literature

Rheumatoid arthritis is a common autoimmune disease characterized by joint inflammation and destruction affecting roughly 1% of the population. Supported by several clinical trials, current guidelines recommend a target-oriented approach to the management of RA in which the physician measures and quantifies clinical disease activity and escalates disease modifying anti-rheumatic drug (DMARD) therapy in patients with elevated scores.[1–3] This "treat-to-target" (T2T) approach is more aggressive, generally resulting in more treatment changes and greater use of more aggressive and expensive therapies. RA is one of the most expensive conditions to treat and there is a critical need to identify ways to reduce the costs of care and minimize medication toxicity while maintaining excellent patient outcomes.[4]

Significant evidence has emerged that composite disease activity scores are frequently inaccurate or biased. For example, elevations in components of disease activity scores are influenced by factors such as prior joint damage, osteoarthritis, depression, fibromyalgia, obesity, and other comorbid conditions.[5–7] In practice, a high proportion of patients are unable to meet definitions of remission or low disease activity. False elevations in disease activity scores can result in inappropriate escalations in therapy that increase costs and expose patients to excess treatment side effects.

Ultrasound has shown promise in objectively measuring disease activity – this modality is less expensive than MRI, has a validated scoring system to grade joint inflammation, and is increasingly widely available, with many rheumatologists now being trained to perform ultrasound at the point of care.[8] While imaging modalities have been found to perform well as imaging biomarkers of disease activity, large clinical trials found no benefit of incorporating imaging-directed treatment targets among patient in clinical remission.[9–11] Yet a critical knowledge gap remains: whether use of ultrasound in patients with *moderate disease activity* can promote more precise use of therapy, reduce the rate of treatment change, and reduce the cost of care and the rate of adverse medication events while maximizing patient outcomes.

2. Study Objectives

2.1 Primary Objective

To determine the frequency of low synovitis scores by ultrasound in patients with RA in moderate or high disease activity with a low number of swollen joints.

2.2 Secondary Objectives

To compare physician treatment recommendations for patients with RA in moderate disease activity before versus after receiving ultrasound results.

3. Investigational Plan

3.1 General Design

This single-arm pilot interventional study will evaluate the potential for ultrasound to improve disease activity assessments for patients with rheumatoid arthritis with clinical scores indicating moderate or high disease activity.

3.2 Allocation to Interventional Group

All eligible and consented participants will receive a bilateral hand/wrist musculoskeletal ultrasound.

3.3 Study Measures

Patient measures:

1. Routine Assessment of Patient Index Data (RAPID)3: A pooled index of the 3 patient reported American College of Rheumatology (ACR) RA core data set measures: function, pain, and patient global estimate of status. Each of the 3 individual measures is scored 0 to 10, for a total of 30, and remission was defined as RAPID3 score ≤ 3. All patients in Penn's rheumatology practice are currently asked to complete the RAPID3 prior to the visit as part of routine patient care. The RAPID3 survey will be used to identify patients more likely to be eligible for the study.

2. Clinical Disease Activity (CDAI): The CDAI is performed by the treating physician at the time of the clinic visit as part of routine care. CDAI is calculated as the sum of swollen joint count (SJC, 0-28), tender joint count (TJC, 0-28), patient global assessment (PGA, 0-10), evaluator global disease activity (EGA, 0-10). Tenderness and swelling are evaluated in the first through fifth metacarpophalangeal joint, the interphalangeal joint of the thumb, the second through fifth proximal interphalangeal joint, the wrists, elbows, shoulders, and knees. The PGA estimate represents the patient's self-assessment of disease activity on a 0-10 scale where 10 means maximal activity. The EGA estimate represents the evaluator's assessment of disease activity on a 0-10 scale where 10 means maximal activity.

CDAI <= 2.8:	Remission
CDAI > 2.8 and <= 10:	Low Disease Activity
CDAI > 10 and <= 22:	Moderate Disease Activity
CDAI > 22:	High Disease Activity

   Provider must indicate CDAI >10 and SJC ≤2 and no large joint involvement for participant to be eligible.

3. Polysymptomatic Distress Questionnaire (PSD): Combined Widespread Pain Index (WPI), or measure of pain severity extent (0-19 scale) and Symptom Severity scale (SS), or measure of symptom severity (0-12 scale). The PSD scale, 0-31, is an overall

measure of pain extent and symptom distress. Used as a diagnostic tool for fibromyalgia by the guidelines set by the 2010 ACR criteria.

4. PROMIS depression, pain, fatigue: Patient-Reported Outcomes Measurement Information System (PROMIS) is a set of set of person-centered measures that evaluates and can monitor physical, mental, and social health in individuals living with chronic conditions. Short form versions of these measures will be used.

5. C-reactive protein (CRP): Substance secreted by the liver. Routine blood test performed as part of standard clinical care to measure inflammation and assess disease activity in RA.

6. Musculoskeletal ultrasound (see below)

Chart review to obtain additional participant information:

- Demographics: Age, sex, race/ethnicity, BMI, smoking
- Medical History: RA disease duration, RF, CCP, current DMARDs, current glucocorticoid dose, current NSAID use, opioid use, number of previous biologics/JAKi
- Comorbidities: Presence of peripheral joint osteoarthritis, chronic back pain/back osteoarthritis, anxiety, depression, sleep apnea, fibromyalgia

Provider measures:

1. Pre-ultrasound assessment/treatment form:
   - Assessment of the patient's disease activity: providers will select whether they think the patient is in remission, low, moderate, or high disease activity (does not need to match the patient's CDAI score)
   - Confidence in the disease activity assessment (1-10) on a visual analog scale (VAS). A VAS tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot be easily directly measured.
   - Treatment recommendations: Providers will be asked whether their recommendation for treatment is as follows: no change, increase disease modifying anti-rheumatic drugs (DMARD) dose, or add/switch DMARD.
2. Post-ultrasound assessment/treatment form:
   - Same as the pre-ultrasound form but completed after ultrasound results are reviewed

Musculoskeletal ultrasound assessment

- Bilateral hands/wrists with gray-scale and power doppler (to be performed by the musculoskeletal ultrasound department or by an ultrasound certified rheumatologist within 3 weeks of visit 1. Synovitis in the metacarpophalangeal joint (MCPs), proximal interphalangeal joint (PIPs), and wrists will be graded as absent, mild, moderate, or severe according to the validated OMERACT scoring system. Images will be stored to allow a second reader to score images to assess inter-rater reliability.
  - OMERACT is the acronym for an international, informally organized network initiated in 1992 aimed at improving outcome measurement in rheumatology. Data driven recommendations are prepared and updated by expert working groups. Recommendations include core sets of measures for most of the major rheumatologic conditions
  - Patients in whom all measured joints have absent or mild synovitis will be considered to have low synovitis scores

3.4 Study Endpoints

3.4.1 Primary Study Endpoint

The proportion of included patients with low synovitis scores will be calculated. Additionally, the proportion of patients with low-synovitis scores among those with disease activity score in 28 joints (DAS28 >3.2) will be evaluated. To assess patient characteristics associated with having low synovitis scores to inform inclusion criteria for a future interventional study, Fisher's exact tests will be used to compare the proportion of low synovitis scores in patients in certain prespecified subgroups:

- patients with long-standing versus earlier RA (>5 years vs ≤5 years)
- biologic vs. non-biologic treated patients, high versus low CRP (>1mg/dL vs. ≤1mg/dL)
- patients with vs. without evidence of central pain sensitization (PSD ≥12 vs <12)
- seropositive vs. seronegative
- patients with depression vs. those without (based on PROMIS vs. PHQ-9)
- moderate vs high disease activity by DAS28 and moderate vs high disease activity by CDAI
- associations with age, comorbidities, CDAI, DAS28, will also be assessed.

3.4.2 Secondary Study Endpoints

The frequency of changes in physician treatment recommendations after ultrasound will be calculated. Fisher's exact tests will be used to compare the proportion of patients for whom treatment escalation (dose increase or DMARD add/switch) is recommended before versus after ultrasound. Differences in disease activity assessment before and after ultrasound will also be compared with Fisher's exact tests, and differences in the provider's confidence in disease activity assessment (5-point Likert scale) before and after ultrasound will be compared with the nonparametric Wilcoxon Signed Rank test.

4. Study Population and Duration of Participation

4.1 Duration of Study Participation

The duration of study participation will include the completion of surveys after a routine clinical visit (remotely or in-person) as well as one research (ultrasound) visit – total time in the study estimated to be approximately one month.

4.2 Total Number of Subjects and Sites

Patients may be recruited from Penn Medicine practices including PCAM, PMUC, Radnor, Valley Forge, and Cherry Hill. It is expected that approximately 40 subjects total will be consented in order to produce 20 total evaluable subjects.

4.3 Inclusion Criteria

- Age ≥18
- Meet ACR 2010 Criteria for RA
- Treatment with a disease-modifying anti-rheumatic drug (DMARD)
- Clinical Disease Activity Index (CDAI) > 10 (Composite score: Swollen Joint Count + Tender Joint Count + Patient Global Score + Physician Global Score)
- Swollen joint count ≤2

4.4 Exclusion Criteria

- Evidence of significant large joint activity with warmth and swelling (knee, hip, shoulder, elbow)

- Joint MRI or musculoskeletal ultrasound in the past 3 months

4.5 Subject Recruitment

Patients scheduled for an upcoming rheumatology appointment at PCAM, PMUC, Radnor, Valley Forge, or Cherry Hill with a rheumatology provider who has opted-in to participate in the study will be pre-screened using EPIC to confirm that they meet criteria for RA, are receiving a DMARD, and are ≥18 years old. If providers find that a particular patient might meet the eligibility criteria, they can also refer their patient to the research team.

4.6 Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5. Study Procedures

5.1 Pre-screening/Screening

Patients with scheduled visits in the rheumatology clinic will be pre-screened for age, RA diagnosis, and DMARD treatment. If patients who are being pre-screened have already completed the RAPID3 survey, the survey score will be assessed for eligibility.

Patients will be contacted through the My Penn Medicine patient portal to inform them about the study and to remind them to complete their RAPID3 survey (sent to all patients in the practice as part of routine care), with the option to opt-out of further pre-screening assessments. Patients without My Penn Medicine or who do not complete the RAPID3 survey will be contacted by phone to inform them about the study and to administer the RAPID3 survey if patients are interested in the study. Patients may still be recruited on the day of their clinic visit, even if a RAPID3 has not been measured or is low, if the patient meets inclusion criteria on the day of the clinic visit.

<u>RAPID3 eligibility criteria:</u>
If RAPID3 ≤6:

- Patients will be informed through MPM and/or phone that they are not likely eligible for the study at this time but might be at a future visit. Providers can still refer these patients to the study and they can be included if they meet inclusion criteria on the day of their office visit.

If RAPID3 >6:

- Patients will be informed through MPM and/or phone that they may be eligible for the study depending on their routine exam in clinic.
- Providers will be notified of potentially eligible patients

Providers will perform routine standard of care assessment of disease activity using the CDAI (see 3.3 Study Measures) at the patient's clinic visit. If the score meets the study eligibility criteria, the patient will be approached either at the clinic visit or by phone and asked if they are interested in the study. If they are, the consent process will be conducted.

5.2 Post-screening Procedures

5.2.1 Visit 1

1. Informed Consent Process / HIPAA Authorization: All subjects for this study will be provided a consent form either in person or electronically describing the study and providing sufficient information for subjects to make an informed decision about their willingness to participate. See

Attachment [consent form number] for a copy of the Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The subject, or legally acceptable surrogate, must sign the consent form in person or electronically, as well as the investigator-designated research professional obtaining the consent. Subjects will be consented by the Clinical Research Coordinator, PI, or Co-Investigator in a private room or by phone followed by electronic signature. Potential subjects will review the consent form in detail with the person designated to consent and have the ability to take the consent home for further review.

2. Patients will complete patient surveys in clinic or will be sent a REDCap link to complete surveys remotely (see 3.3 Study Measures)
3. Physicians will complete the pre-ultrasound assessment (see 3.3 Study measures) in person or will be sent a REDCap link to complete the survey remotely

5.2.2 Visit 2 (Ultrasound assessment)

1. Ultrasound scheduling:
    - After enrollment, the CRC will schedule musculoskeletal ultrasound with either a rheumatologist certified in MSK ultrasound or the Penn Division of Musculoskeletal Radiology (MSK Radiology).
2. During ultrasound visit:
    - If participants did not complete REDCap surveys during or after the clinic visit, then surveys can be done in person at the time of the ultrasound visit.
    - Ultrasound will be performed by trained staff.
3. After the ultrasound:
    - Synovitis will be graded according to the validated OMERACT scoring system.
    - All study visits are complete. Any study related patient questions can be answered by CRC.
    - Results of the ultrasound will be emailed to providers via encrypted email along with an interpretation based on OMERACT scoring and post-ultrasound assessment/treatment form (see 3.3 Study Measures)

5.3 Unscheduled Visits

Given the nature of the study unscheduled visits are not expected.

5.4 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study procedures or ultrasound visit schedules or AEs. Subjects who withdraw early will not have further follow up or data collection. All data collected up until point of withdrawal will be used for analysis.

5.5 Safety Evaluation

All efforts to uphold patient safety will be obtained. Data and privacy protection will be ensured by administering surveys through Penn REDCap. Verbal and written consent will be obtained from potentially eligible or eligible participants before commencement of any study procedures. Staff performing the study ultrasound will have been properly trained., Although the potential for a confidentiality breach does exist, the research team will follow all standard procedures for training, consent, storage, and reporting to minimize potential exposure of patient information.

6. Statistical Plan

The number of patients with evidence of synovitis on ultrasound will be tabulated and compared across key measures such as CDAI, depression scores, polysymptomatic distress questionnaire, and PROMIS pain. The analysis will also summarize and tabulate the number of patients for which the ultrasound information changed the decision-making of the clinical provider.

6.1 Sample Size and Power Determination

This pilot and feasibility study will provide data to support power calculations for subsequent studies. Thus, the sample size was derived based on other considerations such as feasibility and cost.

6.2 Statistical Methods

The statistical analysis will be performed by the study investigators using Stata statistical software (version 15). The goal of the analysis is to provide descriptive evidence to support a larger proposal where hypothesis testing and testing of interventions can be performed.

6.3 Control of Bias and Confounding

As the overall goal of the proposed study is to describe the prevalence of synovitis in this patient population, there will be no adjustment for confounding performed.

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

6.3.2 Analysis of Primary Outcome of Interest

Aim 1 Analysis: The proportion of included patients with low synovitis scores will be calculated. To assess patient characteristics associated with having low synovitis scores to inform inclusion criteria for a future interventional study, Fisher's exact tests will be used to compare the proportion of low synovitis scores in patients in certain prespecified subgroups:

- patients with long-standing versus earlier RA (>5 years vs ≤5 years)
- biologic vs. non-biologic treated patients, high versus low CRP (>1mg/dL vs. ≤1mg/dL)
- patients with vs. without evidence of central pain sensitization (PSD ≥12 vs <12)
- seropositive vs. seronegative
- patients with depression vs. those without (based on PROMIS vs. PHQ-9)
- moderate vs high disease activity by DAS28 and moderate vs high disease activity by CDAI
- associations with age, comorbidities, CDAI, DAS28, will also be assessed.

Aim 2 Analysis: The frequency of changes in physician treatment recommendations after ultrasound will be calculated. Fisher's exact tests will be used to compare the proportion of patients for whom treatment escalation (dose increase or DMARD add/switch) is recommended before versus after ultrasound. Differences in disease activity assessment before and after ultrasound will also be compared with Fisher's exact tests, and differences in the provider's confidence in disease activity assessment (5-point Likert scale) before and after ultrasound will be compared with the nonparametric Wilcoxon Signed Rank test.

7. Safety and Adverse Events

Adverse events related to study participation are expected to be uncommon. Serious adverse events assessed as possibly, probably, or definitely related to the study will be reported to the IRB according to IRB reporting requirements. Events will only be recorded and reported if they occur during the subject's participation in the study (up until the completion of the ultrasound visit).

7.1 Definitions

7.1.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1.2 Serious Adverse Event

Serious Adverse Event
Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- required intervention to prevent permanent impairment or damage
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

7.2 Recording of Adverse Events

The study investigator is ultimately responsible for the recording, and reporting, of adverse events, which occur during the study. All adverse events occurring during the study period will be recorded if related to the ultrasound. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly, probably, or definitely related to the study intervention or study participation will be recorded and reported.

7.3 Relationship of AE to Study

The PI will determine if any adverse events are possibly, probably, or definitely related to study participation. It is anticipated that it would be very unlikely for any adverse events to be related to study participation.

7.4 Reporting of Adverse Events and Unanticipated Problems

Serious adverse events assessed as possibly, probably, or definitely related to the study will be reported to the IRB according to IRB reporting requirements.

7.4.1 Follow-up Report

If an AE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

7.4.2 Data and Safety Monitoring Plan

Given the minimal risk of the study, we will not convene a data safety monitoring board. Instead, the PI and co-investigator will meet at least monthly with the research coordinator to discuss progress, review data for completeness, and to review any adverse events.

8. Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

The study will collect the following in order to contact and track participants.

1. Names
2. All geographical subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
4. Phone numbers
5. Electronic mail addresses
6. Medical record numbers

8.2 Data Collection and Management

All hard-copy documents, including consent forms and source documentation, will be kept in locked cabinets in the Clinical Research Coordinator's office. Coded information from any hard-copy documents will be entered into the Penn REDCap database for further analysis by the Research Coordinator. Upon their enrollment, all patients will be assigned a subject ID. The document linking subject IDs with identifiable PHI will be kept in a separate, protected master list. This list will password protected so as to properly secure the PHI.

8.3 Records Retention

Written files and electronic data that includes identifiers will be retained for up to five years and then destroyed.

9. Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The study PI will be responsible for ensuring the ongoing quality and integrity of the research study. This will include regular conferences with the study staff, as well as ensuring that all data collection and management practices are being completed to the correct standard.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents. The investigator will ensure the capability for inspections of applicable study-related facilities.

10. Ethical Considerations

10.1 Risks

There is minimal risk associated with ultrasound scans, as stated in section 5.6 Safety Evaluation and according to the FDA. There is a small risk related to the disclosure of personal health information to the study. Overall the risks of the study are considered minimal.

10.2 Benefits

The participants should not expect to receive any direct health benefit from their participation in the study. There is the potential benefit of volunteerism. The ultrasound that is performed as part of the research study will be provided to their physician. However, there is insufficient data to determine whether the information provided by the ultrasound scan would be valuable for patients' overall clinical care.

11. Study Finances

11.1 Funding Source

This study is financed through the McCabe Award Pilot Project Fund at the University of Pennsylvania Perelman School of Medicine.

11.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

11.3 Subject Stipends or Payments

Reimbursement for study participation, via the Penn Greenphire ClinCard system, will be $100.

12. Publication Plan

The investigators will have full access to the data and full rights to publication. The investigators aim to publish one abstract and one manuscript from the data.

13. References

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14. Attachments

- Sample Consent Form
- Recruitment Materials
- Screening Scripts

- Appointment Reminder Texts
- Study questionnaires