Validation of Handheld Ultrasound Devices for Point of Care Use in Rheumatology

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GRAPPA Ultrasound Working Group

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1.0 Background

Recently, ultrasonography (US) has experienced a rapid evolution in the field of rheumatology, an evolution certainly driven by the broad applicability of point-of-care (POC) US for the assessment of rheumatic diseases. Despite the use of US in many other medical fields, such as gynecology, emergency or gastroenterology for much longer, the uptake by the rheumatology community was only initiated in the last two decades. This is mostly due to the fact that most of the structures that are assessed in rheumatology are very superficial, and the technology to generate a high resolution view for these superficial structures, to a degree of being able to detect even mild inflammatory changes, have been developed relatively recently.

US is made up of mechanical sound waves that can transmit through different materials like fluids, soft tissues and solids. Different tissues have different properties in terms of how much they transmit or reflect these waves and it makes them appear different on the screen. The Brightness mode (B mode) is the basic mode most commonly used and it is very helpful to determine if there is any inflammation in the investigated structure. In a much more sensitive manner than physical examination, B mode will detect structural changes associated with the presence of inflammation. In addition, it is possible to detect moving objects (such as erythrocytes) with US and convert such signal to an image, which is the principle of the Doppler view. Again, the Doppler has been used for a long time in other fields, such as cardiology, to detect the occlusion of carotid arteries, thrombosis of the deep veins or valvular insufficiencies of the heart. However, high erythrocyte velocities are characteristic of the latter pathologies and this is mostly not applicable to rheumatology practice. The neovascularisation within joints or tendons are at the capillary level and the flow is much slower. Power Doppler mode has been the recent breakthrough imaging technology in rheumatology as it allows the detection of active inflammation in a very sensitive manner.

Nowadays, rheumatologists typically use US for guided injections and for the assessment of joint structures, connective and vascular tissues, and related pathologies.[1] When it comes to the assessment of musculoskeletal (MSK) structures, the value of US lies upon a unifying principle for many arthritides: rapid detection of highly relevant and often times subclinical features of disease. For example, in a rapidly progressing disease like Rheumatoid Arthritis (RA), US allows faster detection of synovitis and bone erosion, resulting in earlier fulfillment of diagnostic criteria.[2]

Early disease detection with US perhaps takes its most relevant sense in psoriatic arthritis (PsA), where efforts are currently being deployed to intercept disease in its transition from psoriasis (PsO).

Three clinically quiet disease stages have recently been proposed between PsO and clinically detected PsA (see illustration 1)[3] :

- A preclinical phase (aberrant activation of the immune system)
- A subclinical PsA phase (soluble biomarkers and imaging findings with no clinical symptoms)
- A prodromal PsA arthralgia and fatigue with no synovitis and or enthesitis on physical exam yet

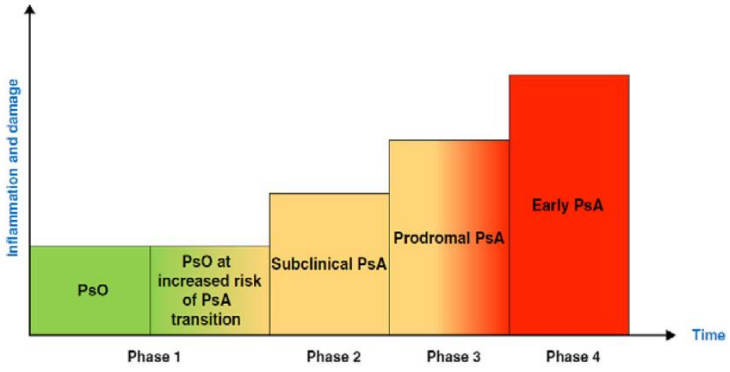

Illustration 1. Transition phases from psoriasis to early PsA

US is the imaging technique at the core of disease characterization during the latter 2 quiet stages. In the sub-clinical phase, several studies report more entheseal inflammation and synovitis on ultrasonography in PsO patients vs. healthy controls (HC). During the prodromal phase, a clinical and sonographic study on PsO patients with arthralgia revealed that sonographically determined tenosynovitis was the most significant contributor to symptoms and that sonographically determined enthesitis was linked to the future evolution of PsA. The identification of specific imaging lesions, associated with overt clinical PsA development, will be the challenge for the coming years, in order to correctly identify PsO patients at risk for PsA development.[3]

The DUET (Diagnostic Ultrasound Enthesitis Tool) study, headed by our group, the GRAPPA US working group, is working towards deriving a sonographic enthesitis scoring system accurately

distinguishing early PsA from non-PsA patients (including osteoarthritis (OA) patients with PsO), over the coming year.[4] Prior to diagnosis, there is great value attributed to PsA screening within the PsO population in the dermatology setting. As such, US was proven to be a great complement to the Early Arthritis for Psoriatic Patients (EARP) screening questionnaires and Psoriasis Epidemiology Screening Tool (PEST), increasing the specificity of referrals from 9% to 77% without compromising sensitivity.[5]

The use of US is not limited to RA and PsA in rheumatology. US detection of subclinical synovitis, seen in a large proportion of systemic lupus erythematosus (SLE) patients, could also reveal to be a great asset for early SLE patient management.[6] Overuse tendinopathies are group of MSK pathologies without a systemic component frequently seen by rheumatologists. Shoulder pain, for example, is second to low back pain as the most frequent MSK complaint leading to referral for rheumatological assessment.[7] Tendinopathies of the rotator cuff are diagnosed with greatest cost-efficiency, sensitivity and specificity using MSK US. The same imaging technique is also used for the guided peritendinous administration of several therapeutic agents, including corticosteroids, Hyaluronic Acid (HA) and sclerosis agents, to avoid intratendinous injections.[8] Combining these two US applications has already shown to improve therapeutic efficiency.[9] OA, the most common form of arthritis (affecting 25–50% of US adults by age 85) and frequent contributor to disability, is another rheumatic disease for which recent advances brought US frontstage.[10] There is growing support for the utility of US in OA assessment, as it is more sensitive than conventional radiography which may allow earlier disease identification. Additionally, US provides detailed imaging of soft tissues and inflammation, allowing detection of a variety of features relevant to OA, including osteophytes, effusions, synovitis, enthesitis, bursitis, and cartilage pathology, in a more cost-effective manner than MRI. [10] The OMERACT group recently released updated definitions of US-detected pathologies with pertinence in OA. The most relevant were synovitis, erosion and enthesitis.[11] One caveat remains in the assessment of OA enthesopathy with US: it is a feature shared with PsA, and thus creates the need for differentiation between early PsA and OA patients suffering from comorbid PsO. Concluding on the broad applicability of POC US in rheumatology, giant cell arteritis (GCA) and Sjögren Syndrome are examples of inflammatory diseases of vascular and connective tissue respectively, for which US plays a role in diagnosis. In GCA, US could contribute to reducing the risk of permanent sight loss associated with diagnostic

delay.[12] In Sjögren, US assessment of salivary glands is an important non-invasive measure supporting the diagnostic process.[13]

Moving on to the subject of ultrasonography scanners as medical devices; more specifically the high quality US scanners and high-resolution transducers required for the practice of rheumatology. A number of barriers persist and stand in the way of a wider use of POC US for the detection, diagnosis and management of rheumatic diseases. A significant one is the acquisition and maintenance costs of high quality instruments, limiting accessibility for community practitioners. There are recent technical and technological advances in the field of handheld ultrasonography that are set to overcome the access barrier. Typically, the cost of acquisition of scanners with a greyscale frequency of at least 13 MHz and a Doppler frequency of at least 8 MHz ranges from 25 000CAD to 90 000CAD. Hand-held US technology promises to take this cost down to a price tag under 10,000CADwith the introduction of affordable high-definition scanners possessing the specifications/requirements for use in the rheumatology practice (Greyscale frequency: 12 - 20 MHz and Doppler frequency: 8 - 12 MHz). Clarius Mobile Health Inc., an innovative company based out of Vancouver B.C., produces such devices. Clarius US scanner have regulatory approval by the FDA and Health Canada. However, before they can be specifically used for the practice of rheumatology, their performance needs to be validated against gold-standard devices for key interventions.

US holds significant promise as an imaging tool in rheumatology and in the future, handheld US could be used at the bedside to provide diagnostic and prognostic information, as well as guide both systemic and local treatment decisions and applications. Through the accurate assessment of disease extension and activity (e.g. presence of enthesitis in a PsA patient presenting with primarily as synovial disease), the bedside application of US in standard assessment of the PsA patients will enable the understanding of which domains are involved and would require treatment/and which treatment based on the domain involved. There are numerous advantages of the hand-held US devices over the existing gold standard devices for being accessible by more physicians, therefore by more patients. The ability to carry the device in their pocket will allow the physicians to be able to use in multiple settings, e.g. in different offices or inpatient vs outpatient clinics. Making the bedside US a part of the clinical assessment will avoid any delays in diagnosis and lead to earlier treatments. In addition, it increases the patients adherence to therapy adjustments. [14] As such, the

goal of this trial will be to validate two affordable handheld MSK US scanner against gold-standard devices through an assessment of their accuracy for:

- visualizing anatomical structures and pathologies
- detecting vascular flow

2.0 Aim

Our aim to test the concurrent validity of the Clarius handheld US devices versus gold-standard device to detect characteristic features of healthy and rheumatic joints (i.e. anatomical structures and vascular flow).

3.0 Study Objectives

Primary objective:

To determine whether handheld US devices (Clarius HD3 L20 and L15 scanners) B mode are as accurate as gold standard device (GE Logic E9/S8) at visualizing intraarticular synovitis

Secondary objectives:

1. To determine whether handheld US devices (Clarius HD3 L20 and L15 scanners) power Doppler mode are as accurate as gold standard device (GE Logic E9/S8) at detecting intrasynovial signals

2. To determine whether handheld US devices (Clarius HD3 L20 and L15 scanners) B mode are as accurate as gold standard device (GE Logic E9/S8) at visualizing tenosynovitis

3. To determine whether handheld US devices (Clarius HD3 L20 and L15 scanners) power Doppler mode are as accurate as gold standard device (GE Logic E9/S8) at detecting intratendineous signals

4. To determine whether handheld US devices (Clarius HD3 L20 and L15 scanners) B mode are as accurate as gold standard device (GE Logic E9/S8) at visualizing bone erosions

5. To determine whether handheld US devices (Clarius HD3 L20 and L15 scanners) B mode are as accurate as gold standard device (GE Logic E9/S8) at grading intraarticular synovitis

6. To determine whether handheld US devices (Clarius HD3 L20 and L15 scanners) power Doppler mode are as accurate as gold standard device (GE Logic E9/S8) at grading intrasynovial signals

7. To determine whether handheld US devices (Clarius HD3 L20 and L15 scanners) B mode are as accurate as gold standard device (GE Logic E9/S8) at grading bone erosions

8. To determine whether handheld US devices (Clarius HD3 L20 and L15 scanners) power Doppler mode are as accurate as gold standard device (GE Logic E9/S8) at visualizing elementary lesions of enthesitis

9. To determine whether handheld US devices (Clarius HD3 L20 and L15 scanners) power Doppler mode are as accurate as gold standard device (GE Logic E9/S8) at detecting entheseal signals

10. To determine whether handheld US devices (Clarius HD3 L20 and L15 scanners) B-mode are as accurate as gold standard device (GE Logic E9/S8) at detecting trilaminar appearance of the nail plate abnormalities

4.0 Approaches and Methods

Number of arms: single arm (repeating an image collection protocol with hand held US and the gold standard devices for each patient)

Blinding: The scoring of the US images will be done in a blinded fashion. The de-identified images from different patients and different scanners will be pooled to ensure the principle investigators (PIs) blindness to both the patients' clinical findings and the scores of other imaging modality.

4.1 Study Population

Adult patients with peripheral PsA that is not in minimal disease activity (MDA) and presenting at least one tender and swollen joint.

Inclusion Criteria

- Age ≥18
- Meets the classification for psoriatic arthritis (CASPAR) criteria
- Able to provide an informed consent
- Having peripheral disease phenotype of PsA
- At least one tender and swollen join on the day of US

Exclusion Criteria

- Having isolated axial PsA
- Being in MDA with no tender and swollen joints

4.2 Clinical Data Collection

There will only be one study visit. The consent, clinical data collection and US assessments will be done with the same study visit.

Clinical Assessment: This will be performed by an experienced rheumatologist on each site. The following information will be collected:

Patient's age, gender, Body Mass Index (BMI), physical activity, smoking, treatments and disease activity, based on 66/68 joint count for tender and swollen joints, Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index, number of dactylitic digits, body surface area for skin disease and presence of nail disease.

For the Patient-Reported Outcomes (PROs), pain Visual Analogy Scale (VAS), patient global and Health Assessment Questionnaire Disability Index (HAQ-DI) will be collected.

Medical device incident collection and documentation: Both US machines are approved by Health Canada and FDA. If any incident occurs, this will be reported to the manufacturer and applicable Health Authorities as per medical device regulations and will also be included in the final report that will be provided to the REB.

4.3 Ultrasound Protocol (Assessment of Joints and Enthesis)

Each patient will have consecutive (same day) US examinations using the Clarius handheld and GE gold-standard devices. All scans will be performed in a darkened room. Power Doppler settings will be standardized with a pulse repetition frequency of 500 Hz and low wall filters. The colour gain will be increased to the highest value where power Doppler signals under the bony cortex are not generated. There will be no further training for this step as the 3 investigators have done multiple research projects together and separately, with reproducibility being tested and presented.[15] However, there will be a investigators meeting prior to data collection to review all anatomical sites, positioning and standard views and agree on labelling. All images will be labeled to identify anatomical site and laterality. A glossary will be provided for labelling, to ensure blinding in the later stages. At least one B mode and one power Doppler image will be saved for each site and lesion. The standard will be saving the images in longitudinal views. Transverse views will be saved if there is an abnormality noted on the long axis.

Representative images will be collected and saved for all of the following structures bilaterally:

Joints (24 total): 2^{nd}-3^{rd} metacarpophalangeal (MCP), 2^{nd}-3^{rd} proximal interphalangeal (PIP), 2^{nd}-3^{rd} distal interphalangeal (DIP), wrist, elbow, shoulder, knee, ankle and 5^{th} metatarsophalangeal (MTP) joints of the foot, bilaterally. For the MCP, PIP and DIP joints, if joints other than the 2^{nd} or 3^{rd} present with swelling (e.g. 4^{th} or 5^{th}) they will be scanned instead. This approach is to ensure a maximum number of swollen joints will be assessed.

Entheses (20 total):

Large entheses: Supraspinatus, triceps, common extensor tendon, quadriceps, patellar ligament (origin and insertion), Achilles tendon, Plantar fascia insertions;

Small entheses: extensor digitorum tendon insertion at the DIP and PIP level

Tendons (4 total): Extensor digitorum tendon of the second digits, tibialis posterior tendon in the ankles

Nail: In case of having a nail PsO, the most involved nail and contralateral side will be assessed. If there is no nail PsO, procedure will be performed on the nail of the 2nd digit of the hands.

All study procedures and that will take place in one study visit, as summarize in Table-1.

Table-1: Assessment schedule

Procedures	**Visit 1**
Obtain informed Consent	x
Inclusion/Exclusion criteria	x
Demographics	x
Relevant medical history	x
Current Psoriatic Arthritis treatment	x
Pain VAS	x
Patient global assessment	x
HAQ-DI	x
Disease activity (66/68 joint count)	x
SPARCC enthesitis index	x
Dactylitis count	x
BSA	x
Presence of nail disease	x
Ultrasound protocol using both machines	x
Documentation of the ESR and CRP (if already done as standard of care)	x
Adverse event collection	x

VAS: Visual Analogue Scale; HAQ-DI: Health Assessment Questionnaire Disability Index; SPARCC: Spondloarthritis Research Consortium of Canada; BSA: Body Surface Area; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive protein

Scanners/probes that will be used for each anatomical site is summarized in Table-2.

Table-2: Probes/scanners, views and anatomical sites

Anatomical site	Views	GE Logic E9/S8	Clarius L15	Clarius L20
2nd MCP joints	dorsal and lateral	X	X	X
3rd MCP joints	dorsal	X		X
2nd-3rd PIP, 2nd-3rd DIP	dorsal	X		X
Wrist	dorsal	X	X	X
5th MTP joints	dorsal and lateral	X		X
Elbow joints	posterior	X	X	
Shoulder joints	posterior	X	X	
Knee joints	anterosuperior	X	X	
Ankle joints	anterior	X	X	
Nails	dorsal	X		X
Achilles tendon insertions	posterior	X	X	X
Supraspinatus tendon insertions	lateral	X	X	
Triceps tendon insertions	posterior	X	X	
Common extensor tendon origins	lateral	X	X	
Quadriceps tendon insertions	anterior	X	X	
Patellar ligament (origin and insertion)	anterior	X	X	

Plantar fascia insertions	plantar	X	X	
Extensor digitorum tendon insertions at DIP and PIP	dorsal	X		X
Extensor digitorum tendon of the second digits	dorsal	X		X
Tibialis posterior tendon	medial	X	X	

MCP: metacarpophalangeal; PIP: proximal interphalangeal; DIP: distal interphalangeal (DIP): MTP: metatarsophalangeal

Subject ID: Every study subject will be given unique study ID. This will consist of site ID and patient number respectively (Site IDs will be 01 for OHRI, 02 for Women College and 03 for University of Florida).

Labelling: During the ultrasound scan every image that is saved will be given a label by the local research assistant.

Exporting: After each scan, all the images of each study subject will be exported in JPEG format. The images will be saved in a file with the subject ID, which will be unique. This file will be send to the central site (OHRI) using Sharepoint by the local research assistant.

Blinding: At the central site (OHRI), the research assistant will give a unique identifier number to each image, for a random quality control and for cross referencing whenever needed. The cropped images, as detailed below, will not have the subject ID visible to the PI at the time of reading but will be accessible for the quality control. (read-only access). The research assistant at OHRI is the only site personnel who has the capacity to uncrop the images in the PowerPoint file (password protected files).

For interim analysis, image reading will be performed after the first 10 patients. Final reading will be done after all patients are recruited. Images will be scored by the principal investigator at OHRI. Images will not contain any identifiable information such as Date of Birth (DOB) or initials. The US images will be transferred to a PowerPoint file by the research assistant at OHRI in JPEG

format. The research assistant will generate an unblinded master list, inaccessible to other site personnel, to link the slide numbers with the patients and scanned anatomical sites and the slide will have no other information on the patient number or ID. For scoring the images by the PI, a random order slide show will be conducted, irrespective of the machine used or the anatomical site or patient assessed, to ensure blindness to data related to the patient identifiers (The PI will not be blinded to the machine that the image was taken with as the JPEG format that is achieved from different machines are identifiable, but due to the random order scoring, images that belong to the same joint by the different machines are not to be scored consecutively). There will be nine separate powerpoint files, for images of joints, tendons, entheses, nail including power Doppler and gray scale findings; and grey scale file for erosions. Scoring will be done using previously validated methods as detailed below.

During the data collection, there will be interim analysis: Interim analysis will be done after 10 patients being recruited. The readings and scorings will be done by the principal investigator at OHRI center, following the exact methodology as above.

The grading of greyscale intraarticular synovitis and power Doppler intrasynovial signals will be done based on the OMERACT definitions (scales of 0-3) as follows[16, 17] :

***Greyscale inflammatory (hypoechoic) synovial hyperplasia*:**

- **Grade 0:** no hypoechoic synovial hyperplasia
- **Grade 1:** minimal hypoechoic synovial hyperplasia (filling the angle between the periarticular bones, without bulging over the line linking tops of the bones)
- **Grade 2:** hypoechoic synovial hyperplasia bulging over the line linking tops of the periarticular bones but without extension along the bone diaphysis
- **Grade 3:** hypoechoic synovial hyperplasia bulging over the line linking tops of the periarticular bones and with extension to at least one of the bone diaphyses

Power Doppler signal:

- **Grade 0:** no flow in the hypoechoic synovial hyperplasia
- **Grade 1:** up to three single spots signals or up to two confluent spots or one confluent spot plus up to two single spots

- **Grade 2:** vessel signals in less than half of the area of the synovium (≤50%)
- **Grade 3:** vessel signals in more than half of the area of the synovium (>50%)

Elementary lesions of enthesitis will be defined and scored as per the GRAPPA US working group's definitions, as used in the multicenter DUET study co-supported by Novartis[18] :

Hypoechogenicity: Distinct loss of homogenous fibrillar pattern with relative hypoechogenicity compared to the rest of the enthesis after correcting for anisotropy.

- **Grade 0:** Absent
- **Grade 1:** Present

Thickening: Increased thickness of the tendon/ligament at the enthesis compared to its body. Thickness may be difficult to judge and should be suspected when accompanied by other entheseal lesions.

- **Grade 0**: Absent
- **Grade 1:** Present

Bone Erosion: A cortical defect confirmed with a step-down contour defect detected in two planes at the insertion of the tendon/ligament to the bone.

- **Grade 0:** Absent
- **Grade 1:** Present

Enthesophyte: A step-up bony prominence at the normal bone contour. Grade the severity of the enthesophyte based on its length. Although the readers are not expected to measure the length of the enthesis we provided suggested cut off points to guide the grading of the enthesophytes

- **Grade 0 :** No enthesophytes
- **Grade 1 :** Small enthesophyte
- **Grade 2:** Medium enthesophyte
- **Grade 3:** Large enthesophyte

Calcification: Hyperechoic linear structures detected within the tendon/ligament at the insertion to the bone but with no congruency with the bone.

- **Grade 0 :** No calcifications
- **Grade 1 :** Punctate hyperechoic area
- **Grade 2:** Linear calcification without acoustic shadow
- **Grade 3:** Egg-shell calcification with posterior acoustic shadow

Doppler Signal: The presence of positive Doppler signal at the enthesis, confirmed in two perpendicular planes and distinguished from reflection of surface artifacts and nutritional vessel signal.

The intensity of the Doppler signal at the enthesis will be graded using a semi-quantitative score.

Note: we will consider any Doppler signal at the enthesis area including signals appearing beyond 2 mm of the bony cortex, however, not including Doppler signals at the bursa which will be scored separately.

We will score the intensity of the Doppler signal on a semi quantitative grading system:

- **Grade 0:** No Doppler signal
- **Grade 1:** A single confluent Doppler signal or up to 3 discrete Doppler spots
- **Grade 2:** Doppler signal affecting less than half of the enthesis
- **Grade 3:** Doppler signal covering more than half of the enthesis

In addition, the **location of each Doppler signal** will be recorded:

- **Zone 1:** ≤2mm from the bone cortex – Zone 1
- **Zone 2:** >2mm from the bone cortex – Zone 2

4.4 Statistical Analysis:

The primary endpoint analysis will be the interrater agreement of detecting any synovitis in B mode with the Clarius and gold standard machine. The kappa coefficients will be evaluated using the guideline outlined by Landis and Koch, where the strength of the kappa coefficients are: 0.01-0.20 slight; 0.21-0.40 fair; 0.41-0.60 moderate; 0.61-0.80 substantial; 0.81-1.00 almost perfect.[19]

For secondary outcomes, the interrater agreement for the presence of Doppler signals within the joints, tenosynovitis, erosions, nail, as well as features of enthesitis (hypoechogenicity, thickening, erosions, enthesophytes, calcifications) will also be evaluated using the same method. The agreement of the semiquantitative grading of the intraarticular findings' severity (synovitis in B mode, Doppler signals, erosions, each being on a scale between 0-3) will be done using weighted kappa analysis.[20]

An interim analysis will be done after 10 patients. A moderate level of interrater agreement within that sample size (primary outcome) will allow parallel initiation of subsequent studies proposed in the research framework.

4.5 Sample Size Consideration

Study agreement analyses will be done per joint. To give a kappa ≥ 0.61 (from substantial interrater agreement to almost perfect agreement) with a confidence interval width of 0.15 and the expectation of approximately 20 % of joints assessed having any synovitis in B mode (based on a previous study by our group), 683 joints would be required.[18] This corresponds to 30 patients if 24 joints per patient are assessed. Non-inferiority margin will be $\kappa \geq 0.61$.

5.0 Impact of the study

The relatively low cost of the hand-held US devices makes them affordable for the everyday rheumatology practices, including the community and academic centers. Although the study is focused on PsA patients, the wide range of lesions that will be investigated in this study will help to prove the validity of the hand-held US in comparison to the high-end machines for other uses of US in the field of rheumatology. We hope that our results will increase the uptake up MSK US in daily practice that will allow earlier diagnosis and more accurate assessment of disease activity on a large scale. US itself has been characterized as more sensitive than either X-ray or Magnetic Resonance Imaging (MRI) at detecting joint involvement in PsA.[21] Adding to this increased sensitivity, handheld POC US also has the potential to accelerate the patient journey to diagnosis

and optimized therapy by circumventing the long waiting lists associated to MRI imaging that plague the Canadian healthcare system. In fact, the Conference Board of Canada estimates that, by 2022, the average wait will be 133 days for MRI, greatly exceeding the acceptable target of 30 days[22]. This is concerning when it has been shown that, for PsA, a diagnostic delay of more than 6 months (180 days) is associated to irreversible joint damage and poor functional outcomes.

6.0 Translation of CRF

The physician Case Report Form (CRF) does not need to be translated. The patient CRFs and consent forms will be available in English and in French. The PROs have already been validated in French.

7.0 Ethical and regulatory aspects

The primary site for ethics submission will be the Ottawa Hospital/the Ottawa Hospital Research Institute; 1967 Riverside Dr., Ottawa, ON, Canada K1H 7W9. The Principal Investigator is Sibel Aydin, MD.

7.1 Participant consent

Eligible patients will be approached for study recruitment during their visits in rheumatology. Patients who are willing to participate will be asked for a signed informed consent. All patients will receive detailed information about the study at the time of enrollment. The participants will have the opportunity to leave the study at any time. According to the participant's will data previously recorded could be kept in the database for analysis, in case they withdraw consent.

7.2 Personal information management

The local investigators will keep a confidential correspondence list of patient identifiers and of patient numbers. The centralized information will consist entirely of de-identified data.

7.3 Regulations and Review Board

The study will be conducted in accordance with the protocol, Good Clinical Practice (GCP), ethical principles that have their origin in the Declaration of Helsinki and all applicable local regulations.

Independent Ethics Committee or Institutional Review Board approval of the protocol will be obtained prior to commencing the study at each site, through the principal investigator and designated investigators.

An Institutional Review Board approved, study-specific informed consent will be reviewed, signed and dated by the subject (and the investigator) prior to the performance of any study-related procedures.

8.0 Data Quality Assurance

Data management

Patients will be identified by a local number at each investigator site, which will have a 2-letter code for a site and a number for each patient. Each site will keep a confidential subject identification code list, so that if there are missing data this information will be available locally to clarify the information.

Two paper CRFs, patient and physician CRFs, will be filled for each patient during the visit and these will be the source documents. The CRFs will be scanned and uploaded to the SharePoint at each center, within 3 day after the visit. In addition, US images of each patient will be uploaded to the SharePoint. US images and CRFs uploaded from each center will be reviewed by the research assistant at Ottawa Hospital Research Institute (OHRI) center. If there are any missing or erroneous data, it will be ensured that the errors and deficiencies are corrected by contacting the center. Any queries will be confirmed with the site within a week of the data entry. Center will then correct and update the physician CRF as per Good Documentation Practices and re-scan the CRF to the sharepoint. Then the analyzed CRFs data will be transferred to Research Electronic Data Capture (REDCap) (version 12.4.18 - © 2023 Vanderbilt University) by the research assistant at OHRI.

After all the data is transferred to REDCap, the data in Sharepoint will be deleted. The data in REDCap will also be deleted when the data is exported and the analysis is completed. The exported data will be locked and stored in a secure and password protected computer at The Ottawa Hospital, according to the requirements by the Research Ethics Board (REB) at The Ottawa Hospital. The paper CRFs, which are the source documents, will also be maintained on site for 10

years . The electronic data will be stored for 15 years. For both devices already being Health Canada and FDA approved, a Data Monitoring Committee is not deemed to be needed by the PIs.

Publication, Study Results and Authorship Criteria

The study will be registered on clinicaltrials.gov including a study report at the end of the study. The results will be presented in EULAR 2023 congress and subsequent national and international rheumatology congresses. A manuscript will be generated to be published in a peer reviewed rheumatology journal with the possibility of subsequent publications on post-hoc analysis. To be eligible to be included in publications, investigators will be required to have a significant contribution to one of the following aspects of the study, in compliance with the ICMJE (International Committee of Medical Journal Editors) recommendations and criteria:

1) Conception of the study and development of the methodology. This will include members of the steering and advisory committee.
2) Data collection. Each investigator will be required to recruit 10 cases.
3) Data analysis
4) Contribute to the publication by reviewing and approving the final abstract/manuscript.

Timetable:

Action	**Timeframe**
Ethics application- approval	September-October 2022
Contracts	November-December 2022
Recruitment	January -April 2023
Analysis and Abstract submission for ACR 2023 congress and subsequent national and international rheumatology congresses	May 2023
Writing the manuscript	May-July 2023

References

1. Kang T, Emery P, Wakefield RJ. A brief history of ultrasound in rheumatology: where we are now. Clin Exp Rheumatol. 2014 Jan-Feb;32(1 Suppl 80):S7-11. Epub 2014 Feb 17. PMID: 24529159.
2. Filer A, de Pablo P, Allen G, Nightingale P, Jordan A, Jobanputra P, Bowman S, Buckley CD, Raza K. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. Ann Rheum Dis. 2011 Mar;70(3):500-7. doi: 10.1136/ard.2010.131573. Epub 2010 Nov 29. PMID: 21115552; PMCID: PMC3033529.
3. Zabotti A, Tinazzi I, Aydin SZ, McGonagle D. From Psoriasis to Psoriatic Arthritis: Insights from Imaging on the Transition to Psoriatic Arthritis and Implications for Arthritis Prevention. Curr Rheumatol Rep. 2020 May 16;22(6):24. doi: 10.1007/s11926-020-00891-x. PMID: 32418006; PMCID: PMC7230038.
4. Eder L, Kaeley GS, Aydin SZ. Development and Validation of a Sonographic Enthesitis Instrument in Psoriatic Arthritis: The GRAPPA Diagnostic Ultrasound Enthesitis Tool (DUET) Project. J Rheumatol Suppl. 2020 Jun;96:50-52. doi: 10.3899/jrheum.200128. PMID: 32482769.
5. Solmaz D, Bakirci S, Al Onazi A, Al Osaimi N, Fahim S, Aydin SZ. Musculoskeletal ultrasound can improve referrals from dermatology to rheumatology for patients with psoriasis. Br J Dermatol. 2020 Mar;182(3):804-806. doi: 10.1111/bjd.18515. Epub 2019 Nov 28. PMID: 31505032.
6. Iagnocco A, Ceccarelli F, Rizzo C, Truglia S, Massaro L, Spinelli FR, Vavala C, Valesini G, Conti F. Ultrasound evaluation of hand, wrist and foot joint synovitis in systemic

lupus erythematosus. Rheumatology (Oxford). 2014 Mar;53(3):465-72. doi: 10.1093/rheumatology/ket376. Epub 2013 Nov 14. PMID: 24231444.

7. Möller I, Szkudlarek M. Imaging of regional pain syndromes; from syndromes to conditions using imaging? Best Pract Res Clin Rheumatol. 2016 Aug;30(4):707-719. doi: 10.1016/j.berh.2016.06.001. Epub 2016 Oct 13. PMID: 27931963

8. Aicale R, Bisaccia RD, Oliviero A, Oliva F, Maffulli N. Current pharmacological approaches to the treatment of tendinopathy. Expert Opin Pharmacother. 2020 Aug;21(12):1467-1477. doi: 10.1080/14656566.2020.1763306. Epub 2020 Jun 8. PMID: 32511031.

9. Roy JS, Braën C, Leblond J, Desmeules F, Dionne CE, MacDermid JC, Bureau NJ, Frémont P. Diagnostic accuracy of ultrasonography, MRI and MR arthrography in the characterisation of rotator cuff disorders: a systematic review and meta-analysis. Br J Sports Med. 2015 Oct;49(20):1316-28. doi: 10.1136/bjsports-2014-094148. Epub 2015 Feb 11. PMID: 25677796; PMCID: PMC4621376

10. Nelson AE. Turning the Page in Osteoarthritis Assessment with the Use of Ultrasound. Curr Rheumatol Rep. 2020 Aug 26;22(10):66. doi: 10.1007/s11926-020-00949-w. PMID: 32845396.

11. Bruyn GA, Iagnocco A, Naredo E, Balint PV, Gutierrez M, Hammer HB, Collado P, Filippou G, Schmidt WA, Jousse-Joulin S, Mandl P, Conaghan PG, Wakefield RJ, Keen HI, Terslev L, D'Agostino MA; OMERACT Ultrasound Working Group. OMERACT Definitions for Ultrasonographic Pathologies and Elementary Lesions of Rheumatic Disorders 15 Years On. J Rheumatol. 2019 Oct;46(10):1388-1393. doi: 10.3899/jrheum.181095. Epub 2019 Feb 1. PMID: 30709946.

12. Chrysidis S, Terslev L, Christensen R, Fredberg U, Larsen K, Lorenzen T, Døhn UM, Diamantopoulos AP. Vascular ultrasound for the diagnosis of giant cell arteritis: a reliability and agreement study based on a standardised training programme. RMD Open. 2020 Sep;6(3):e001337. doi: 10.1136/rmdopen-2020-001337. PMID: 32978303.

13. Milic V, Petrovic R, Boricic I, Radunovic G, Marinkovic-Eric J, Jeremic P, Damjanov N. Ultrasonography of major salivary glands could be an alternative tool to sialoscintigraphy in the American-European classification criteria for primary Sjogren's syndrome. Rheumatology (Oxford). 2012 Jun;51(6):1081-5. doi: 10.1093/rheumatology/ker431. Epub 2012 Feb 1. PMID: 22302061

14. Tan YK, Teo P, Saffari SE, Xin X, Chakraborty B, Ng CT, Thumboo J. A musculoskeletal ultrasound program as an intervention to improve disease modifying anti-rheumatic drugs adherence in rheumatoid arthritis: a randomized controlled trial. Scand J Rheumatol. 2022 Jan;51(1):1-9. doi: 10.1080/03009742.2021.1901416. Epub 2021 Jun 10. PMID: 34107851.

15. Eder L, Aydin S, Kaeley G., The Reliability of Scoring Sonographic Entheseal Abnormalities – the Diagnostic Ultrasound Enthesitis Tool (DUET) Study. Arth. & Rheumatol. 2020; 72 (suppl 10)

16. D'Agostino MA, Boers M, Wakefield RJ, et. al., Exploring a new ultrasound score as a clinical predictive tool in patients with rheumatoid arthritis starting abatacept: results from the APPRAISE study, RMD Open. 2016; 2(1), 1-7

17. D'Agostino MA, Wakefield RJ, Berner-Hammer H, et. al., Value of ultrasonography as a marker of early response to abatacept in patients with rheumatoid arthritis and an

inadequate response to methotrexate: results from the APPRAISE study, Ann Rheum Dis. 2016 Oct; 75(10): 1763–1769

18. Tom S, Zhong Y, Aydin SZ, Development of a Preliminary Ultrasonographic Enthesitis Score in Psoriatic Arthritis - GRAPPA Ultrasound Working GroupJ Rheumatol, 2019 Apr;46(4):384-390

19. Landis JR, Koch GG, The measurement of observer agreement for categorical data, Biometrics, 1977, 33(1):159-74

20. Cohen J, Weighed kappa: Nominal scale agreement with provision for scaled disagreement or partial credit. Psychological Bulletin.1968, 70 (4): 213–220

21. Wiell C, Szkudlarek M, Hasselquist M et al (2007) Ultrasonography, magnetic resonance imaging, radiography, and clinical assessment of inflammatory and destructive changes in fingers and toes of patients with psoriatic arthritis. Arthritis Res Ther 2007;9(6):R119.

22. Sutherland, G, Russell, N, Gibbard, R, Dobrescu, A. The Value of Radiology, Part II. Ottawa, ON: The Conference Board of Canada; 2019. https://www.conferenceboard.ca/e-library/abstract.aspx?did=10328.