Domain Match and Feasibility of Plain Radiographic Instruments for Structural Damage in peripheral joints in Psoriatic Arthritis: A Report from the GRAPPA-OMERACT Working Group

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ABSTRACT:

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)-Outcome Measures in Rheumatology (OMERACT) Psoriatic Arthritis (PsA) Core Set working group is focused on the development of a core set of instruments used to assess the domains described in the 2016 PsA Core Domain Set. At the 2021 annual GRAPPA meeting, the working group presented an update on the domain of structural damage, which was one of four domains prioritised at the 2019 GRAPPA annual meeting. In this report, we discuss the steps taken to assess the domain match and feasibility of plain radiographic instruments in the assessment of structural damage in PsA.

Introduction

Structural damage can be defined as abnormalities in the structure or integrity of a joint, bone or tendon that are likely to be attributable to psoriatic arthritis (PsA). Despite advances in diagnosis and therapeutics, the prevalence and progression of structural damage remain high when assessed using plain radiography of the hands and feet (1-4).

Structural damage is in the middle circle of the 2016 PsA Core Domain Set and as such, should be measured at least once in the development of a new therapeutic (5, 6). It is a domain that has been consistently prioritised by individuals with PsA, in large part due to its well-recognised impact on physical function (5, 7, 8). Radiographic structural damage has been shown to be associated with disease activity and is known to precede clinical damage (9, 10). There is also a well-described discordance between disease activity and radiographic progression in the treatment arms of biologic randomised controlled trials (RCTs), suggesting that structural damage is not a redundant outcome measure (11-13).

In this report, we summarise the progress made in advancing a radiographic instrument for the assessment of structural damage through the OMERACT Framework Instrument Selection Algorithm (OFISA) as presented at the 2021 GRAPPA meeting and report the working group's final vote on the domain match and feasibility of plain radiographic instruments.

Domain Definition

The domain definition describes the *(i)* target population, *(ii)* intended use for the domain (e.g. clinical trials), *(iii)* target domains (e.g. joint space narrowing), *(iv)* qualitative or literature support, and *(v)* sources of variability. This document needs to be modality-specific, as different modalities have different sensitivities, specificities and reliabilities for different target domains. Furthermore, operational definitions for target domains include image acquisition parameters and joint positioning, which are specific to the modality being used.

The domain definition document was drafted (AA, WT), discussed in two virtual working group calls, and revised accordingly. Members of the working group were cognisant of the importance of content expert radiologist opinions in drafting these documents, and thus the document was subsequently reviewed by 5 content expert radiologists who provided feedback via a survey (Supplementary Material). A revised domain definition was then circulated to members of the working group for feedback before being finalised (Supplementary Material).

The target population for this domain definition were adults aged 18 years and older with peripheral PsA and its intended use was for RCTs comparing a disease-modifying anti-rheumatic drug to a placebo or active comparator. Specifying the population and intended use ensures that when an instrument is eventually endorsed, it is used in the right population and setting.

Potential target domains were elicited from a review of the literature (14, 15). The target domains selected were joint space narrowing and joint erosion due to the frequency of these radiographic features, associations with disease activity and functional outcomes, and progression over time in RCTs (Supplementary Material). Other features such as subluxation, ankylosis, tuft resorption, new bone formation and osteolysis are uncommon and/or progress slowly when assessed by plain radiography (Supplementary Material). New bone formation including shaft or tuft periostitis and juxta-articular osteoproliferation, while discriminative enough to form part of the classification criteria for PsA, has not shown to progress significantly in RCTs utilising tumour necrosis factor (TNF) inhibitors up to a follow-up of 2 years when assessed using plain radiography (16, 17). Therefore, while it may be desirable to compare new bone formation in head-to-head trials assessing different therapeutic pathways, plain radiography may not be the appropriate modality.

The domain definition focusses on the assessment of structural damage in the hands, wrists and feet. There is paucity of data to support the use of plain radiography to assess structural damage in other joints in peripheral PsA. The assessment of large joints is a key knowledge gap given the frequency of this phenotype, however plain radiography may not be adequately sensitive to assess progression of structural damage in large joints in the timeframe of an RCT.

The working and operational definitions for the target domains and sources of variability are described in the domain definition (Supplementary Material).

Domain Match

The working group then proceeded to the domain match exercise. Candidate instruments identified from a recent literature review were assessed against the domain definition document for content validity (15). Seven instruments were included: modified Larsen, modified Steinbrocker, modified Total Sharp Score version B (mTSS-B), modified Sharp van der Heijde score, reductive X-Ray score for Psoriatic Arthritis and Simplified Psoriatic Arthritis Score (SPARS) (15).

The domain match questionnaire was adapted from the OMERACT handbook and administered to participating working group members via an online survey platform (n=13 participants, inclusive of 1 patient research partner) with reference material including radiologist feedback and a summary of the instruments (Supplementary Material). The results of the initial vote and available distribution data were discussed at an online working group meeting to optimize consensus. A second round of voting was undertaken (n=14) where respondents were asked if the instrument was 'Good to Go' (GREEN), 'Some Cautions, but

Okay" (AMBER) or "Not Right for this Application" (RED). A 50% majority response was accepted as supportive (agreement) while a 70% majority response was accepted as consensus. A >15% RED response ("Not Right for this Application") was considered a hurdle for domain match and feasibility.

In the final vote (Figure 1; Supplementary Material), there was agreement from the working group that the mTSS-B and the mSvdHs had content validity (GREEN), with both target domains being assessed in the joints of the hands, wrists. and feet. There was a lack of agreement on the Ratingen score, which scores for osteoproliferation and the composite domain of 'destruction' but not joint space narrowing. The final rating for the Ratingen was RED given a significant proportion of respondents (n=6/14 [43%]) rated the instrument RED. There was consensus from the working group that the modified Larsen, modified Steinbrocker, SPARS. and ReXSPA were not appropriate for use in this setting (RED).

Feasibility

Feasibility of plain radiography of the hands and feet was assessed among patient research partners (PRPs). A live webinar followed by a Q&A session was held with PRPs. PRPs were invited to attend and/or watch a recording of the webinar at their convenience and complete a feasibility survey adapted from the OMERACT handbook. The webinar and questionnaires were developed in concert with PRP input. The webinar discussed the importance and impact of structural damage, types of structural damage and the ways in which it can be measured, examples of the radiographic findings in PsA, factors influencing the modality chosen to assess structural damage, the methods by which structural damage is assessed in clinical trials, and the potential risks and benefits of plain radiography.

Of the 9 PRPs who completed the feasibility survey (Supplementary Material), 8 had had plain radiography of their hands and feet. Seven PRPs felt it was easy to undergo and that the time required was reasonable, although it was noted that imaging needed to be requested by a doctor and that it could be inconvenient to wait for the imaging. Three PRPs (33%) were uncertain about the potential from harm of plain radiography, making the point that the risks of radiation should be explained but that those risks may not be prohibitive. Three PRPs (33%) opined that there may be discomfort from having plain radiography, citing the discomfort of positioning with underlying joint pain or deformities. Two thirds of PRPs felt that the costs of plain radiography were acceptable. Eight PRPs (89%) felt that there may be benefits to having plain radiography, but some commented that this might be the case in RCTs rather than necessarily for themselves at an individual level.

In the working group survey, 11 of 13 respondents felt it was easy to access plain radiography. After a first round of voting (n=13), the results were discussed by members of the working group in an online meeting to optimise consensus. Many members of the working group who had utilised the instruments assessed felt they were feasible, however some members expressed concern regarding the lack of a training platform or image atlas for any of the available instruments. There was concern that this might affect the fidelity of all instruments in the long-term and negatively impact equitable access to radiographic scoring in centres where training is unavailable.

Following a second round of voting (n=14), there was consensus that most instruments were AMBER based on the results of the initial survey balanced against the absence of training material (Figure 1; Supplementary Material). The exceptions were the modified Steinbrocker and modified Larsen score, where 21% and 29% of respondents respectively felt that the instruments were not feasible while >70% of respondents felt both instruments could proceed with caution. It is important to note that the modified Steinbrocker has been utilised for decades to assess long-term structural damage in observational cohorts.

Conclusion

In the assessment of structural damage in peripheral PsA in RCTs assessing a therapy against a comparator or a placebo, plain radiography is feasible and acceptable to patients. The mSvDHs and mTSS-B have content validity (GREEN) and all instruments are potentially feasible (AMBER). Key gaps highlighted in this exercise are the need for imaging instruments for the assessment of large peripheral joints and the need for a training platform to optimise the feasibility and accessibility of plain radiographic instruments. The next step will be to evaluate the measurement properties of the mSvdHs and mTSS-B in RCTs.

FIGURE 1: DOMAIN MATCH AND FEASIBILITY FINAL WORKING GROUP VOTES

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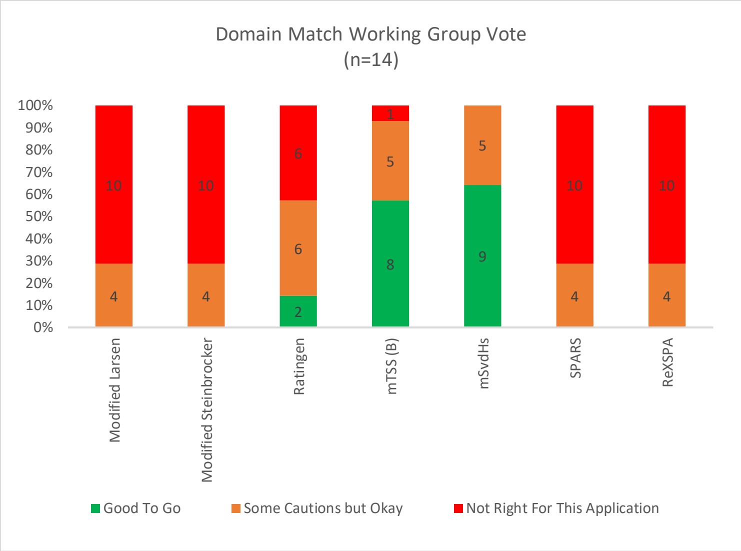
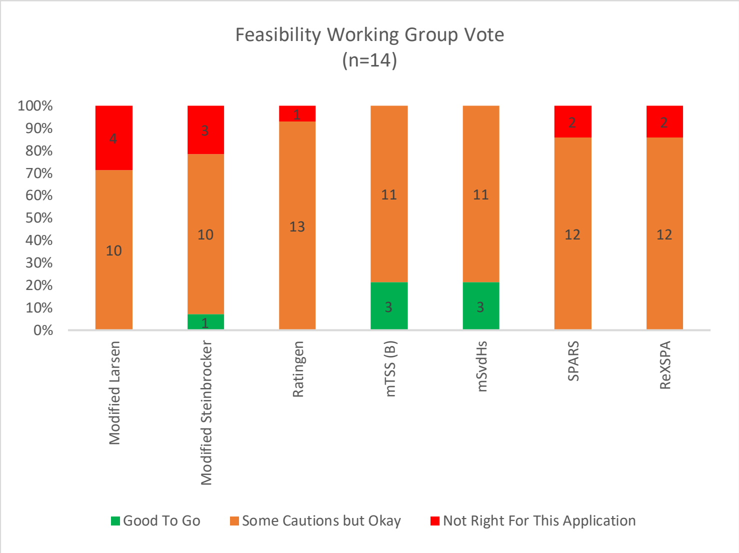
Working Group Key Discussion Points

Instruments	Domain Match			Feasibility		
	Results	PROs	CONs	Results	PROs	CONs
Modified Larsen	RED	Includes joint space narrowing and erosions.	Damage assessed as a composite outcome that predominately quantifies the % of joint surface destroyed by erosions, but also includes features such as soft tissue swelling and osteoporosis. Unable to demonstrate deterioration in existing joint space narrowing. Wrist scored as a single joint	RED	No licensing fee No additional/specialised equipment	Limited feasibility data No image atlas or formal training platform
Modified Steinbrocker	RED	Includes joint space narrowing and erosions. Includes lysis, ankylosis and subluxation.	Damage assessed as a composite outcome that includes features such as soft tissue swelling and osteoporosis. Unable to score joint space narrowing without erosive disease. May miss a spectrum of disease between mild joint space narrowing/erosions and joint ankylosis/lysis. Wrist scored as a single joint	RED	No licensing fee No additional/specialised equipment Estimated training time available from previous feasibility exercise (2 hours to develop familiarity with the components and a further 50 hours to score 100 radiographs covering a range of findings/severity with the supervision of a radiologist, followed by a blinded inter- and intra-rater reliability exercise) Time to Score from previous feasibility exercise 6.2 minutes	No image atlas or formal training platform
Ratingen	RED	Includes erosions, ankylosis and osteoproliferation.	Does not include joint space narrowing Wrist scored as a single joint	AMBER	No licensing fee No additional/specialised equipment Estimated training time available from previous feasibility exercise (2 hours to develop familiarity with the components and a further 50 hours to score 100 radiographs covering a range of findings/severity with the supervision of a radiologist, followed by a blinded inter- and intra-rater reliability exercise)	No image atlas or formal training platform Time to Score from previous feasibility exercises approximately 10 minutes
mTSS(B)	GREEN	Includes joint space narrowing, erosions, ankylosis and osteolysis. Multiple carpal joints scored. Utilised successfully in RCTs	Does not include osteoproliferation, which is a key feature of PsA, albeit slowly progressive. Triquetrum can be difficult to assess	AMBER	No licensing fee No additional/specialised equipment Estimated training time available from previous feasibility exercise (2 hours to develop familiarity with the components and a further 50 hurs to score 100 radiographs covering a range of findings/severity with the supervision of a radiologist, followed by a blinded inter- and intra-rater reliability exercise)	No image atlas or formal training platform Time to Score from previous feasibility exercise 14.6 mintues
mSvdHs	GREEN	Includes joint space narrowing, erosions, ankylosis and osteolysis. Multiple carpal joints scored. Utilised successfully in RCTs	Does not include osteoproliferation, which is a key feature of PsA, albeit slowly progressive	AMBER	No licensing fee No additional/specialised equipment Estimated training time available from previous feasibility exercise (2 hours to develop familiarity with the components and a further 50 hours to score 100 radiographs covering a range of findings/severity with the supervision of a radiologist, followed by a blinded inter- and intra-rater reliability exercise)	No image atlas or formal training platform Time to Score from previous feasibility exercise 14.4 minutes
SPARS	RED	Includes joint space narrowing, osteoproliferation and erosions.	Wrist scored as a single joint Each feature assessed in each joint as a binary outcome.	AMBER	No licensing fee No additional/specialised equipment Estimated training time from developers: 4 hours in clinicians familiar with plain radiography in PsA Time to Score from previous feasibility exercise 4.5 minutes	
ReXSPA	RED	Includes joint space narrowing, osteoproliferation and erosions.	Only radiocarpal joints scored in wrist Limited number of joints assessed.	AMBER	No licensing fee No additional/specialised equipment Estimated training time extrapolated from previous feasibility exercise (2 hours to develop familiarity with the components and a further 50 hours to score 100 radiographs covering a range of findings/severity with the supervision of a radiologist, followed by a blinded inter- and intra-rater reliability exercise)	Time to score not available

Figures 1a) and 1b) Domain Match and Feasibility Working Group Vote


Domain Match Working Group Vote
(n=14)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Modified Larsen
Modified Steinbrocker
Ratingen
mTSS (B)
mSvdHs
SPARS
ReXSPA
10
10
6
1
5
5
10
10
4
4
6
2
8
9
4
4
Good To Go
Some Cautions but Okay
Not Right For This Application


Feasibility Working Group Vote
(n=14)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Modified Larsen
Modified Steinbrocker
Ratingen
mTSS (B)
mSvdHs
SPARS
ReXSPA
4
3
1
2
2
10
10
13
11
11
12
12
1
3
3
Good To Go
Some Cautions but Okay
Not Right For This Application