Running Title: Composite outcome measures for PsA

Initiating evaluation of composite outcome measures for psoriatic arthritis: 2022 updates 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) working group (including rheumatologists, dermatologists, methodologists, and patient research partners) provided updates at the 2022 GRAPPA annual meeting on its work to evaluate composite outcome measures for PsA. Ten composite outcome measures were considered. Initial steps were to define the population, the purpose of use, and the proposed pros and cons of the ten candidate composites instruments for PsA. Preliminary Delphi exercises within the working group and GRAPPA stakeholders confirmed a high priority for evaluating Minimal Disease Activity (MDA); moderate priority for Disease Activity in PsA (DAPSA), and ACR response criteria; Psoriatic Arthritis Disease Activity Score (PASDAS), Composite Psoriatic Disease Activity Index (CPDAI), and 3/ 4 Visual analogue scale (VAS); and low priority for Disease Activity Score-28 (DAS28), Psoriatic Arthritis Responder Criteria (PsARC), and Routine Assessment of Patient Index Data 3 (RAPID 3). Further appraisal of candidate composite instruments is ongoing.

Introduction

Following the update of the core domain set for psoriatic arthritis (PsA) in 2016 (1), the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) - Outcome Measures in Rheumatology (OMERACT) working group has been developing an outcome measurement set for important domains for clinical trials of psoriatic arthritis (PsA) (1). Over the years, several instruments have been fully/ provisionally endorsed for some of the core domains (Table 1). The group aspires to evaluate candidate composite outcome measures for PsA. This report summarizes the current plans to prioritise further evaluation of these composite outcome measures under the OMERACT filter 2.2 framework (2).

Why do we need composite outcome measures for PsA?

Composite outcome measures allow the combination of outcomes measuring several domains of similar significance to clinicians and patients to generate a single score to give an estimate net clinical benefit of an intervention. Typically, the US Food and Drug Administration (FDA) defines “composite event endpoints” as the occurrence of any of the events (3). On the contrary, composite outcome measures have been commonly used for measuring the concept of disease activity in rheumatology, and recognised by the European Medicines Agency (EMA) guideline (4). The potential benefits of using composite outcome measures include the potential to reduce the sample size, duration of follow-up in clinical trials, thus avoiding statistical adjustment for multiple testing. Composite outcome measures also reduce the risk of underestimating disease through the measurement of multiple domains as they incorporate patient and clinician perspectives and enhance face validity of the outcome measure (5).

Recently, OMERACT has set forth a 4-step framework for the evaluation of composite outcome measures (5), including choosing the domains to be combined, selecting high

quality instruments for the domains, weighing the domains in the composite, and finally putting the composite outcome measures through the OMERACT filter 2.2 to comprehensively appraise an outcome measure's validity of Truth, Discrimination, and Feasibility (2). Composite outcome measures were further subclassified by the OMERACT filter 2.2 into composite outcome domain (COD) and multi-outcome domain (MOD) measures which can be conceptualized as categorical and continuous composite outcome measures respectively.

Several existing composite outcome measures have been used in PsA clinical trials and longitudinal studies, yet consensus on which measure to use in different settings has not been reached (6). None of the composite outcome measures have undergone comprehensive evaluation using the OMERACT filter. As OMERACT initiates new methodology guidance on evaluation of composites (5), the use of composite outcome measures in PsA is being revisited.

The composite outcome measures working group

A working group of 16 persons, including 11 rheumatologists, 1 dermatologist, 3 patient research partners (PRP), and 1 methodologist was set up. The goal of the project is to develop recommendations on composite outcome measures for PsA to be used in clinical trials and longitudinal studies. The working group opted for evaluating existing composite outcome measures rather than developing a new instrument. They may consider the latter if none fulfils the measurement requirements. To succeed, each of the candidate composite outcome measures should be evaluated in a specified population, for use in a well-defined context with intended purpose of use. There could be different composite outcome measures appropriate for different settings.

The candidate composite outcome measures.

The working group elaborated ten candidate composite outcome measures and carefully defined the population and context of use (Table 2 and Supplement). Notably, none of the existing composite outcome measures encompass all components of the core domain set (Table 3). Some examples of composite outcome measures stratified according to domains, scoring, and weighting were illustrated during the GRAPPA annual congress. The working group acknowledged the Psoriatic Arthritis Impact of Disease (PsAID) as a composite outcome that measures the impact of PsA on multiple aspects of patients' lives. As the PsAID12 has been endorsed by both GRAPPA and OMERACT as a measure of the health-related quality of life (HRQoL) domain (7), the working group decided not to include the PsAID in the present project.

The working group then conducted a preliminary Delphi exercise in June 2022. For each composite outcome measure, participants rated 1) the agreement on the defined purpose of further evaluation and the 2) priority to be evaluated using the OMERACT filter on a scale of 1 to 9 with 1-3 not important, 4-6 important but not critical, and 7-9 critically important. A similar, but more succinct Delphi exercise for a broader GRAPPA stakeholder was conducted subsequently. There were 149 members who participated (77.4% rheumatologists, 15.1% dermatologists, 2.7% PRPs, and 4.8% others). In the working group Delphi, the ACR response criteria (8), MDA (9), and DAPSA (10) received consensus rating as critically important to move forward; PASDAS (11), CDPAI (12), and 3/4 VAS (13) were important but not critical; DAS28, PsARC, and RAPID3 were rated low priority/not important to proceed with further evaluation. In contrast, in the Delphi exercise for GRAPPA stakeholders, only MDA received consensus rating as critically important (Table 2).

Patient perspective

It is important for patients to have a composite outcome measure that provides a reliable indicator of how they are doing. However, no existing composite outcome measure accounts for all domains in the core domain set that both patients and clinicians recognized as essential to include in all PsA clinical trials (1). There are some additional points that would be important from the patient perspective. First, the composite outcome measures should be comprehensive, measuring as many domains as possible that are important to patients. Secondly, the measures should be disease specific. There are numerous composite outcome measures developed for other conditions that are still utilized in clinical trials for PsA and may not represent a match to the domains relevant to PsA patients. Although a change towards using PsA-specific composite outcome measures may not be immediate, the conversation towards such a change should be continued. Thirdly, composite outcome measures developed with patient participation should be encouraged. Some of the important domains to not exclude were fatigue and skin disease activity.

In the question-and-answer session during the annual GRAPPA meeting in July 2022, PRPs once again echoed the importance of the comprehensiveness of composite outcome measures. At the same time, patients may experience flares in some domains, while other domains are getting better. Therefore, it may be useful to evaluate the changes in different domains in response to treatment to help select the best domains to be combined in the composite outcome measures. This is especially important for composite outcome measures used as responder criteria in trials.

Conclusion

The composite outcome measure working group has set the stage to re-evaluate the use of composite outcome measures in PsA. Preliminary Delphi exercise indicated a high priority

for evaluating MDA among GRAPPA stakeholders; moderate priority for DAPSA, ACR responder criteria, PASDAS, CPDAI, and 3/4VAS. Further evidence-based evaluation of composite outcome measures will follow to enable consensus in the selection of relevant composite outcome measures for use in PsA clinical trials.

Table 1. Update on the overall project for Core Measurement Set for PsA

Core Domains	Core Instruments/ Work progress	Team Lead
MSK disease activity		
- Peripheral joints*	Fully endorsed: 66/68 Swollen/Tender joint count	YYL
- Enthesitis*	Work on clinical enthesitis in progress SLR on US enthesitis completed, development of new instrument required and in progress	AO LE
- Dactylitis*	Work in progress	
- Axial	Awaiting formal definition of Axial involvement	
Skin	-	
Pain	-	
Patient Global Assessment	-	
Physical Function*	Provisionally endorsed: HAQ-DI, SF-36 PF	YYL
HRQoL*	Provisionally endorsed: PsAID	AMO
Fatigue*	Work in progress	AMO
Systemic inflammation	SLR completed, more data needed	LE
Structural Damage*¥	SLR completed, more data needed	WT

*Prioritized domains.

¥ This is not in the inner circle of core domain set but required at least once in the development program of intervention.

Abbreviations. HAQ-DI: Health Assessment Questionnaire-Disability Index; HRQoL: health-related quality of life; PsA: psoriatic arthritis; PsAID: Psoriatic Arthritis Impact of Disease; SF-36 PF: Medical Outcome Short Form 36- Physical Functioning domain; SLR: systematic literature review.

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Table 2. Defined purpose of use of candidate composite measures and results of Delphi exercises from working group and GRAPPA stakeholders

Candidate composite measures	Defined population	Purpose of Use	Working group votes[¥] (n=13)		GRAPPA stakeholder votes[¥] (n=149)
			Agreement* ≥7, (%)	Priority* ≥7, (%)	Priority* ≥7, (%)
ACR20/50/70	PsA patients with active disease	Use in RCTs, as a primary efficacy responder index for peripheral arthritis	92.3	76.9	60.4
PsARC	PsA patients with active disease	Use in RCTs, as an efficacy outcome responder index for peripheral arthritis	38.5	15.4	NA[§]
MDA/ VLDA	PsA patients with active disease	Use in RCTs, as a responder index for psoriatic disease to assess low disease activity/ remission In LOS, as a treatment target in clinical management	100	100	87.9
DAS28	PsA patients with active disease	Use in RCTs/ LOS, as a measure of disease activity in peripheral arthritis Cut-offs can be used as responder index in RCTs or treatment targets in LOS	7.7	0	NA[§]
CPDAI	PsA patients with active disease	Use in RCTs or LOS, as a measurement of disease activity	50	33.3	42.3
DAPSA/ cDAPSA	PsA patients with active peripheral arthritis	Use in RCTs or LOS, as a measurement of peripheral arthritis disease activity Cut-offs can be used as responder criteria in RCTs or treatment targets in LOS	76.9	83.3	68.5

PASDAS	PsA patients with active disease	Use in RCTs/ LOS, as a measurement of psoriatic disease activity Cut-offs can be used as responder index in RCTs or treatment targets in LOS	76.9)	69.2)	57.1
3VAS	PsA patients	Use in LOS/clinical practice, as a measurement of psoriatic disease activity	61.5[P]	53.8[P]	45.0
4VAS					49.7
RAPID3	PsA patients	Use in RCTs/LOS/clinical practice, as a measurement of psoriatic disease activity	30.8	23.1	NA[§]

[¥] Rated on scale 1-9: (1-3 not important) (4-6 important, but not critical) (7-9 critically important).
*≥70% of participants rating 7 and above would be considered agreement.
[P] 3VAS/4VAS were voted together in working group Delphi.
[§] These composite outcome measures were excluded in the Delphi exercise for GRAPPA stakeholder.
Abbreviations. ACR20/50/70: American College of Rheumatology 20/50/70% reduction; MDA: Minimal Disease Activity; CPDAI: Composite Psoriatic Disease Activity Index; DAPSA: Disease Activity Index for Psoriatic Arthritis; cDAPSA: clinical DAPSA; LOS: longitudinal observational studies; PsA: psoriatic arthritis; PASDAS: Psoriatic Arthritis Disease Activity Score; RCT: randomized controlled trial; VAS: Visual Analogue Scale; VLDA: Very Low Disease Activity.

Table 3. Mapping candidate composite measures to core domains for PsA

		Core Domains for PsA										
		MSK disease activity				Skin	Pain	PGA	HRQoL	Fatigue	Physical Function	Systemic Inflam -mation
		Arthritis	Enthesitis	Dactylitis	Axial							
(COD)	PASDAS	✓	✓	✓				✓			✓	✓
	DAPSA/cDAPSA	✓					✓	✓				✓
	DAS28	✓						✓				✓
	3 VAS					✓		✓				
	4 VAS	✓				✓	✓					
	RAPID 3						✓	✓			✓	
	CPDAI	✓	✓	✓	✓	✓			✓		✓	
(MOD)	ACR20/50/70	✓					✓	✓			✓	✓
	MDA/VLDA	✓	✓			✓	✓	✓			✓	

Abbreviations. ACR20/50/70: American College of Rheumatology 20/50/70% reduction; COD: composite outcome domain; CPDAI: Composite Psoriatic Disease Activity Index; DAS28: Disease Activity Score-28 joints for rheumatoid arthritis; DAPSA: Disease Activity Index for Psoriatic Arthritis; cDAPSA: clinical DAPSA; HRQoL: health-related quality of life; LOS: longitudinal observational studies; MDA: Minimal Disease Activity; MOD: multi-outcome domain; MSK: musculoskeletal; PsA: psoriatic arthritis; PASDAS: Psoriatic Arthritis Disease Activity Score; PGA: patient global assessment; RCT: randomized controlled trial; RAPID 3: Routine Assessment of Patient Index Data **3;** VAS: Visual Analogue Scale; VLDA: Very Low Disease Activity.

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