

REiNS - Enhancing Patient Engagement in Neurofibromatosis Clinical Trials

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Increasing patient engagement in arthritis studies: the OMERACT experience

Disclosures



REiNS objectives

1. To educate neurofibromatosis researchers and clinicians about the utility of increased patient engagement in developing endpoints for clinical trials
2. To engage patients, family members, and other stakeholders in the NF community in the REiNS collaboration
3. To generate a roadmap for developing patient engagement guidelines in REiNS subgroups



Overview

Part 1

To educate neurofibromatosis researchers and clinicians about **the utility of increased patient engagement in developing endpoints for clinical trials**

Part 2

How to engage patients, family members, and other stakeholders in the NF community in the REiNS collaboration

Part 3

To generate a roadmap for developing patient engagement **guidelines** in REiNS subgroups





Part I

*“Researchers can easily overlook the complexity and capriciousness of living with a chronic disease, reducing the meaning of life experiences to abstract themes and models”. **

* Schipper, K. (2011). *Patient participation & knowledge [thesis]*. VU University, Amsterdam (p.232)

“Where do we come from?”



- ▶ The patient as passive recipient, following doctor's prescription
- ▶ One way communication
- ▶ Patient is study participant

“Where are we going?”



- ▶ The patient as an equal partner in the decision making process
- ▶ Two way communication
- ▶ Patient as collaborative partner

Why actively involving patients in health research?

- ✿ Ethical argument
In a democracy patients have the right to speak for them selves
- ✿ Content argument
Experience based knowledge makes research outcomes more relevant and fitting better with the context of daily life
- ✿ Political argument
Legitimacy and chances for implementation increase
- ✿ *Empowerment of patients and researchers*



Have a say
in science

Patient participation in theory and
practice

Abma & Broerse
2007



Biannual worldwide conference on: Outcome Measurement in Rheumatology Clinical Trials



- ✿ First conference in 1992 in Maastricht
- ✿ Aim: To achieve consensus about endpoints for clinical trials in rheumatology
- ✿ Characteristics:
 - 👉 Data-driven, iterative consensus process
 - 👉 Inclusive, interactive, non-commercial
 - 👉 A broad stakeholders approach

Tugwell P, Boers M, OMERACT Conference on outcome measures in Rheumatoid Arthritis clinical trials: Introduction, *Jrn of Rheum* 1993;**20**:3 528-530.

OMERACT agrees 'core sets' for measuring outcome in rheumatic diseases

At OMERACT 1 (1992) the **core set** for rheumatoid arthritis (RA) was agreed

- Pain
- Swollen joints
- Tender joints
- Physician global assessment
- Patient global assessment
- Physical function
- Acute phase response



M. Boers, P. Tugwell, D.T. Felson, et al , World Health Organization and International League of Associations for Rheumatology Core Endpoints for Symptom Modifying Antirheumatic Drugs in RA Clinical Trials , Jrn Rheum 1994, 21, WHO/ILAR suppl.

Why involving patients in outcome research? **OMERACT 5**

- In 2000 OMERACT participants discussed the definition of a 'clinically important change' in response to treatment.
- In the final voting session participants agreed that this questions could only be answered by patients.

For OMERACT 6 (2002)
11 patients were
invited to review the
OMERACT core set.



Involving patient research partners has a significant impact on outcomes research: a responsive evaluation of the international Outcome Measures in Rheumatology (OMERACT) conferences

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John

Koelewijn-van Loon,² Sarah Collins,³

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► Prepublication history for this paper are available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2012-002241>).

ABSTRACT
Objectives
international
Rheumatology
has influenced
research
Design
internal
proceedings
including
Setting

conference OMERACT 10 (Malaysia, 2010).
Participants: Senior researchers (n=10), junior researchers (n=2), representatives of the pharmaceutical industry and regulators (n=2), conference staff (n=2), new patient delegates (n=8) and experienced patient delegates (n=8).



PATIENT PARTICIPATION IN
RHEUMATOLOGY RESEARCH
A four level responsive evaluation

Maarten de Wit

ARTICLE SUMMARY

Article focus

- Since 2002, patients have participated as collaborative partners in the biannual conference on Outcome Measures in Rheumatology (OMERACT).
- Although the contribution of patients has been praised and there is a widespread call for scientific publications on the impact of engaging with patients, no systematically obtained evidence has been published to support the idea that the structural involvement of patients in research conferences is beneficial.
- Our qualitative study reports the combined results of a thematic document analysis and 32 semistructured interviews with all stakeholders including researchers, patient participants, and



The example of fatigue in RA



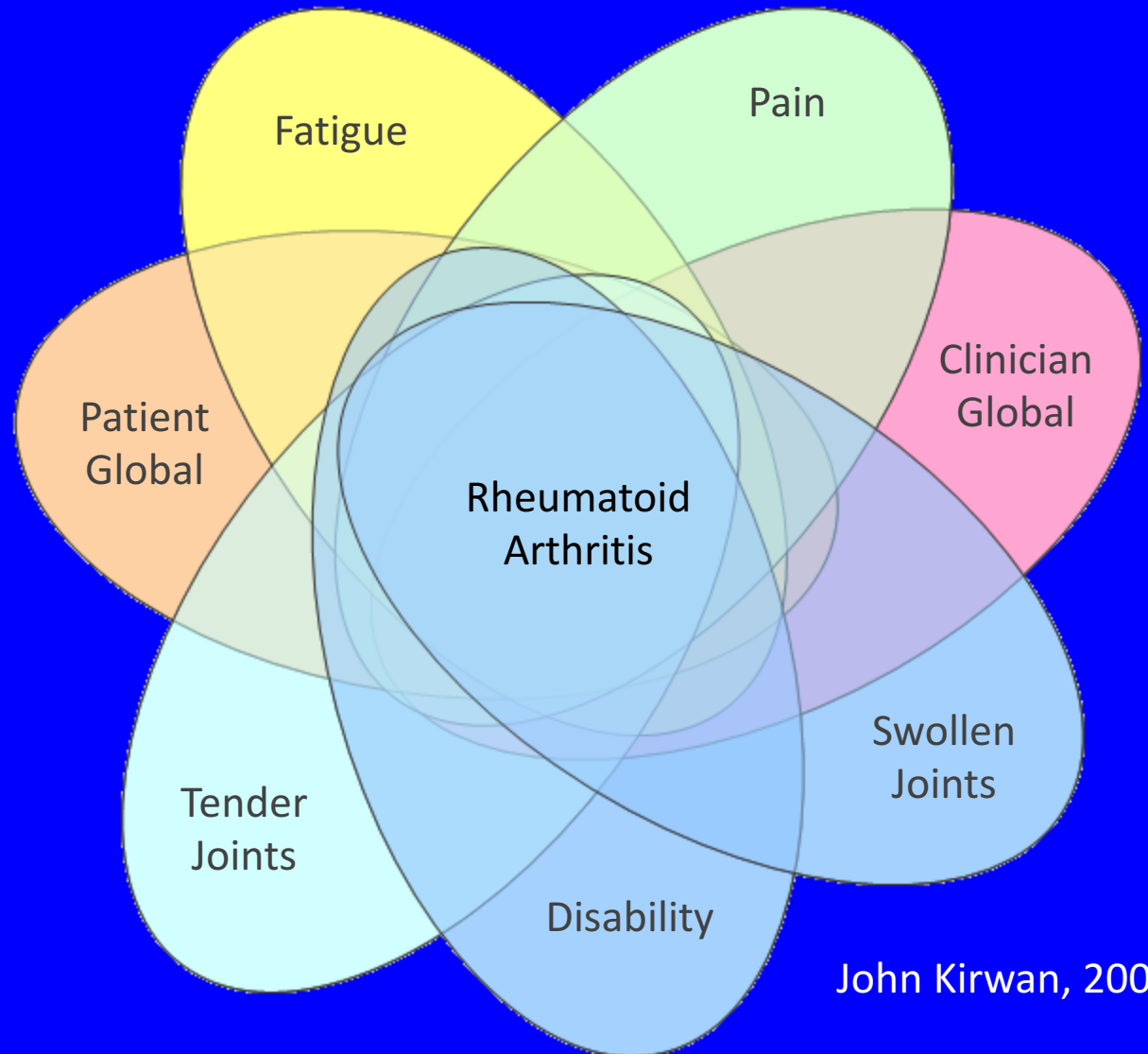
Early descriptions at OMERACT 6 & 7 led to substantial qualitative research establishing the importance of RA fatigue

“Fatigue is overwhelming and different from normal tiredness; it permeates every sphere of life; and self-management is variable, but professional support is rare”

Hewlett S, et al. Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. *Arthritis Rheum* 2005

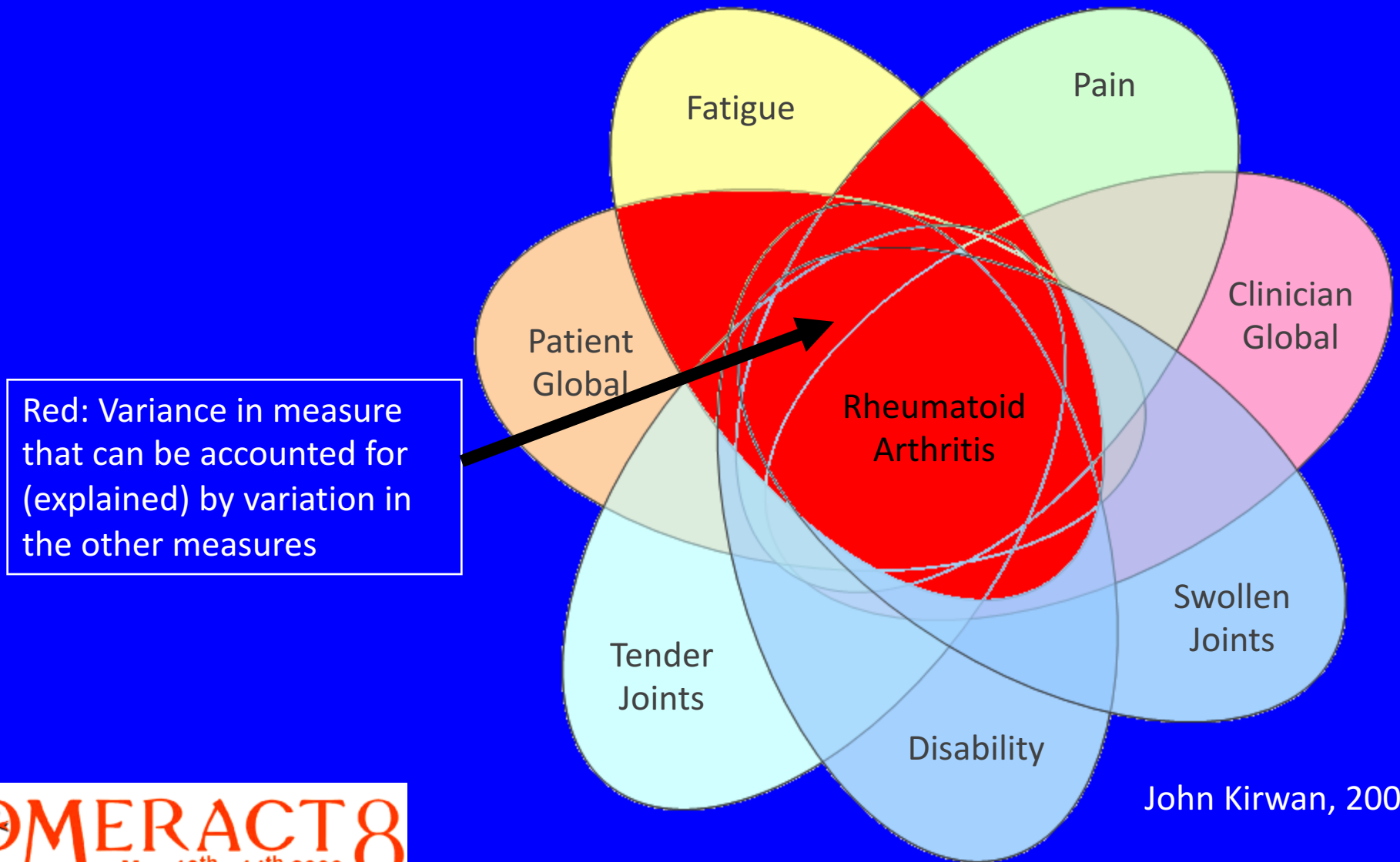
Nicklin, J., et al., Collaboration with patients in the design of patient-reported outcome measures: Capturing the experience of fatigue in rheumatoid arthritis. *Arthritis Care Res* 2010.

Qualitative work showed that measuring fatigue adds new information to the existing core set for RA



John Kirwan, 2006

Contribution of different variables to measuring rheumatoid arthritis

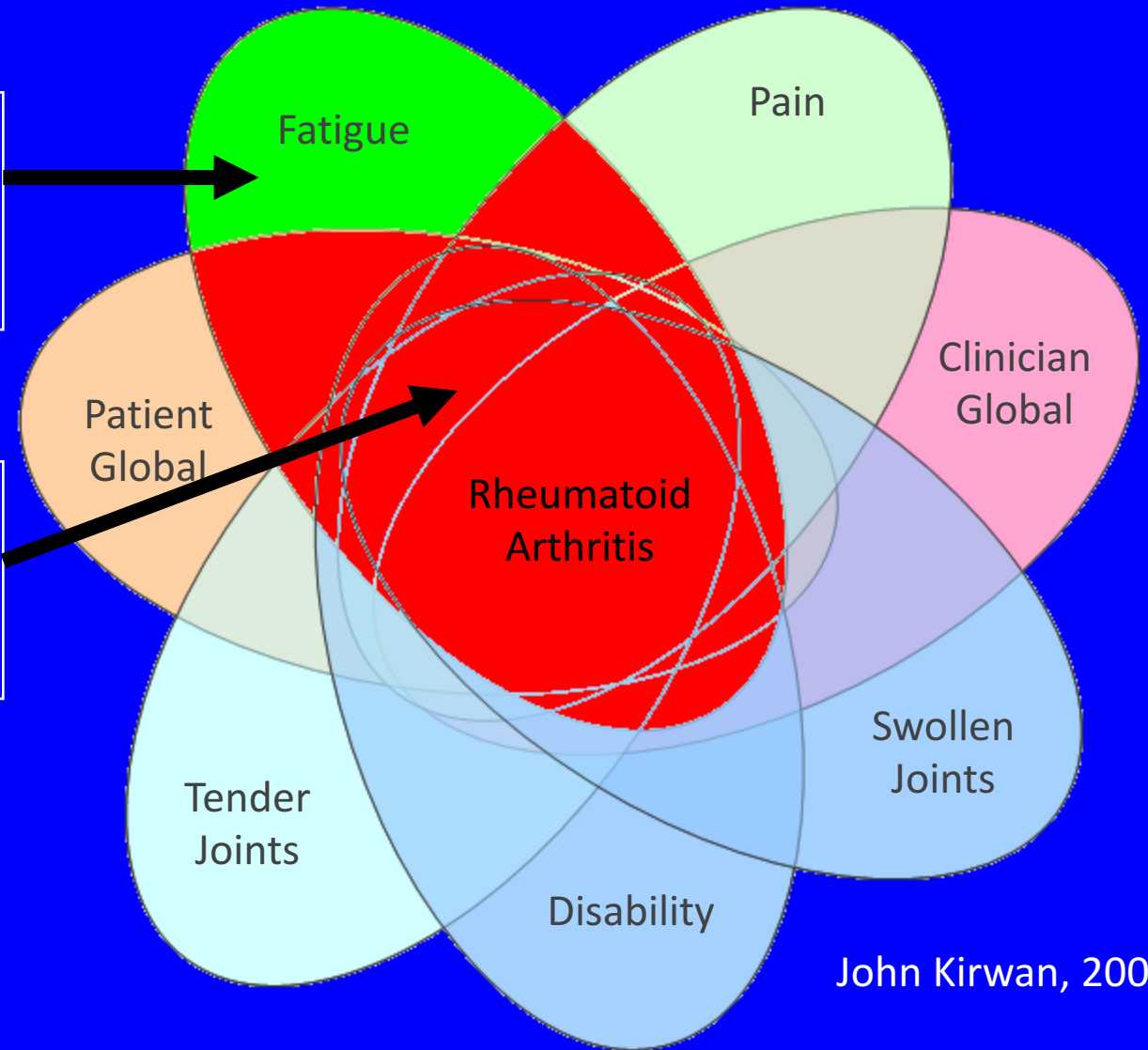


John Kirwan, 2006

Contribution of different variables to measuring rheumatoid arthritis

Green: Variance in measure that cannot be explained by variation in the other measures

Red: Variance in measure that can be accounted for (explained) by variation in the other measures




John Kirwan, 2006

Result


- Fatigue was added to the core-set, to be included as outcome in every new clinical trial in RA.
- More powerful instruments for measuring fatigue in RA have now been devised, and are increasingly used in clinical trials.

This would never have happened without the direct involvement of patient delegates in the OMERACT process






“We were first discussing on fatigue and to be honest I never ever had before heard of fatigue being a problem in rheumatology. So it got into my mind and then I got thinking about it and then, when I was back, I asked patients if they felt fatigue and I got nearly a 100% positive response. So it was like a coming out, you know. I listened to the patients before but bringing it to a specific topic, that was really what I learned at OMERACT.” [RC]



*“We were first discussing on fatigue and to be honest **I never ever had before heard of fatigue being a problem** in rheumatology. So it got into my mind and then I got thinking about it and then, when I was back, I asked patients if they felt fatigue and I got nearly a 100% positive response. So it was like a coming out, you know. I listened to the patients before but bringing it to a specific topic, that was really what I learned at OMERACT.” [RC]*



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Conclusion

“Clinical trials are only as credible as their endpoints” *

** Peter Tugwell & Maarten Boers, The Journal of Rheumatology 1993; 20:3*



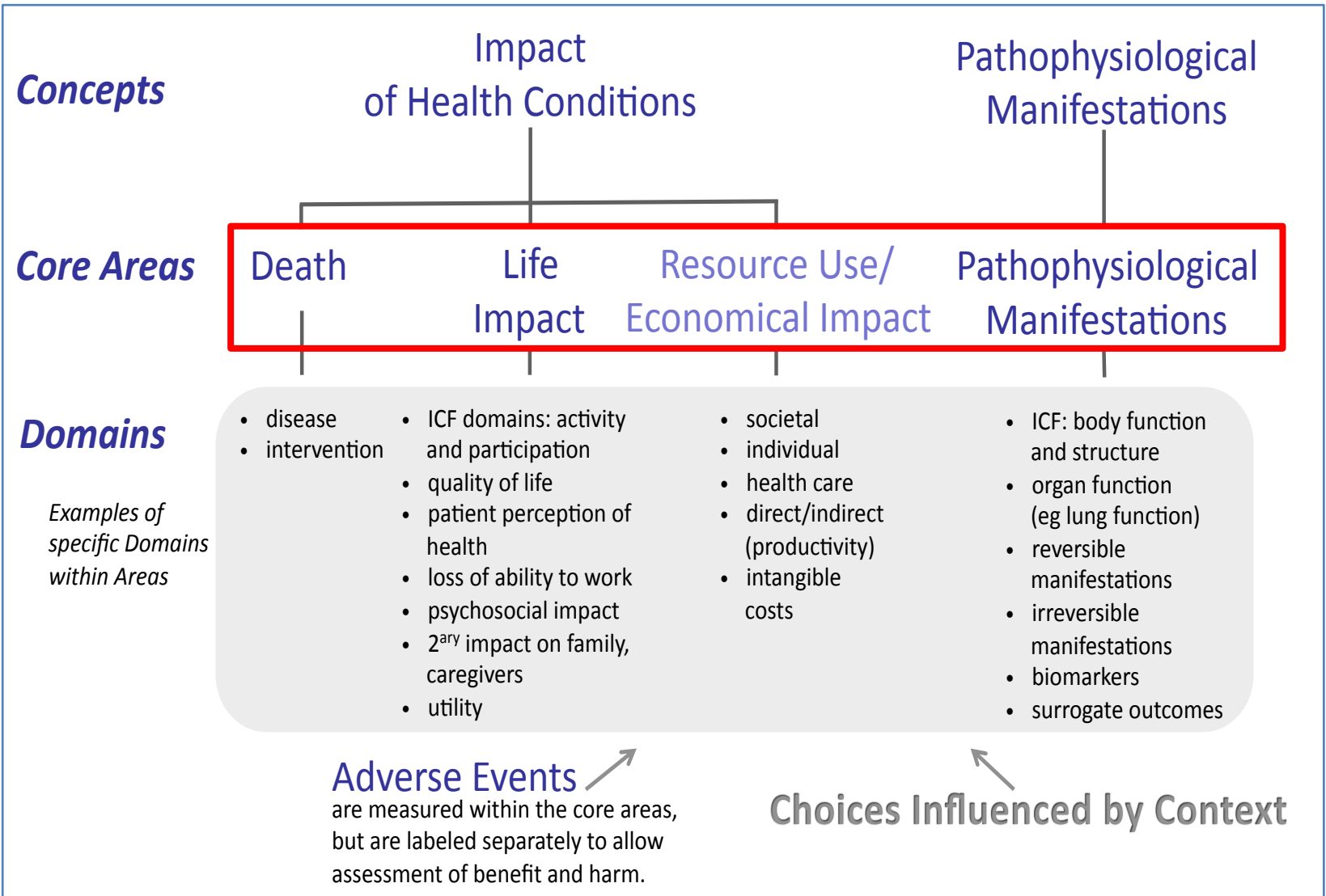
Part II

Core domain set development according to the OMERACT filter 2.0

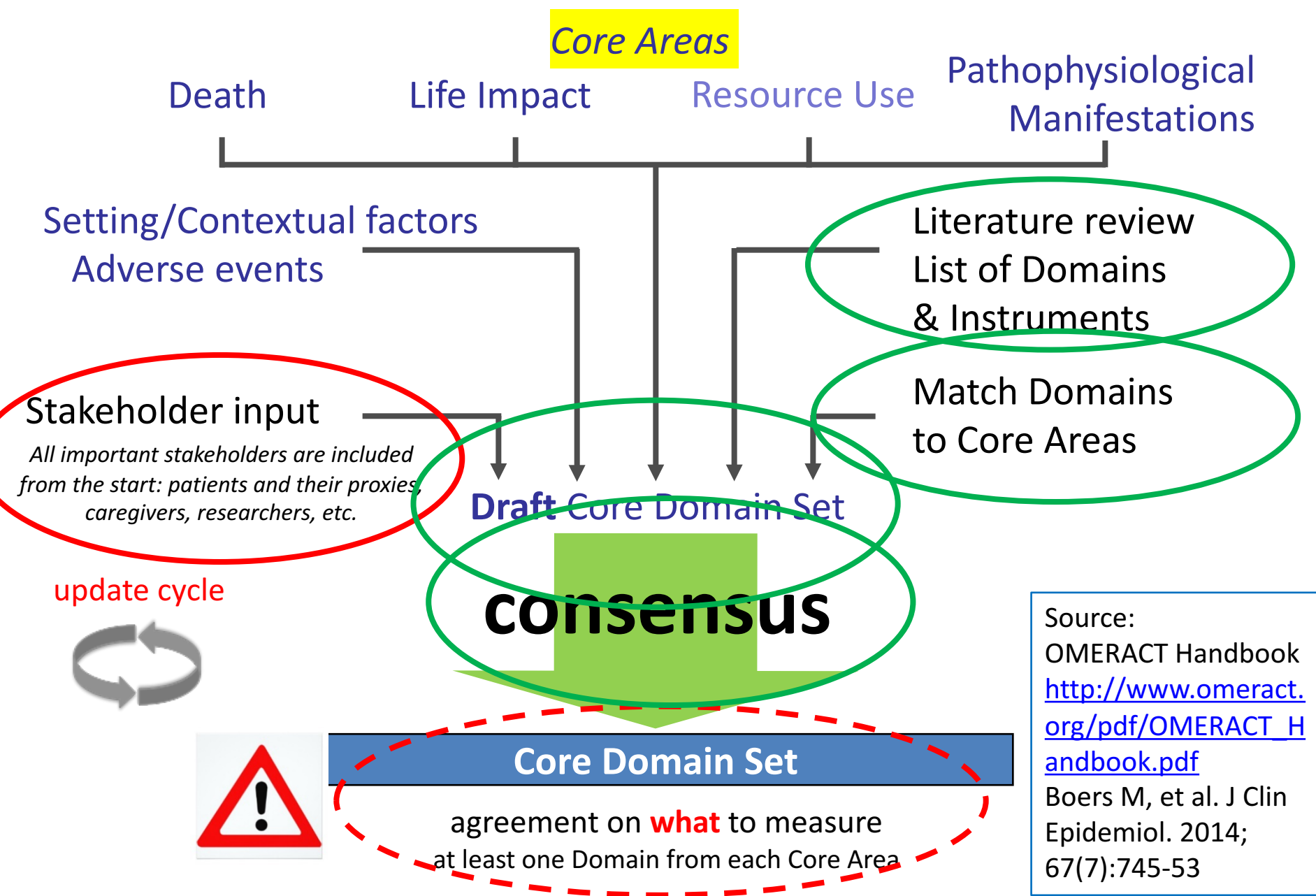
Boers M, Kirwan J, Tugwell P, et al. The OMERACT Handbook. In: OMERACT; 2014.

Boers M, Kirwan JR, Wells G, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol 2014;67(7):745-53.

OMERACT disease specific core domain sets

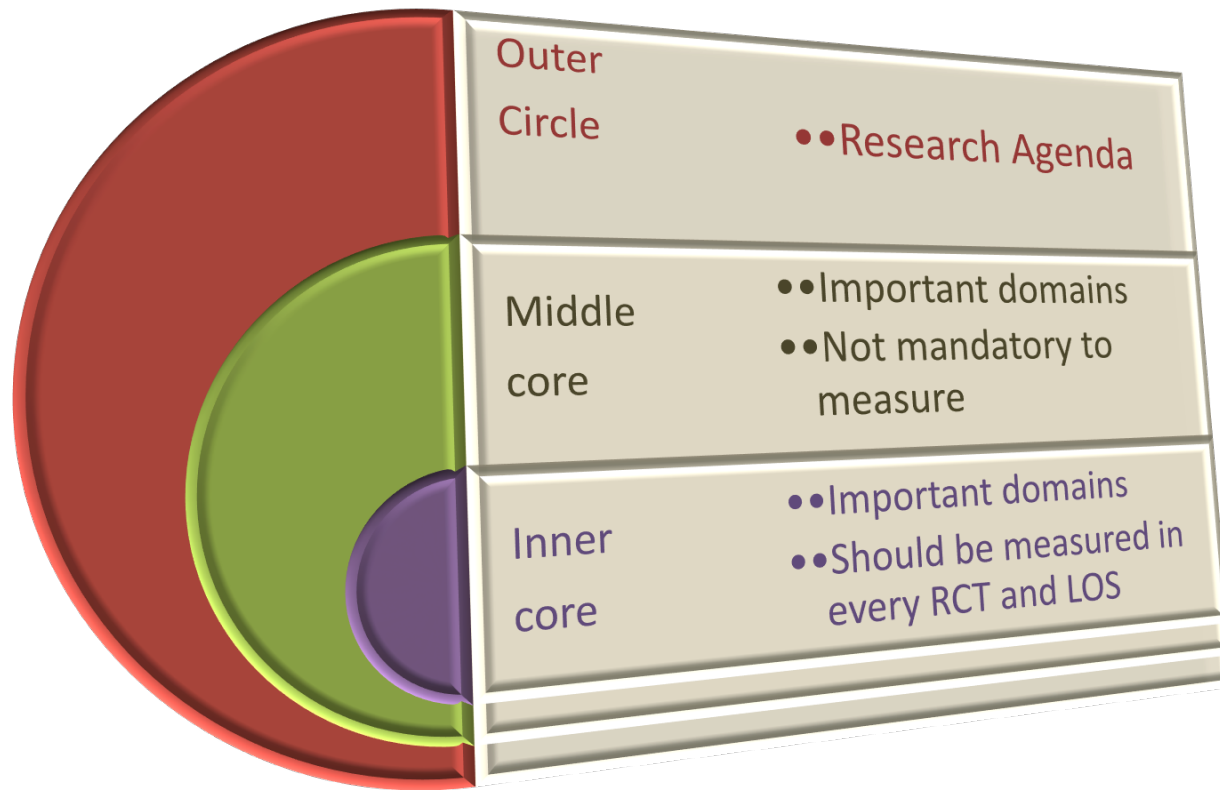


OMERACT Filter 2.0: Developing a Core Domain Set



Source:
OMERACT Handbook
http://www.omeract.org/pdf/OMERACT_Handbook.pdf
Boers M, et al. J Clin Epidemiol. 2014; 67(7):745-53

Template of an OMERACT core domain set



COMET– Core Outcome Measures in Effectiveness Trials

- ❖ Core outcome set (COS) is an agreed standardized set of outcomes to be measured and reported as a minimum in all trials in a specific health related area.*
- ❖ COMET database is an international repository of studies relevant to the development of COS, planned, ongoing and completed.**

* Gargon E, et al. Choosing important health outcomes for comparative effectiveness research: a systematic review. *PLoS One* [internet], 2014; 9(6):[e99111 p.]. Available from: 10.1371/journal.pone.0099111.

** www.comet-initiative.org



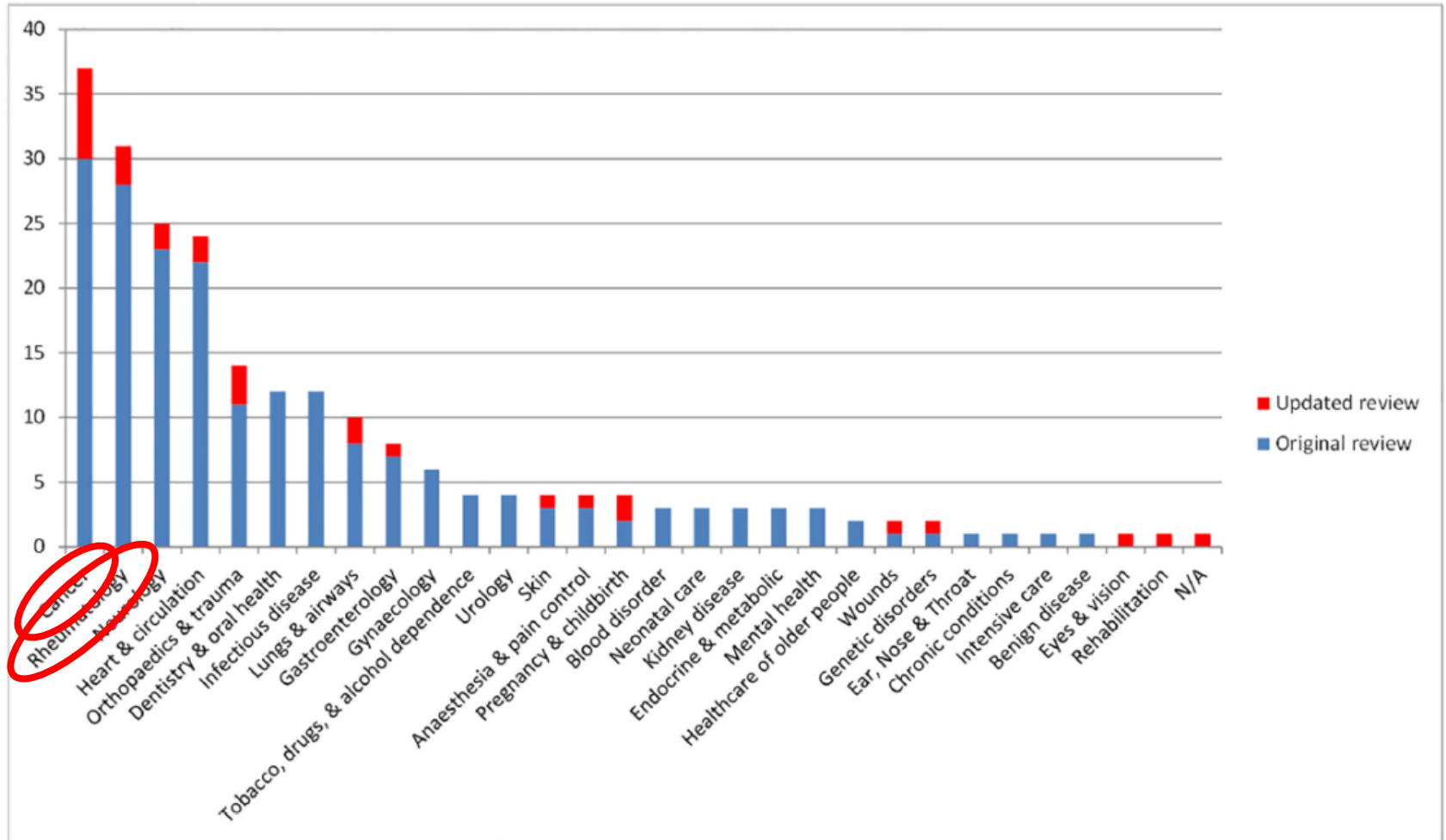
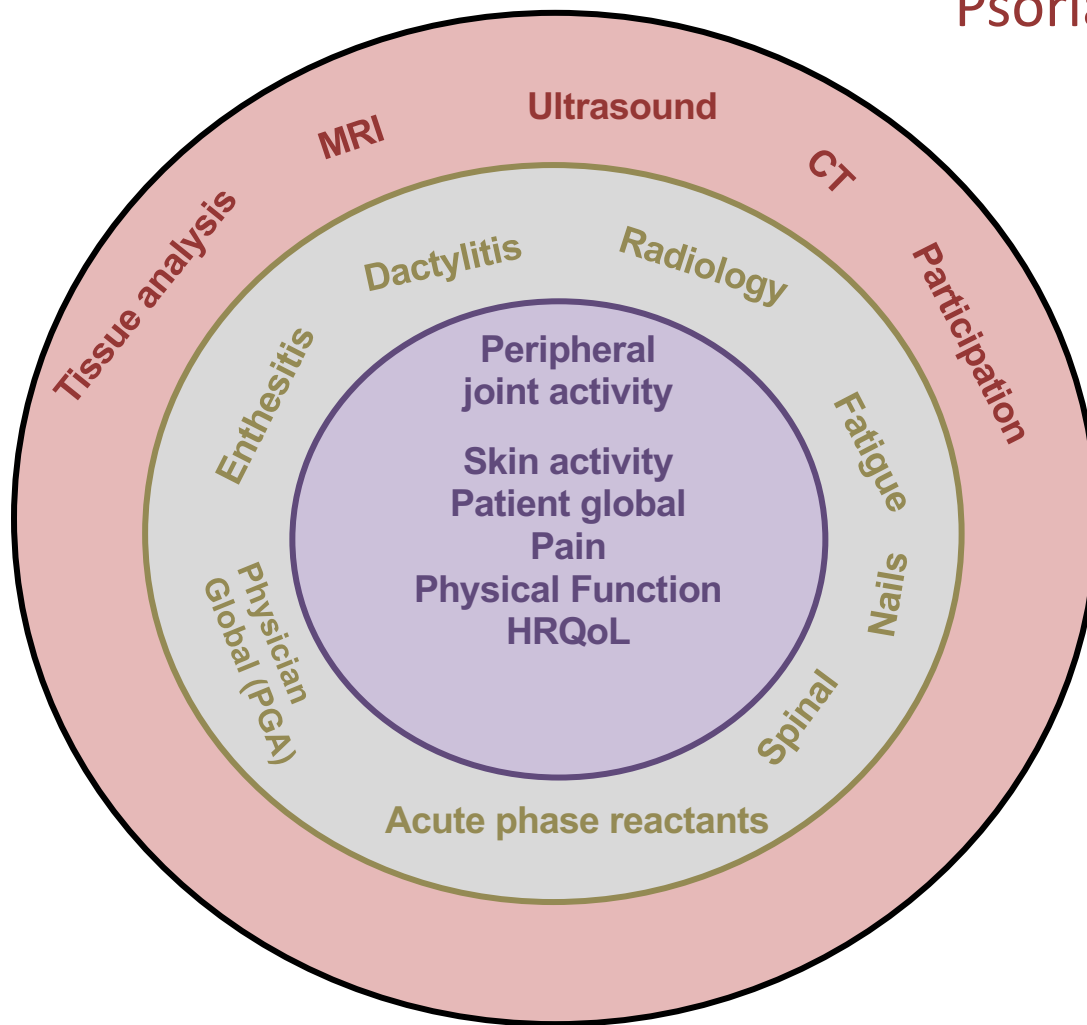


Fig 3. Number of COS developed in each disease category (n = 227).

OMERACT-GRAPPA Psoriatic Arthritis core set

2006



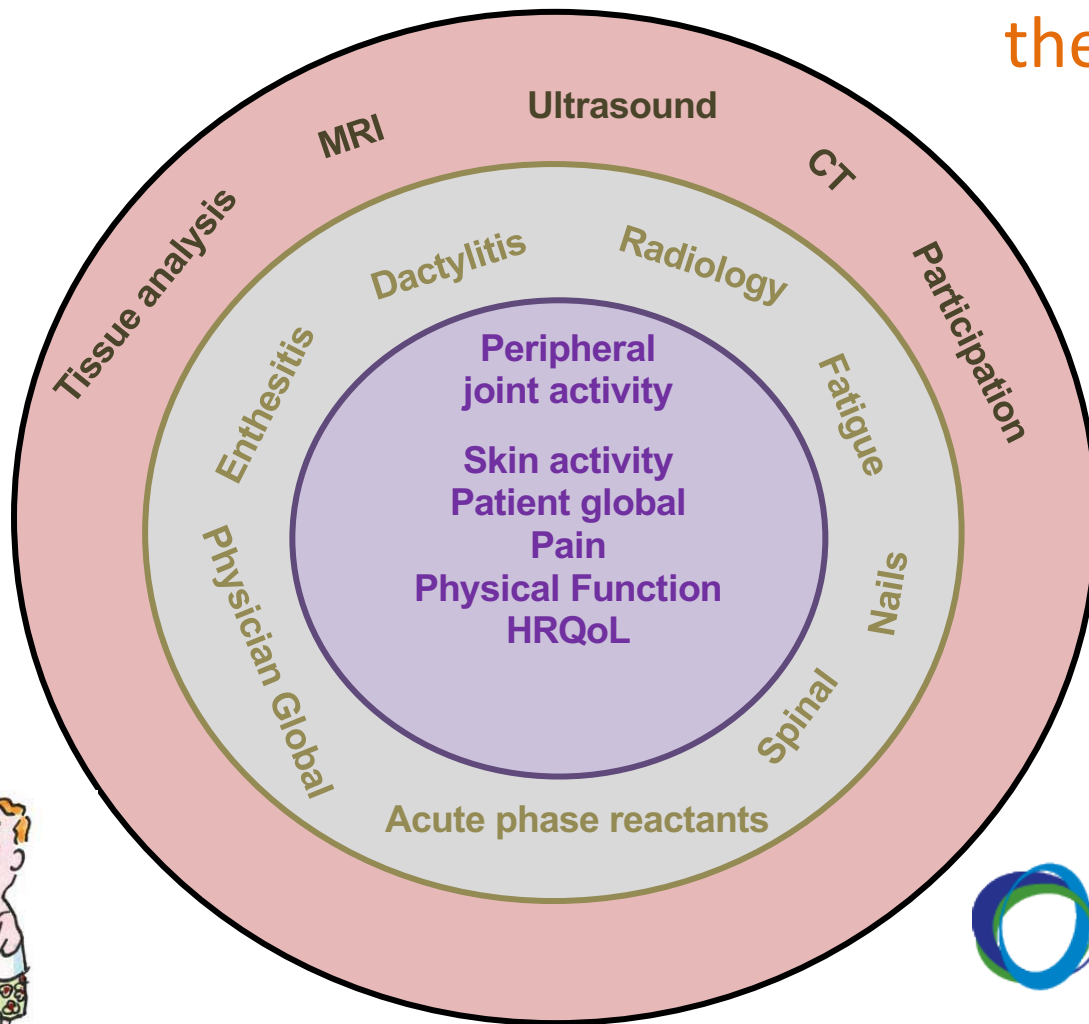


2006

2012

2013

Why updating the PsA COS?



Tillett W, Adebajo A, Brooke M, et al. Patient involvement in outcome measures for psoriatic arthritis. *Curr Rheumatol Rep* 2014;16(5):418.

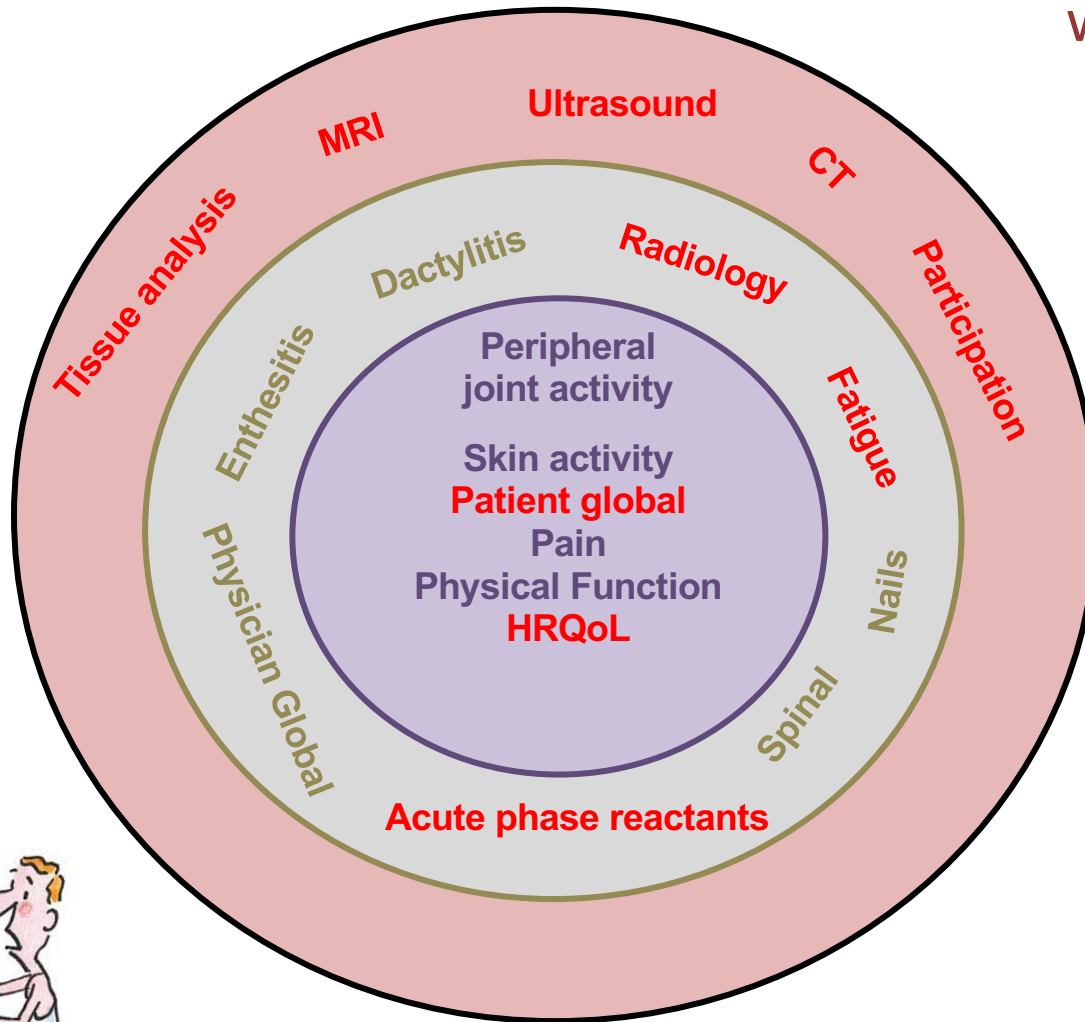


2006

2012

2013

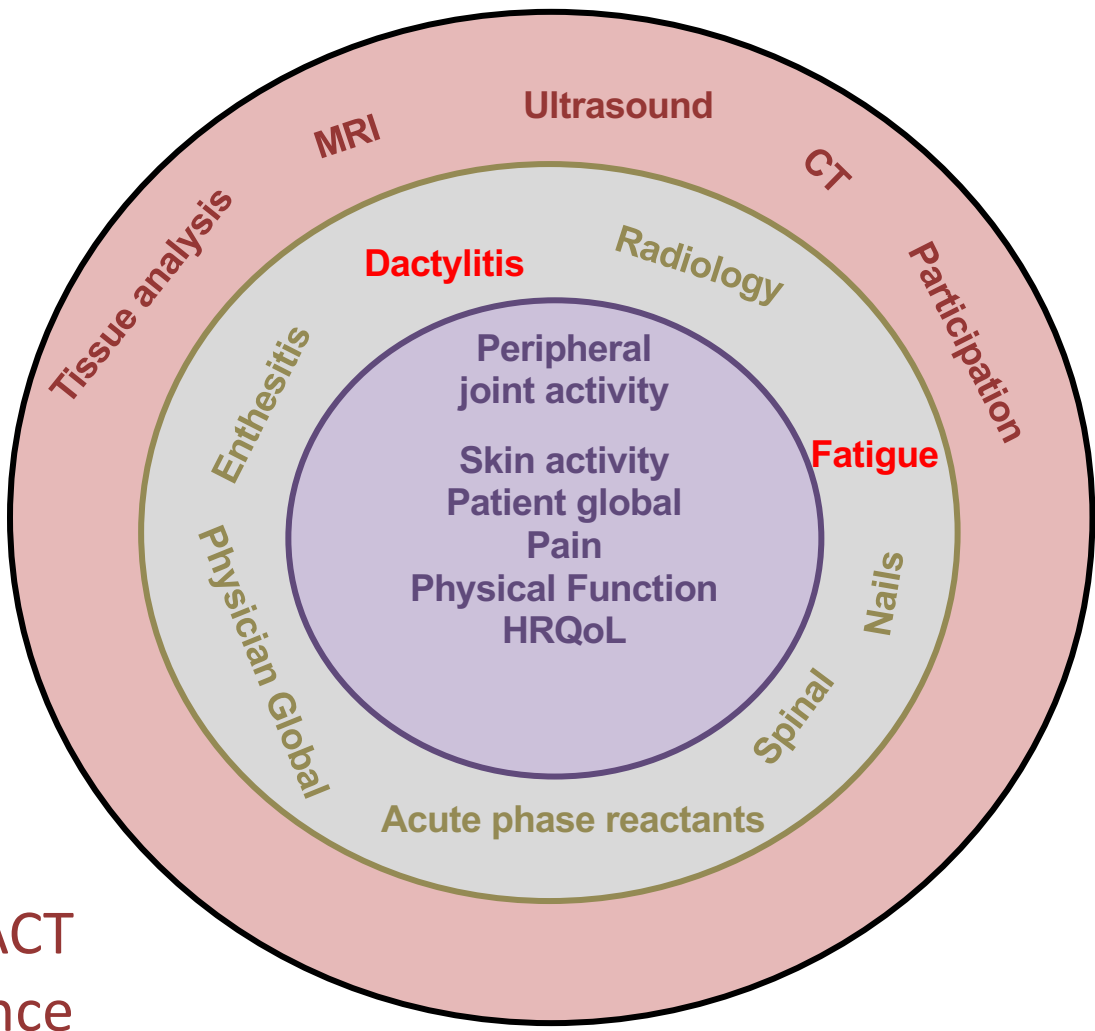
Core set discussed with patients



Tillett W, Adebajo A, Brooke M, et al. Patient involvement in outcome measures for psoriatic arthritis. *Curr Rheumatol Rep* 2014;16(5):418.



- 2006
- 2012
- 2013
- 2014



Need to update the PsA core set with active patient involvement

OMERACT conference 2014

Tillett W, Eder L. Enhanced patient involvement and the need to revise the core set- report from the PsA workshop at OMERACT 2014. *Jrn of Rheum*, 2015



A best practice of patient participation in COS development

Updating the core domain set for Psoriatic Arthritis



Methods of involvement

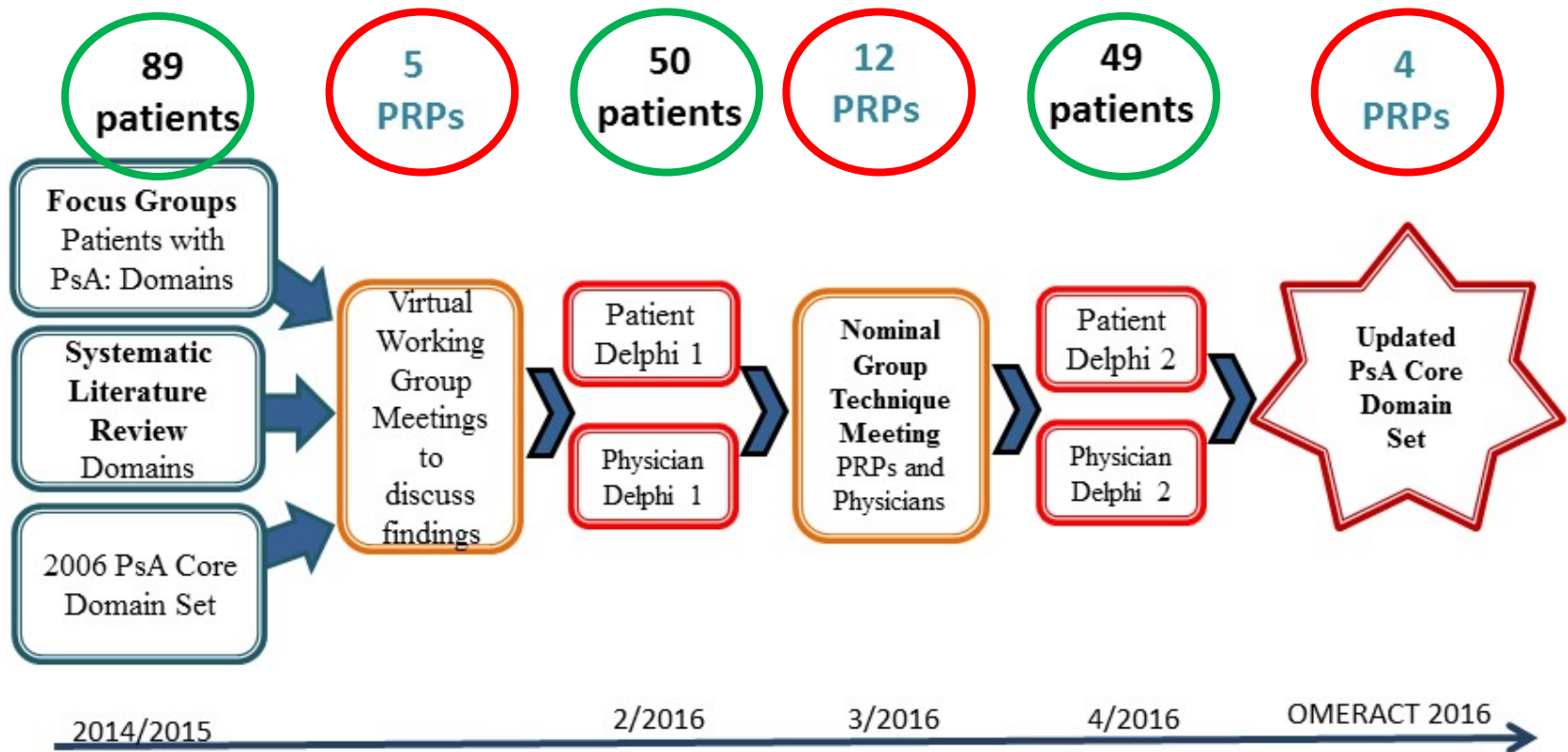
Patient participation – following OMERACT recommendations*

The patient voice was sought through

1. Active partnership of five patient research partners (PRPs) in the working group and one PRP in the Steering Group
2. International focus group study representing five continents and including seven countries
3. Delphi study
4. Consensus meeting

- Cheung PP ea Recommendations for the Involvement of Patient Research Partners (PRP) in OMERACT Working Groups. *The Journal of rheumatology* 2016;43(1):187-93)
- De Wit M ea, Successful Stepwise Development of Patient Research Partnership: 14 Years' Experience of Actions and Consequences in OMERACT, *The Patient* 2016,

Trying to ensure representativeness



Work streams Update core outcome set for Psoriatic Arthritis



Following OMERACT recommendations

The Journal of
Rheumatology

Recommendations for the Involvement of Patient Research Partners (PRP) in OMERACT Working Groups. A Report from the OMERACT 2014 Working Group on PRP

Peter P. Cheung, Maarten de Wit, Clifton O. Bingham 3rd, John R. Kirwan, Amye Leong, Lyn M. March, Pam Montie, Marieke Scholte-Voshaar, and Laure Gossec

ABSTRACT. *Objective.* Patient participation in research is increasing; however, practical guidelines to enhance this participation are lacking. Specifically within the Outcome Measures in Rheumatology (OMERACT) organization, although patients have participated in OMERACT meetings since 2002, consensus about the procedures for involving patients in working groups has not been formalized. The objective is to develop a set of recommendations regarding patient research partner (PRP) involvement in research working groups.

What about PRPs Tasks?

	Steering group	Working group	Study design	SLR	FG protocol	FG moderation analysis	Delphi Design	NGT meeting
PRP 1		X	X	X	X	X	X	X
PRP 2		X	X		X		X	X
PRP 3		X	X	X	X		X	X
PRP 4	X	X	X	X	X	X	X	X
PRP 5					X			
PRP 6					X			
PRP 7					X	X	X	X
PRP 8								
PRP 9								
PRP 10								
PRP 11		X	X	X	X			
PRP 12								
PRP 13						X		
PRP 14					X			
TOTAL	1	5	5	4	9	4	5	5

What about PRPs' recognition?

Co-authorship



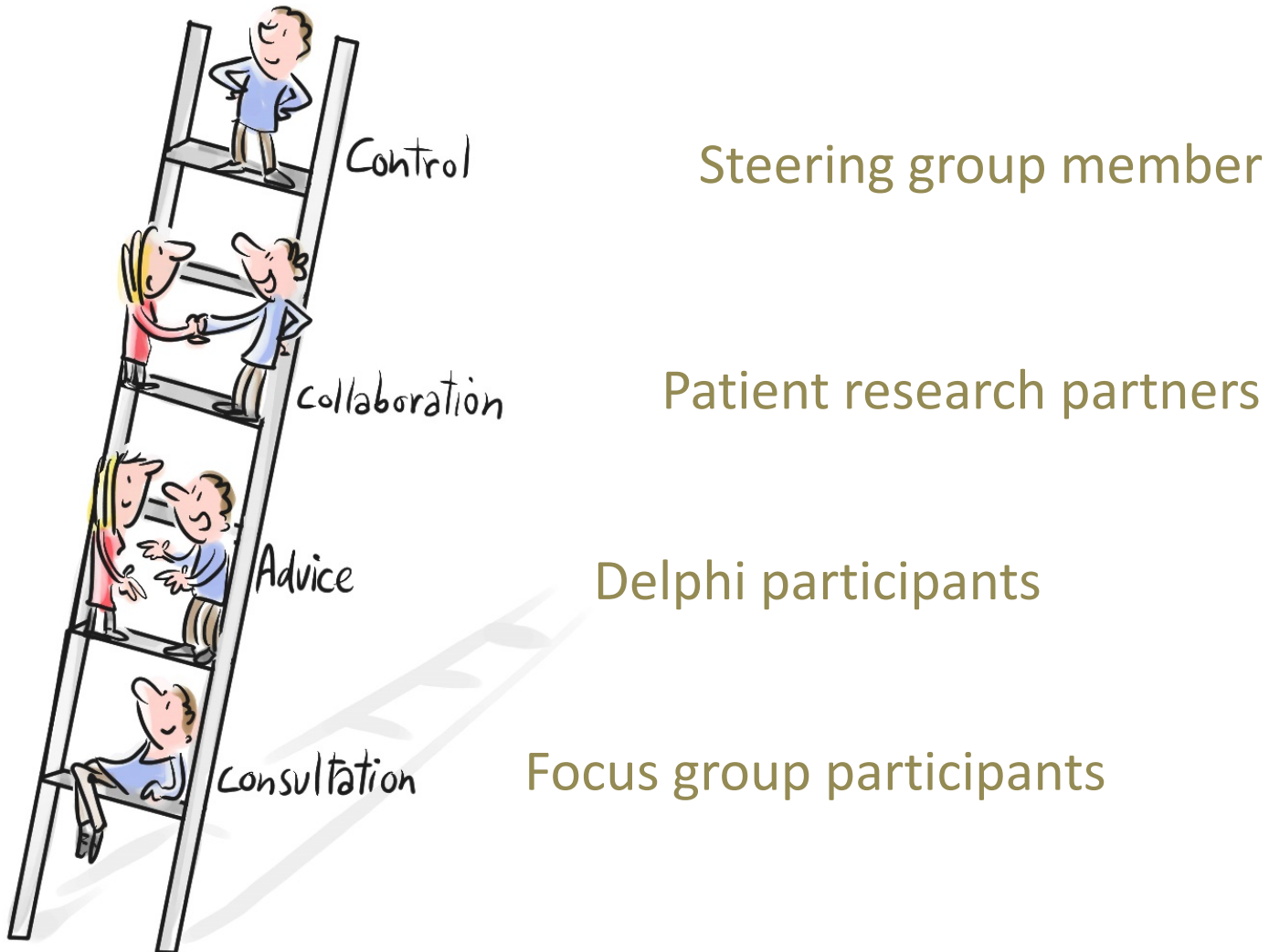
	Steering group	Working group	Study design	SLR 1	FG protocol	FG moderation analysis	Delphi Design	NGT meeting
PRP 1		X	X	X	X	X	X	X
PRP 2		X	X		X		X	X
PRP 3		X	X	X	X		X	X
PRP 4	X	X	X	X	X	X	X	X
PRP 5					X			
PRP 6					X			
PRP 7					X	X	X	X
PRP 8								
PRP 9								
PRP 10								
PRP 11		X	X	X	X			
PRP 12								
PRP 13						X		
PRP 14					X			
TOTAL	1	5	5	4	9	4	5	5

Extended PRP involvement

	Steering group	Working group	Study design	SLR 1	FG protocol	FG moderation analysis	Delphi	NGT meeting
PRP 1		X	X	X	X	X	X	X
PRP 2		X	X		X		X	X
PRP 3		X	X	X	X		X	X
PRP 4	X	X	X	X	X	X	X	X
PRP 5					X		X	X
PRP 6					X		X	X
PRP 7					X	X	X	X
PRP 8							X	X
PRP 9							X	X
PRP 10							X	X
PRP 11		X	X	X	X		X	X
PRP 12							X	X
PRP 13						X		
PRP 14					X		X	
TOTAL	1	5	5	4	4	4	13	12

PRP participation as integral part of research

Evolving Patient Roles





2006

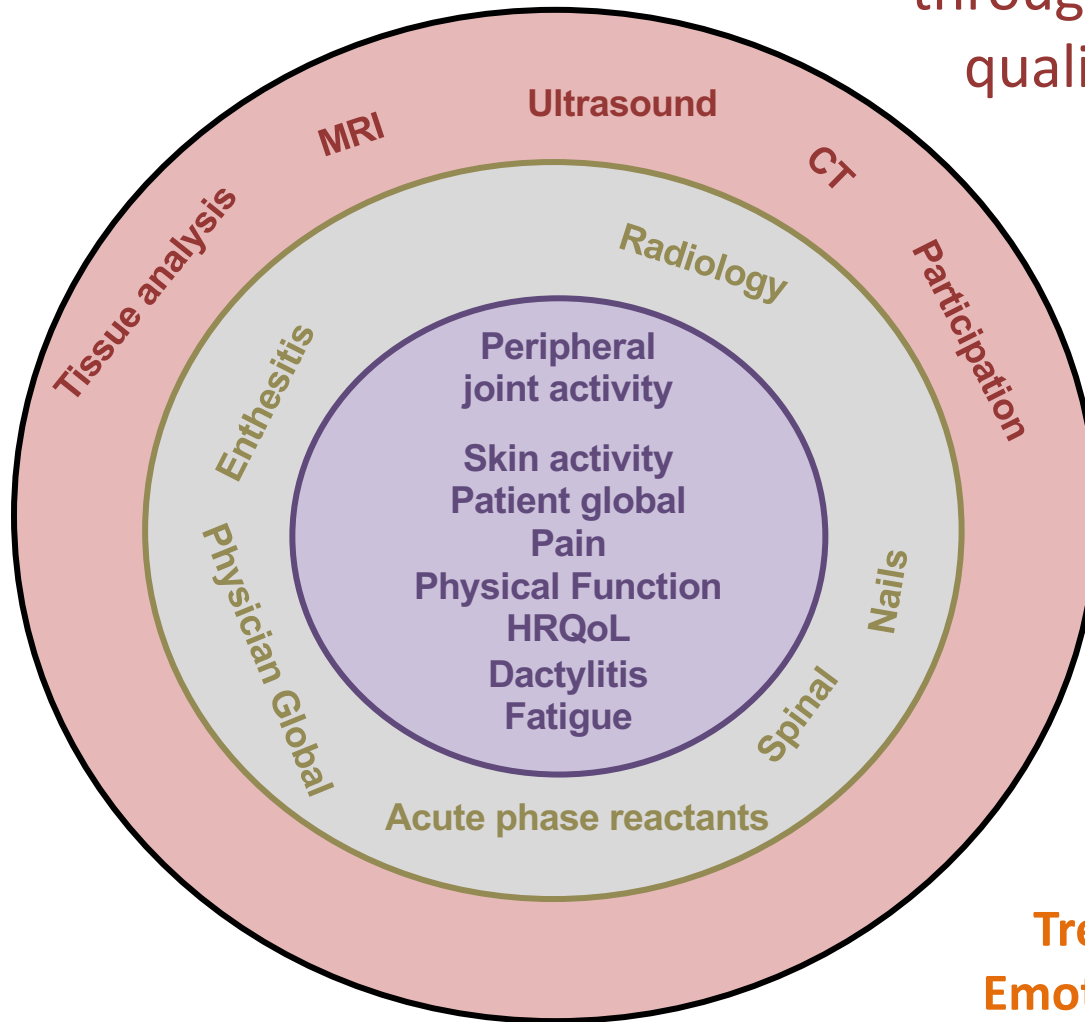
2012

2013

2014

2015

New domains identified through SLR and the qualitative studies



Systemic inflammation

Independence
Stiffness

Sleep
Treatment burden

Emotional wellbeing

Economic costs

New domains identified through SLR and the qualitative studies

2006

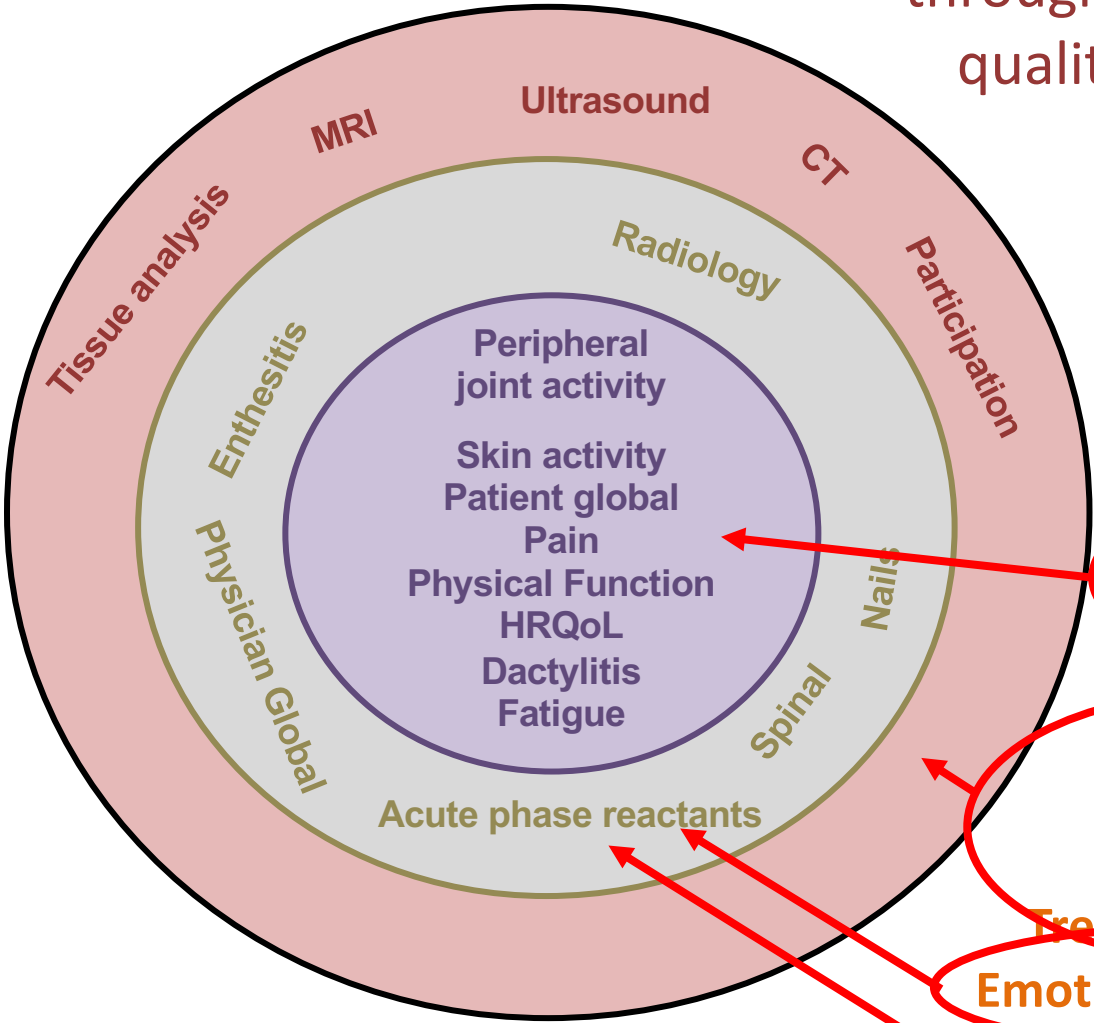
2012

2013

2014

2015

2016



Systemic inflammation

Independence
Stiffness
Sleep
Treatment burden

Emotional wellbeing

Economic costs



What were challenges of involving patients in the COS update process?

1. Unanticipated Work Load for PRPs and researchers
2. Communication and equal collaboration

How to enhance new approaches and attitudes

3. Ensuring broad representativeness of patients' perspectives

In demography, geography, disease severity and in numbers

4. Keeping PRPs and researchers motivated to collaborate
5. Preserving the patient perspective throughout the research process



What were challenges of involving patients in the COS update process?

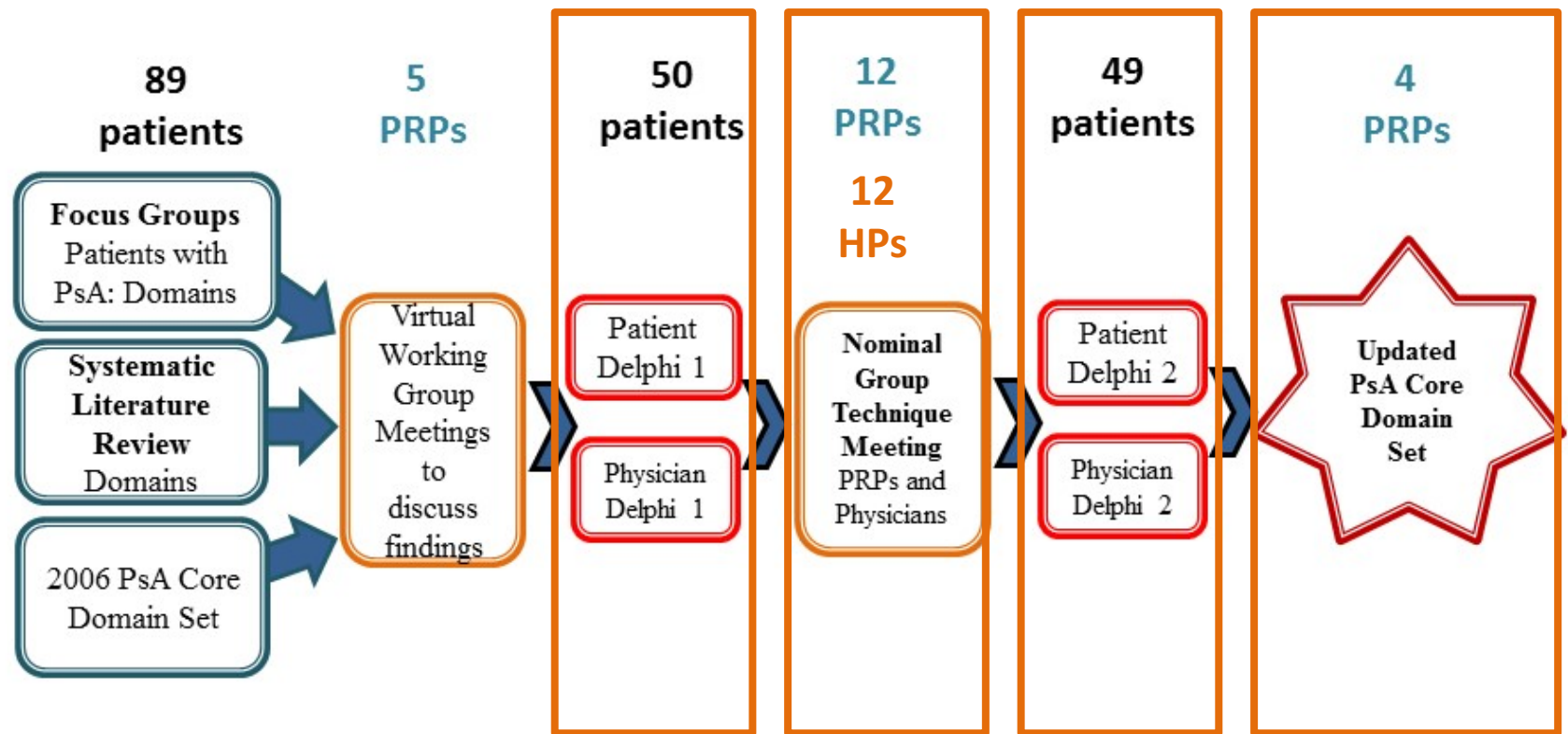
1. Unanticipated Work Load for PRPs and researchers
2. Communication and equal collaboration
How to enhance new approaches and attitudes
3. Ensuring broad representativeness of patients' perspectives,
In demography, geography, disease severity and in numbers
4. Keeping PRPs and researchers motivated to collaborate
5. Preserving the patient perspective throughout the research process

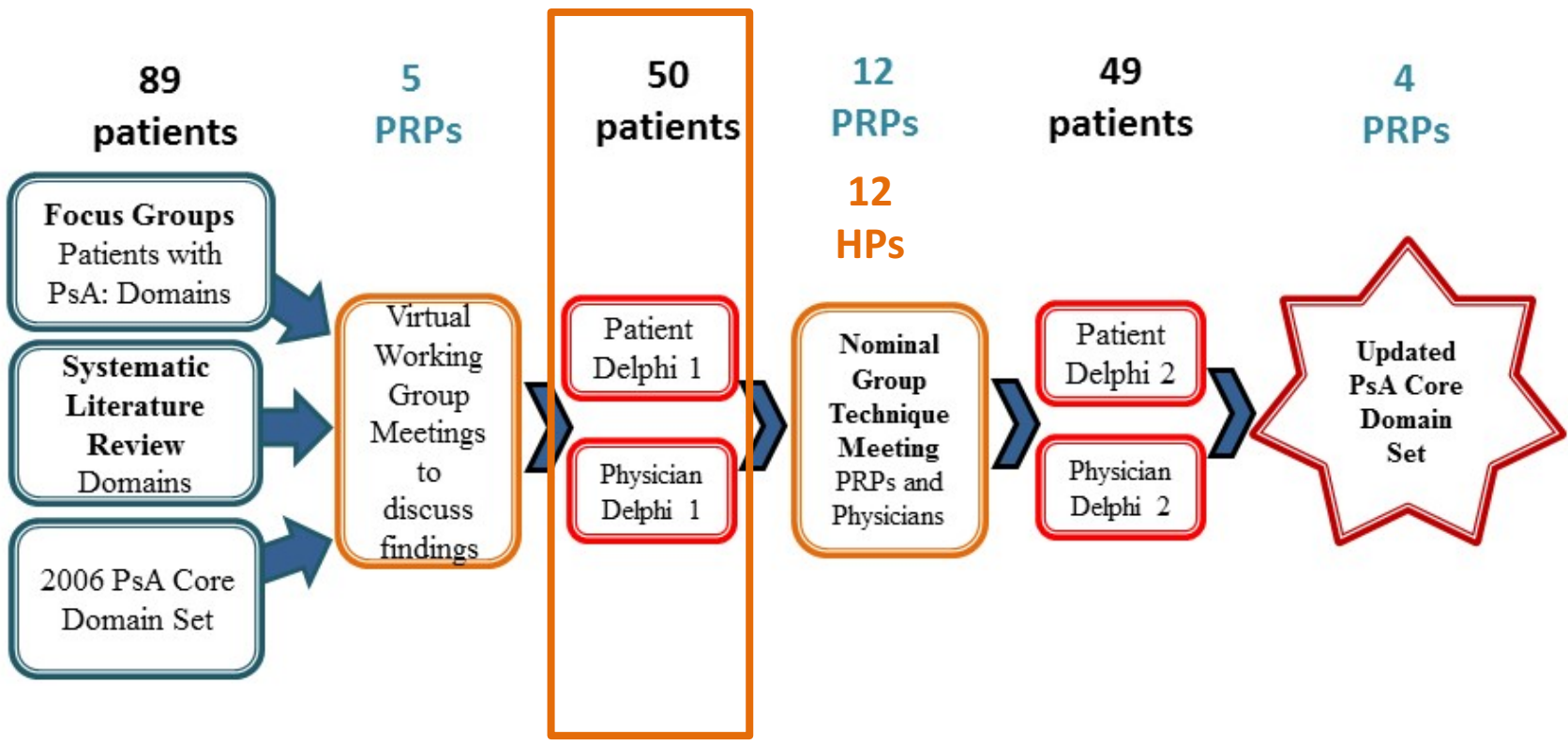


Preserving the patients' perspectives

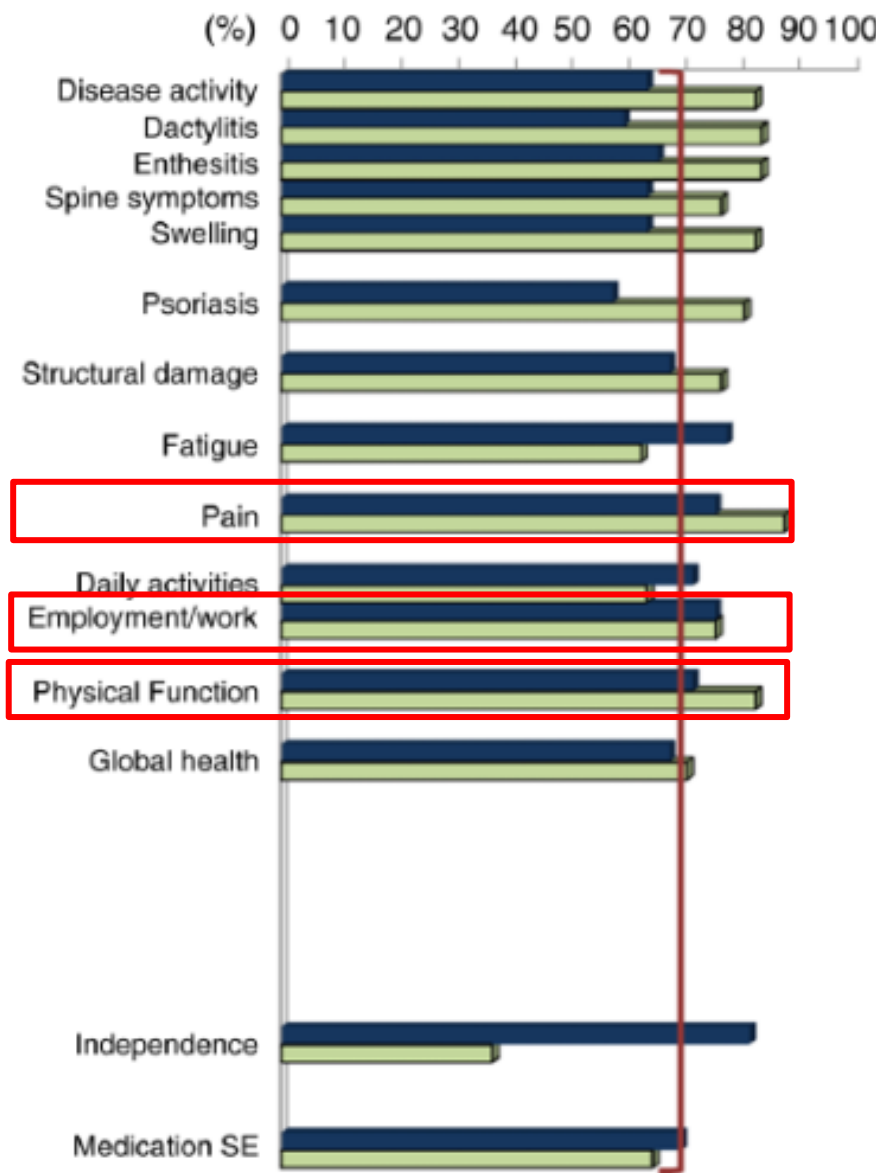
- Core domain sets should be short and feasible to measure, and based on stakeholder input and consensus.
- But how can we guarantee that consensus is obtained without losing important domains for patients and hence content validity of the core set?

PRP participation as integral part of the consensus building

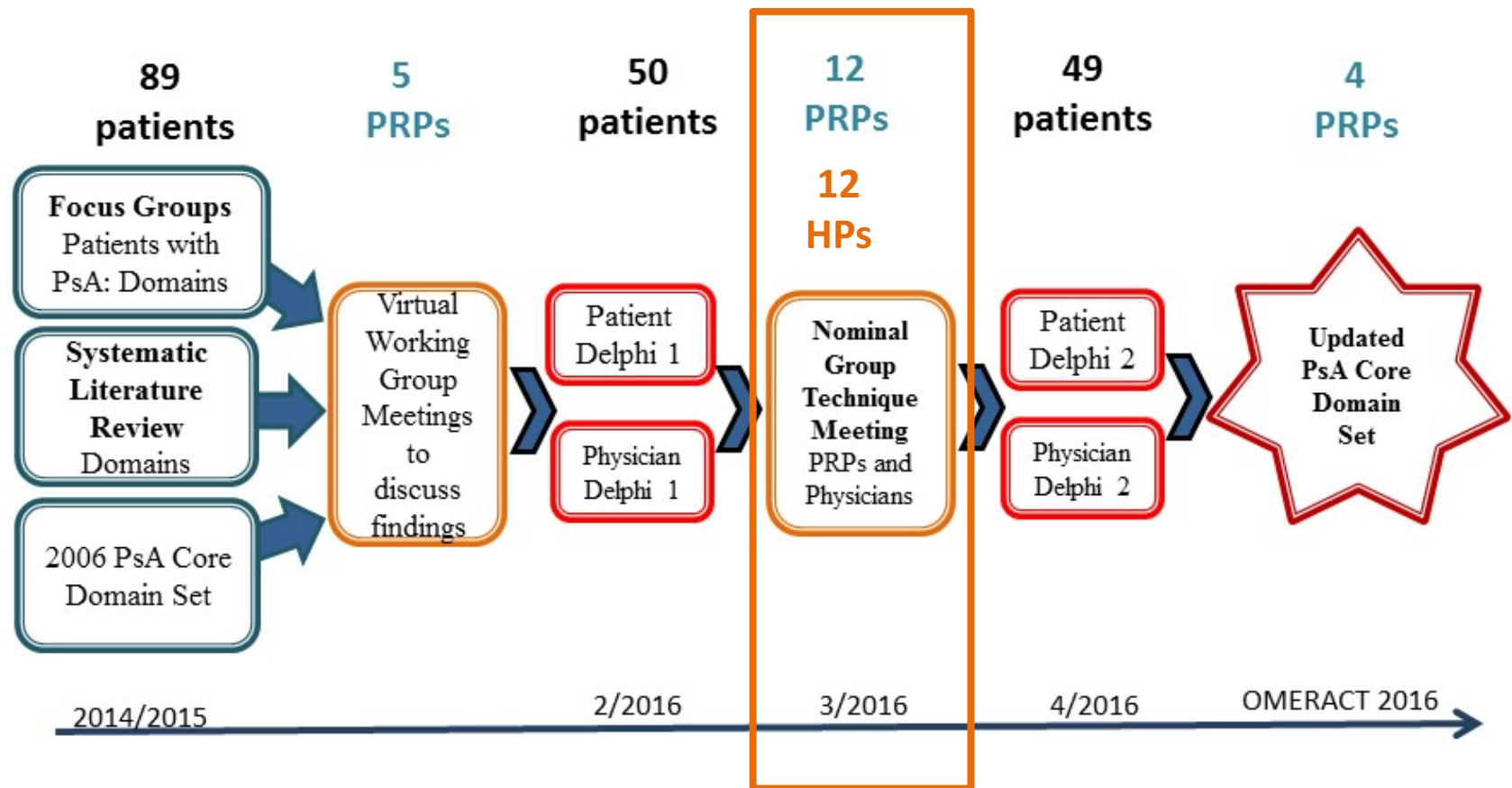




First patient and physician survey



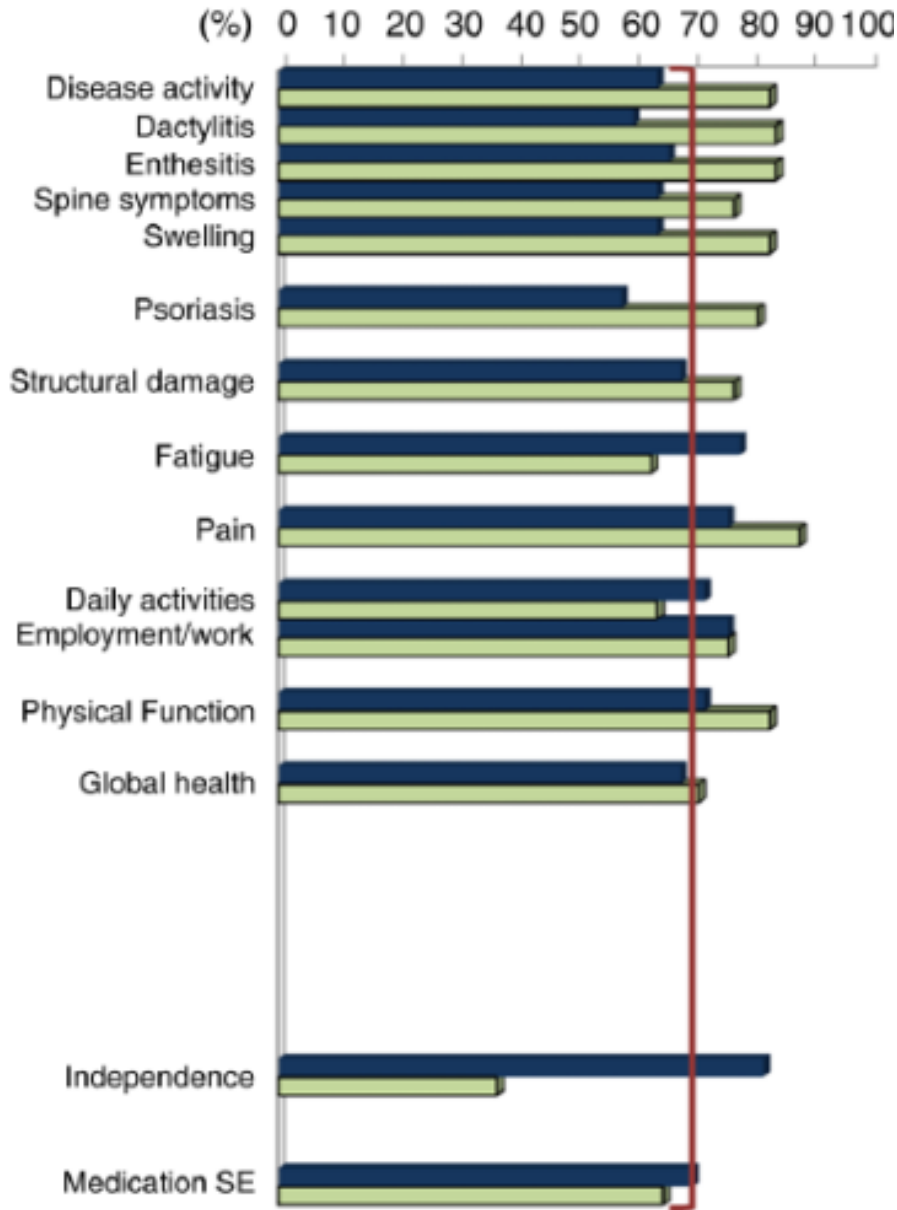
Orbai AM ea, International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. *Annals of the rheumatic diseases* 2016.



- Full day consensus meeting
- Equal representation
- Independent facilitator
- Open dialogue

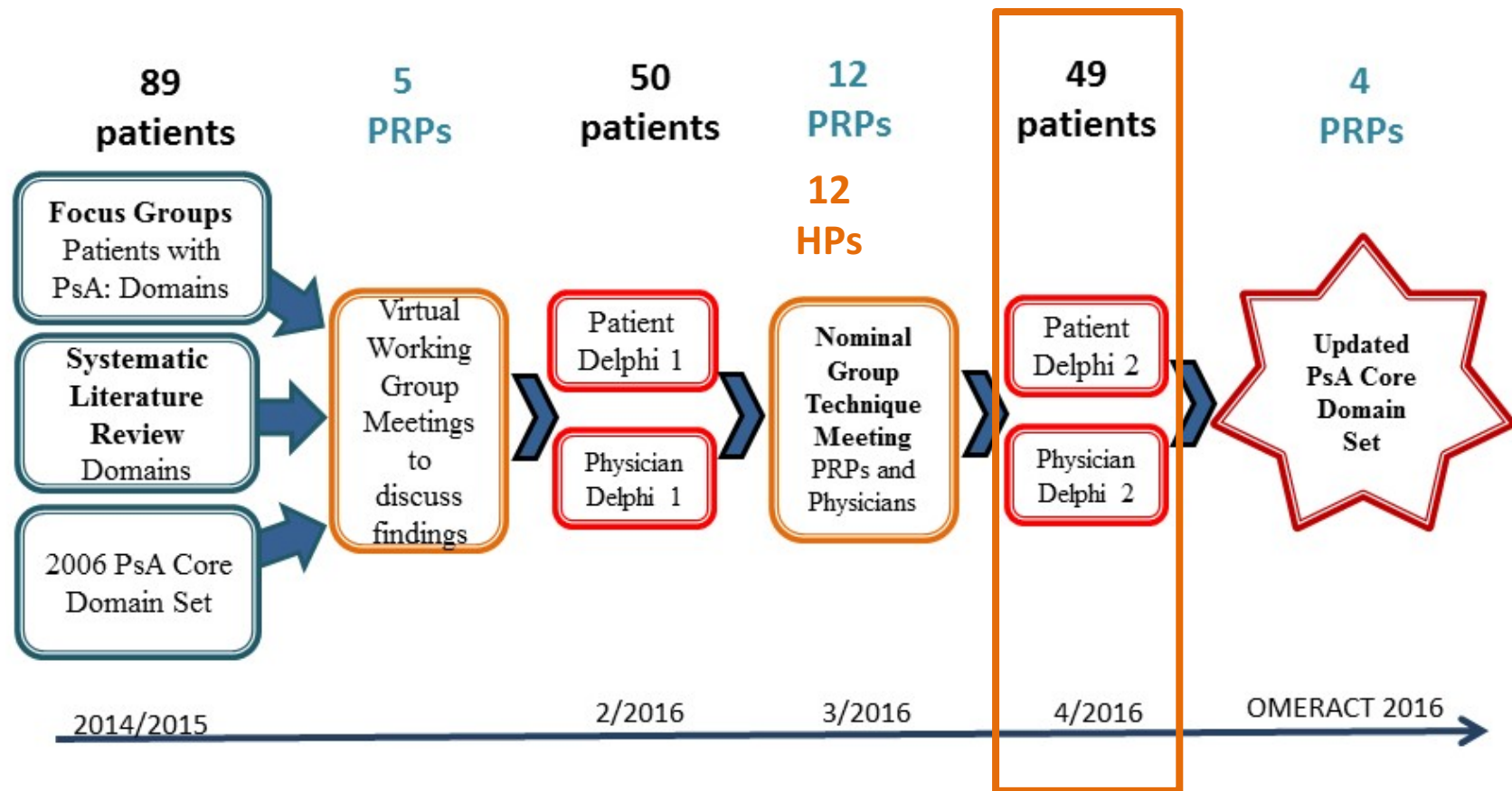
} Preliminary consensus on the updated PsA core domain set

First patient and physician survey

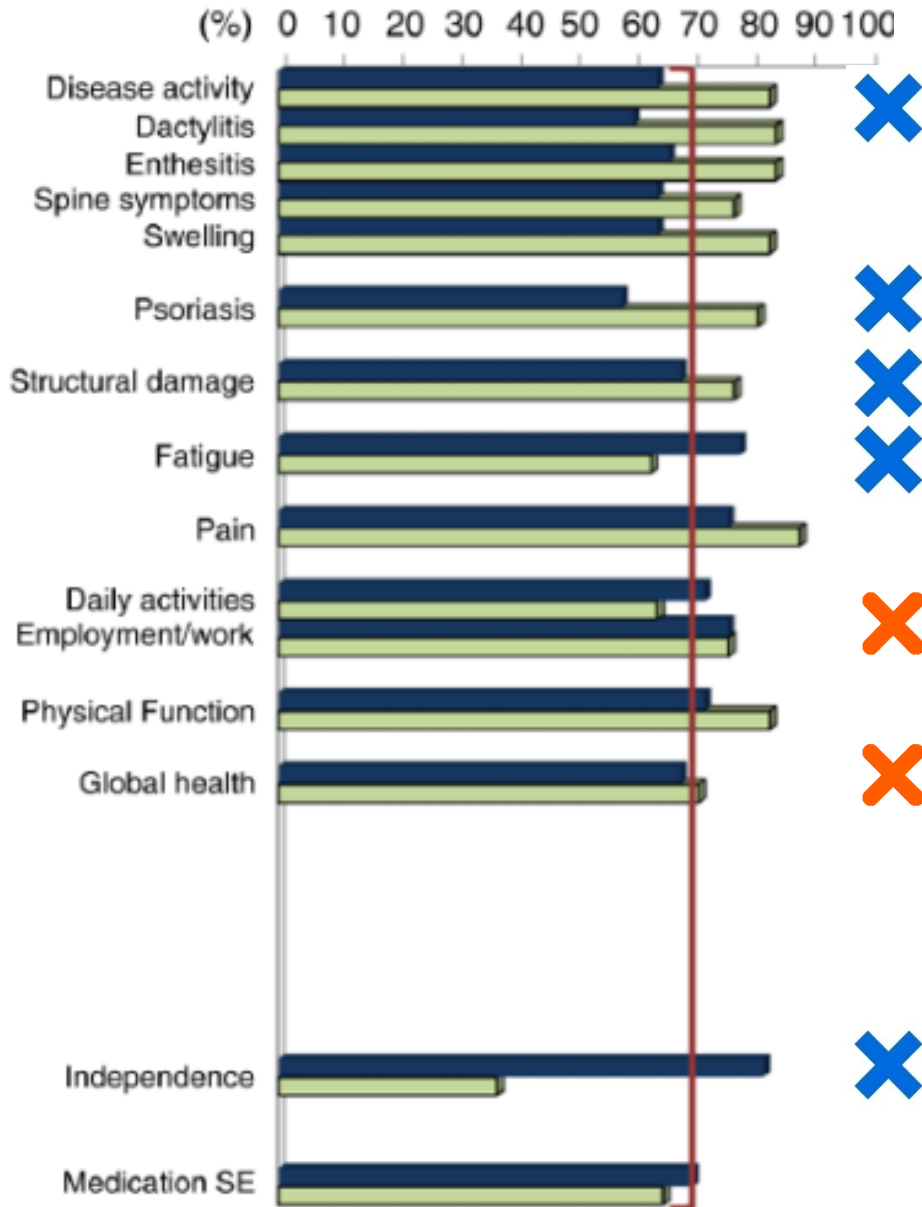


- MSK disease activity
- Skin disease activity
- Structural damage
- Fatigue
- Pain
- Participation
- Physical Function
- Patient Global
- Systemic inflammation
- Emotional well-being

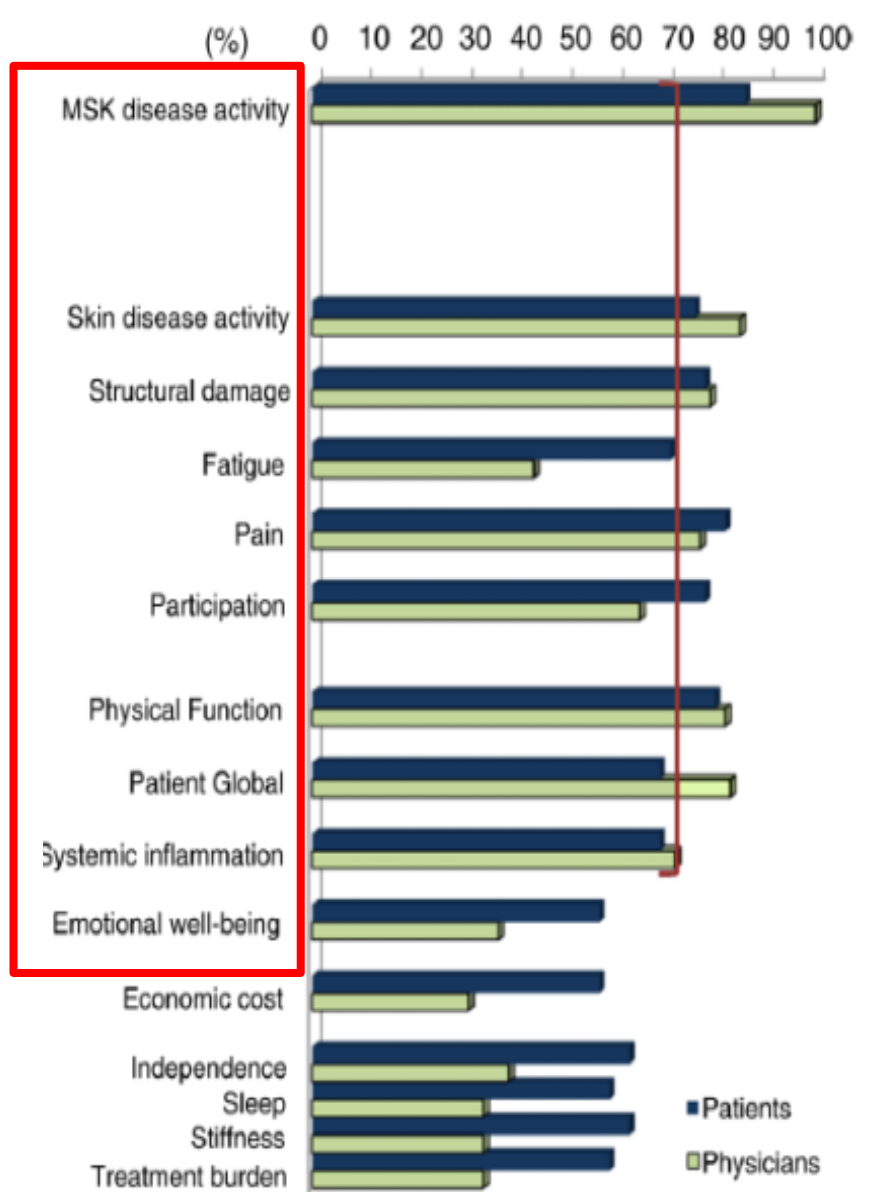
- Economic cost
- Independence
- Sleep
- Stiffness
- Treatment burden

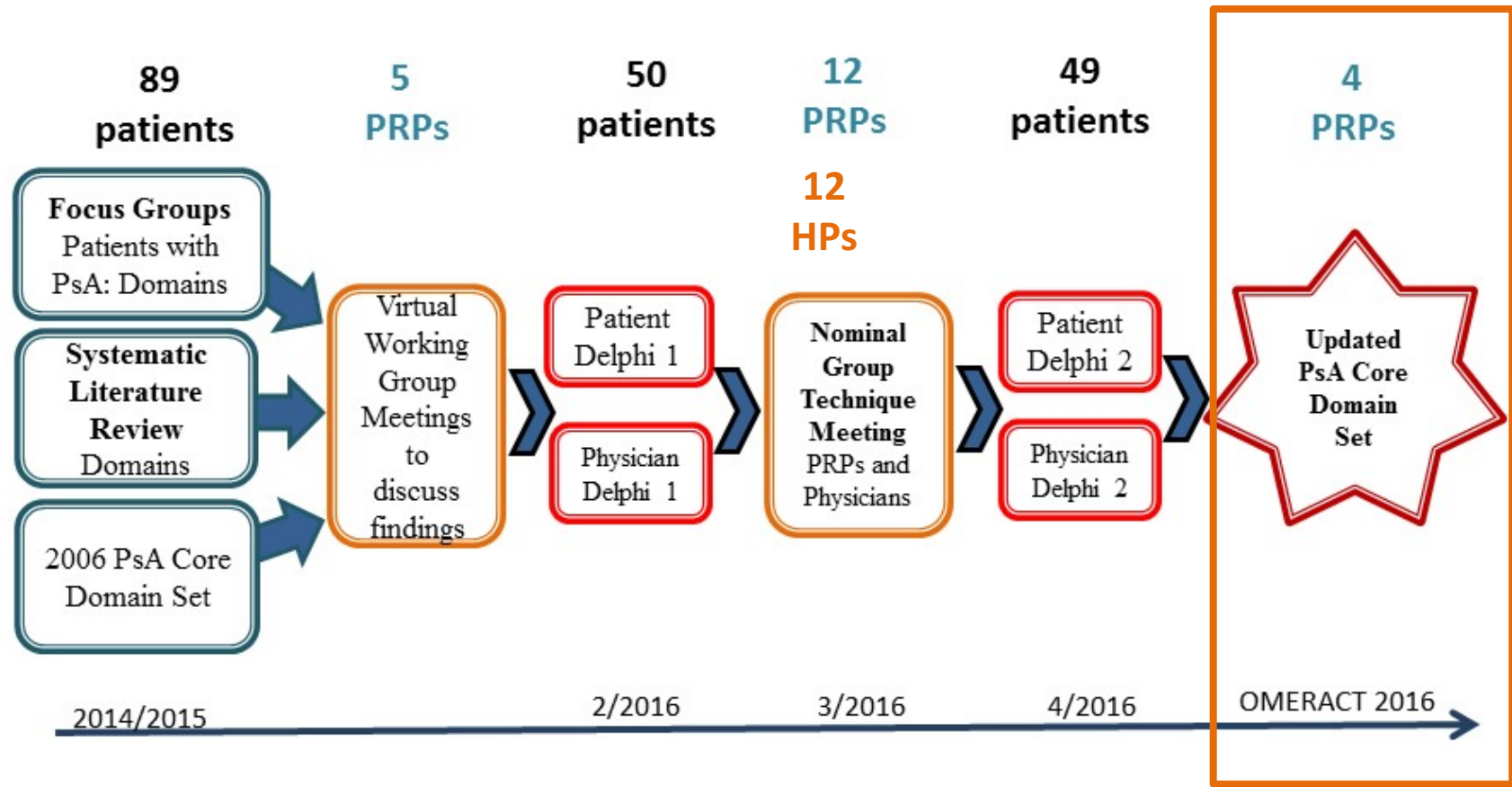


First patient and physician survey

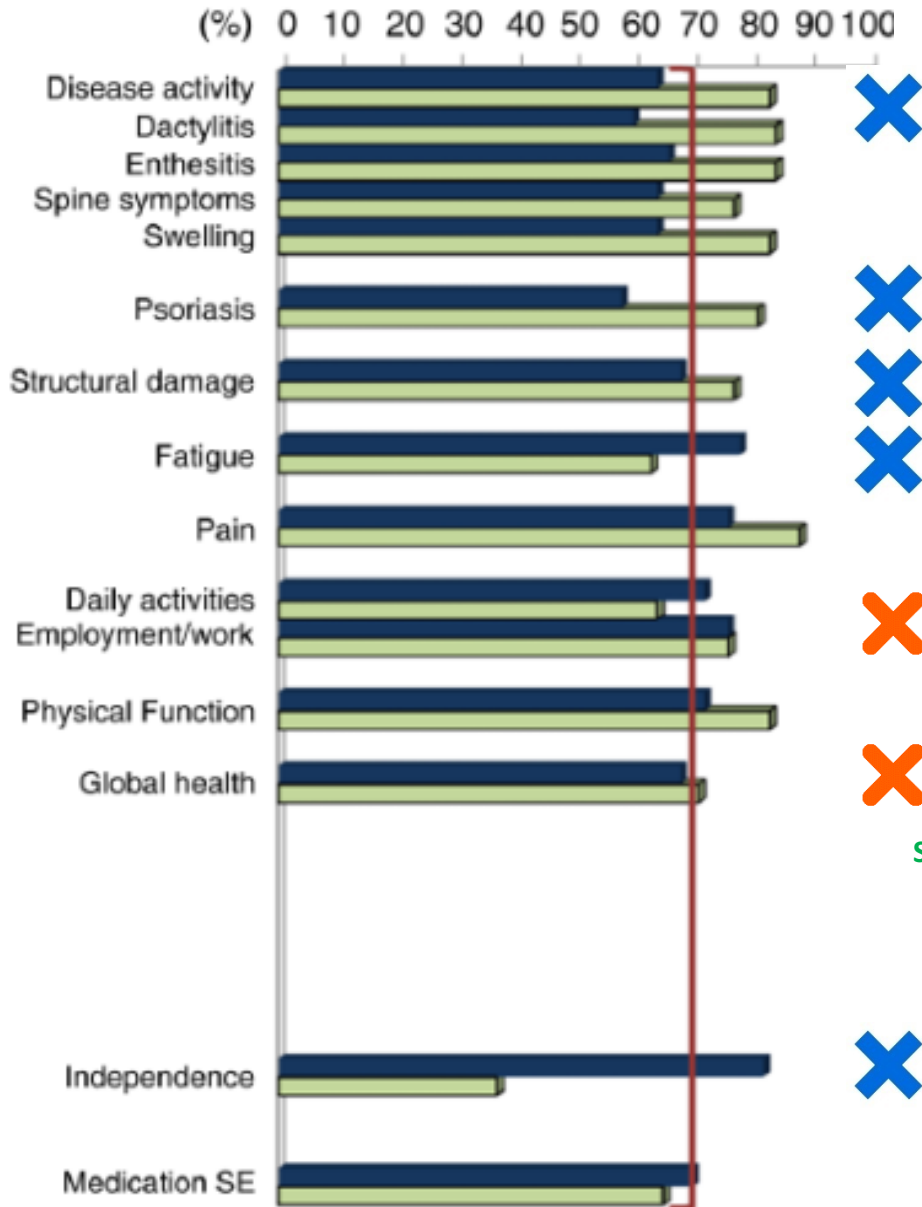


Second patient and physician survey

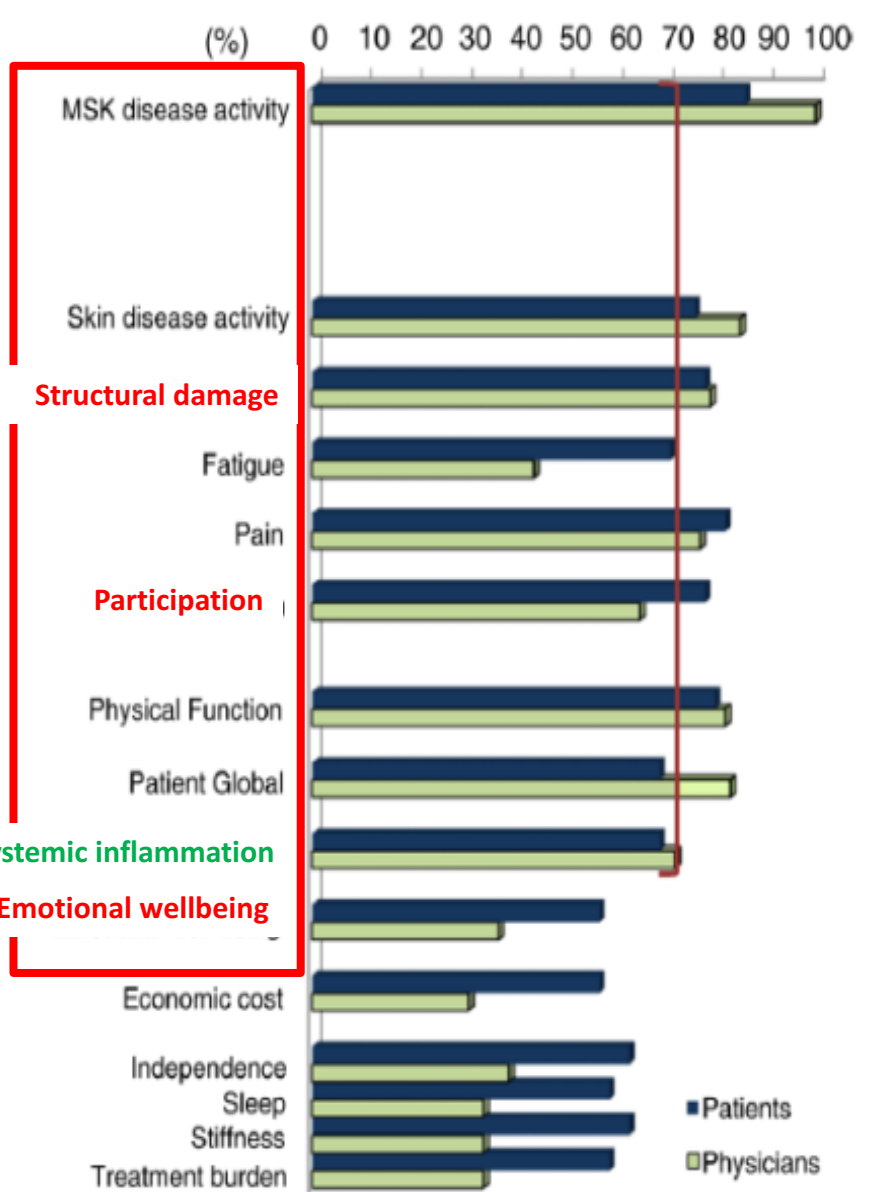




First patient and physician survey



Second patient and physician survey



MSK disease activity

Skin disease activity

Structural damage

Participation

Systemic inflammation

Emotional wellbeing

■ Patients
□ Physicians



What has been the impact of patient and PRP involvement?

- PRP involvement in coding focus group transcripts ensured domains important to patients were captured.
- PRP involvement in developing the domain Delphi list ensured that domain descriptions were phrased in a manner understandable to patients.
- Integration of the patient perspective in a meaningful and representative manner provided face validity to the COS
- PRP involvement in the consensus process resulted in new domains on the research agenda and in the middle core. No patient relevant domains were added to the inner core.



How can this be explained?

Potential factors to look at....

- Risk of patient representatives aligning with physicians views and priorities?
- Influence of existing power imbalances?
- Influence of clinical relationships?
- Lack of proportional representation in numbers?

Part III



Domecq JP et al. Patient engagement in research: a systematic review. *BMC Health Serv Res* 2014;14(1):89.

Boote J et al. Involving the public in systematic reviews: a narrative review of organizational approaches and eight case examples. *J Comp Eff Res* 2012;1(5):409-20.

Oliver SR, Rees RW, Clarke-Jones L, Milne R, Oakley AR, Gabbay J, et al. A multidimensional conceptual framework for analysing public involvement in health services research. *HEX* 2008;11(1):72-84.

Staniszewska S et al. Patient and public involvement in patient-reported outcome measures: evolution not revolution. *Patient* 2012;5(2):79-87.

Legare F et al. Patient and public involvement in clinical practice guidelines: a knowledge synthesis of existing programs. *Med Decis Making* 2011;31(6):E45-74.

Serrano-Aguilar P et al. Patient involvement in health research: a contribution to a systematic review on the effectiveness of treatments for degenerative ataxias. *Social science & medicine* 2009;69(6):920-5.

Staley K. Exploring Impact: Public involvement in NHS, public health and social care research. Eastleigh: INVOLVE, 2009:116.

Brett J et al. The PIRICOM Study: A systematic review of the conceptualisation, measurement, impact and outcomes of patients and public involvement in health and social care research. The University of Warwick, 2009.

Mockford et al. The impact of patient and public involvement on UK NHS health care: a systematic review. *Int J Qual Health Care* 2012;24(1):28-38.

Barber R et al. Evaluating the impact of public involvement on research. In: *Critical Perspectives on User Involvement*. Bristol, 2012:217-23.

Crawford MJ et al. Systematic review of involving patients in the planning and development of health care. *BMJ* 2002;325(7375):1263.

Brett J et al. Mapping the impact of patient and public involvement on health and social care research: a systematic review. *Health expectations*, 2012.



Publications

- 
- 👉 **De Wit M**, Abma T, Koelewijn-van Loon M, Collins S, Kirwan J. Involving patient research partners has a significant impact on outcomes research: a responsive evaluation of the international OMERACT conferences. *BMJ Open* 2013;3:e002241 Doi:10.1136/bmjopen-2012-002241
 - 👉 **De Wit M**, Koelewijn-van Loon MS, Collins S, Abma TA, Kirwan JR. "If I wasn't this robust": Patients' expectations and experiences at the Outcome Measures in Rheumatology Conference 2010. *The Patient* 2013;2013/06/06. Doi: 10.1007/s40271-013-0017-0.
 - 👉 **De Wit M**, Abma TA, Koelewijn-van Loon M, Collins S, Kirwan J. Facilitating and inhibiting factors for long term involvement of patients in outcome research - Lessons learned from a decade of collaboration at OMERACT conferences. *BMJopen* 2013;3:e003311 Doi:10.1136/bmjopen-2013-003311
 - 👉 **De Wit M**, Abma TA, Koelewijn-van Loon M, Collins S, Kirwan J. What have we learned from a decade of patient participation in OMERACT and its effect on trial outcome assessments? *The Journal of rheumatology* 2014;41(1):177-84.
 - 👉 **de Wit M**, Kirwan JR, Tugwell P, et al. Successful Stepwise Development of Patient Research Partnership: 14 Years' Experience of Actions and Consequences in Outcome Measures in Rheumatology (OMERACT). *Patient* 2016.
 - 👉 **de Wit M**, Elberse JE, Broerse JE, Abma TA. Do not forget the professional - the value of the FIRST model for guiding the structural involvement of patients in rheumatology research. *Health expectations*. 2015; **18**: 489-503
 - 👉 **De Wit M**, Kvien T, Gossec L. Patient participation as an integral part of patient reported outcomes development guarantees the representativeness of the patient voice – A case-study from the field of rheumatology. *RMD-open* 2015;1.
 - 👉 **de Wit M**, Berlo SE, Aanerud GJ, Aletaha D, Bijlsma JW, Croucher L, et al. European League Against Rheumatism recommendations for the inclusion of patient representatives in scientific projects. *Annals of the rheumatic diseases* 2011;70:722-6.



Conditions for participation

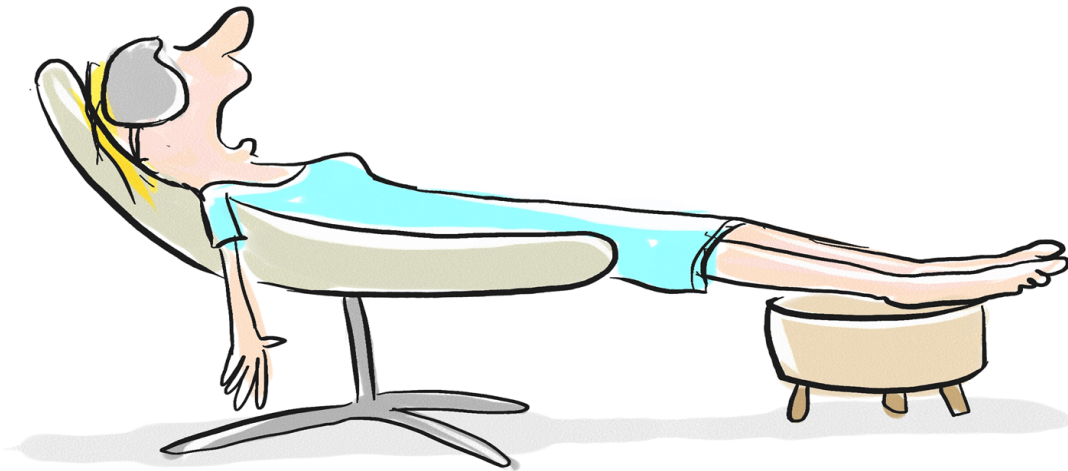
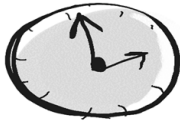
- Participation is a process
- The role of the principal investigator is key in providing adequate support to patients
- Participation should always be tailor made, there is no concept that fits all
- It requires multiple forms of participation
- It requires always an extra effort: in time, money and energy
- A structural approach guarantees sustainability
- Willingness for mutual learning



Conclusion

- PRP involvement is needed to ensure face validity of a core domain set.
- Attributes for an effective consensus meeting are:
 - Equal numbers of patients and other stakeholders
 - An independent facilitator
 - Open dialogue
 - Inclusion of opinions of all participants via consensus techniques (Nominal Group Technique).
- More research is needed to explore strategies to preserve the patients' perspectives in the consensus building process and final core domain set.

Thanks for your attention



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