Toward Consensus Development:
Qualifying Endpoint Measures for RA Clinical Trials

Concept of Measurement: RA-Defining Symptoms - Fatigue, Stiffness, and Other Symptoms

Clifton O. Bingham III, MD
Associate Professor of Medicine, Johns Hopkins University
Director, Johns Hopkins Arthritis Center
Associate Director, Rheumatic Diseases Research Core Center

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Objectives

- Describe important disease-related symptoms identified by RA patients
- Review RA-related fatigue and its measurement
- Discuss RA-related stiffness and its measurement

Addressing the patient's perspective…

- *"Patients* define the relevant questions and hold the answers to prevention, rational therapy, and cure of the rheumatic diseases".

Antony Rosen, MD Chief, Division of Rheumatology Johns Hopkins University

- "It's good to feel better but it's better to feel good and even better to feel good as soon as possible for as long as possible".

Strand V, et al, J Rheumatol, 2011;38:1720–7.

PCORI recognizes that the patient's voice should be heard in the health care decision making process and should be responsive to the preferences, values and experiences of patients in making health care decisions and the impact diseases and conditions can have on daily life.

"**Patients tell PCORI what health care outcomes they value.** PCORI's research results will be provided to patients and clinicians in ways that are responsive to their needs and interests and easy to understand."

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What symptoms and disease features are important to people with RA?

- Several groups have evaluated and reported on domains deemed to be important in people with RA

- RAID
- RAPP-Pi
- RA Flare– OMERACT and French
- OMERACT Patient Partners

RAID—Rheumatoid Arthritis Impact of Disease

- Conducted by the European League against Rheumatism (EULAR)
- 10 patients (10 countries) identified 17 domains
- 96 patients ranked 7 most important
- 505 patients in 12 countries performed relative weighting
- Construct validity, reliability, and sensitivity to change was good compared to DAS28

Seventeen domains of health ranked for importance by 96 patients with RA		
Domain*	Order of domains by median	Patients giving rank 1–7 to the domain (%)
Pain	1	78.1
Functional disability	2	64.6
Fatigue	3	61.4
Physical well-being	5	44.8
Coping	5	41.7
Sleep	4	45.8
Emotional well-being	5	33.3
Being a burden to others	9	40.6
Family life	11	38.5
Satisfaction with health care	5	37.5
Anxiety	9	37.5
Ability to fulfil social role	11	35.4
Depression	11	32.3
Drug side effects	15	33.3
Professional life	11	33.3
Sexuality	16	23.9
Socioeconomic issues	17	27.1

Gossec L, Ann Rheum Dis 2009;11:1680-5

RA Patients Prioritize Multiple Aspects of Health When Seeking Improvement with Pharmacologic Interventions

- RA Patient Prioritization of Pharmacologic Interventions (RAPP-PI)
- Nominal groups of 26 UK RA patients identify 63 domains
- Survey to prioritize in 254 RA patients, 4 UK centers
- Resultant 8 areas prioritized using principal component analysis

RAPP-PI

Pain
Activities of Daily Living
Visible Joint Damage
Mobility
Enjoy Life Again
Independence
Fatigue
Valued Life Activities

Sanderson TC, Arthritis Care Res (Hoboken). 2010 May;62(5):647-56

RA Patients Identify Multiple Areas of Health Affected by Flares

OMERACT RA Flare Group

- Focus groups (>60 RA patients, 5 countries) to identify domains
- Delphi of > 200 international RA patients to prioritize domains

Pain
Function
Tender/Swollen Joints
Stiffness
Participation
Self-management
Fatigue
Systemic Features
Sleep
Emotional Distress

French FLARE

- 102 patient interviews
- Reduced to 10 domains by expert review

Fatigue
Loss independence/need help
Painful Joints
Depression
Irritability
Sleep disturbance
Stiffness
Impact daily activities
Analgesic and steroid use

Bingham CO J Rheumatol 2009, Hewlett SH Rheumatology 2012, Bingham CO J Rheumatol 2011, Bartlett SJ Arthritis Care Res 2012, Berthelot JM Ann Rheum Dis 2012, Bingham CO Ann Rheum Dis 2012

OMERACT Patient Involvement

- Recognition of the importance of patient perspective of disease and its impact
- Involvement of patients in consensus meetings initiated in 2002
- Identification of domains important to patients not contained within the RA Core Set of measures
- Recommended inclusion of Fatigue in RA Clinical Trials
- Evaluation of sleep recommended
- Defining MCID/PASS important
- Developed and refined framework for patient participation in research
- Established framework for PRO development and validation through OMERACT Filter

Tugwell PS J Rheumatol 2011;38:1702-10. Wells GA J Rheumatol 2009;36:2077-86. Kirwan JR, J Rheumatol 2007; 34: 1174-7. Kirwan JR J Rheumatol 2005;32:2250-6. Kirwan JR J Rheumatol 2003;30:868-72.

Fatigue in RA is Common, Often Severe, and Has Considerable Life Impact

- Up to 97% of RA patients report fatigue
- 42 – 69% report severe fatigue
- 40 – 48% report daily fatigue

➢ Differentiates between levels of RA disease activity and HRQoL

➢ Predicts deterioration in quality of life

➢ Impacts paid employment

Belsa 1993, Wolfe 1996, Katz 1998, Suurmeijer 2001, Milton 2002, Rupp 2004, Hewlett 2005, Ødegård 2008, Hoogmoed 2010

Fatigue is Highly Prioritized by RA Patients

- In evaluating the relative importance of domains contained within AIMS (does not include fatigue):
  - 70% prioritized pain in the 3 most important
  - When fatigue was included as an option, 65% prioritized fatigue, 48% prioritized pain

RAPP-PI	**RAID**	**OMERACT RA Flare**
Pain	Pain	Pain
Activities daily living	Function	Function
Visible joint damage	Fatigue	Tender/Swollen Joints
Mobility	Sleep	Stiffness
Enjoy life again	Physical well-being	Participation
Independence	Emotional well-being	Self-management
Fatigue	Coping	Fatigue
Valued activities		Systemic Features
		Sleep
		Emotional Distress

Minnock 2003, 2004; Gossec 2009; Sanderson 2010; Bingham 2011, Bartlett 2012

Assessment of Fatigue in RA

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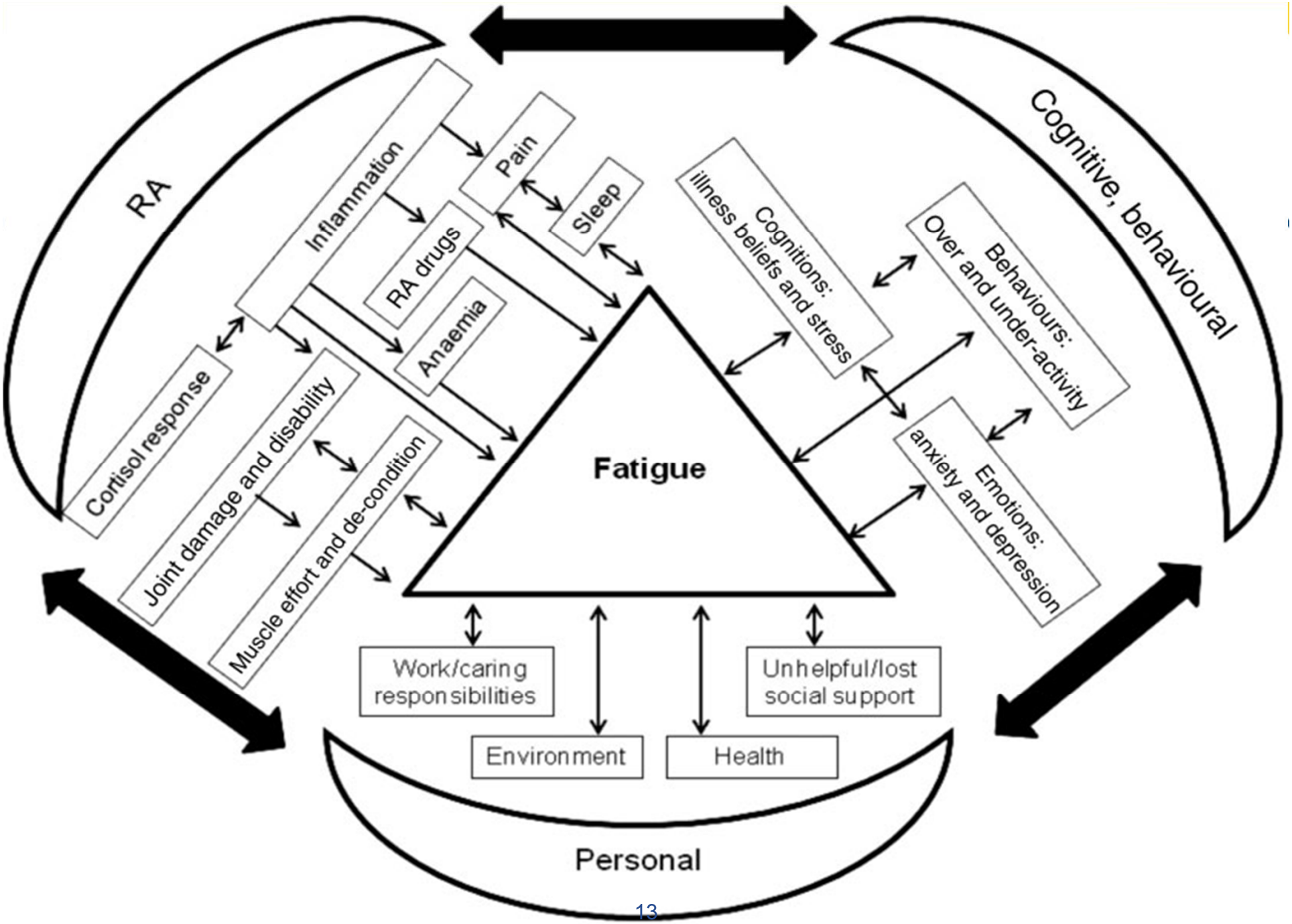
- Patient participants identified fatigue as a specific problem in rheumatoid arthritis [1,2]
- Early descriptions at OMERACT 6 and 7 led to substantial qualitative research establishing importance of fatigue in RA[3,4,5,6,7,8]
  - Focus groups in UK, Sweden and Ireland
- Subsequent qualitative work showed that measuring fatigue added new information to existing core set for RA [9,10,11,12]

1 Kirwan J et al. J Rheum 2003; 30:868-72.
2 Carr A et al. J Rheum 2003; 30:880-3.
3 Minnock P, Bresnihan B. A+ R 2004;50 :S471.
4 Hewlett S et al. Musculoskel Care 2005; 3: 131–142.
5 Kirwan JR et al. J Rheum 2005; 32: 2246-9.
6 Kirwan JR et al. J Rheum 2005;32:2250-6.
7 Hewlett S et al. AC&R 2005;53:697-702.
8 Ahlmen M et al. Rheumatology 2005;44:105-10.
9 Kirwan J et al. J Rheumatol 2009;36:2071–6
10 Kirwan J et al. J Rheumatol 2009;36:2067–70
11 Minnock P et al. Rheumatol 2009; 48:1533-1536.
12 Kirwan J, Hewlett S. J Rheum 2007; 34: 1171-3



Hewlett S, et al. Fatigue in Rheumatoid Arthritis: Time for a conceptual model. Rheumatol 2011;50:1004-6

Assessment of Fatigue in RA

- 23 instruments to measure fatigue in RA evaluated
  - Sufficient validation: FACIT-F; MAF; POMS; VAS
  - SF36 vitality scale queries “pep/energy” and “worn out/tired” and is responsive to Rx but does not necessarily track with fatigue VAS
  - VAS Scales not standardized (e.g. anchors)
  - MID/PASS established for some measures

- The aspects of fatigue identified by RA patients (cognition, coping, emotion, energy, frequency, impact, planning, quality of life, relationships, severity, sleep, and social life) are either not covered or are inadequately covered by the instruments above

Kirwan J et al. J Rheum 2007; 34:1174-7.Hewlett S et al. AC&R 2007; 57: 429-39. Heiberg T Ann Rheum Dis 2008. Cella J Rheumatol 2005;32:811-9

Existing fatigue instruments do not capture the multiple dimensions identified by RA Patients

Patient Categories	MAF	SF36	FACIT(F)	POMS
Frequency/Severity	**Yes**	Limited	Limited	Limited
Duration	Limited	Limited		
Coping				
Emotion	Limited			
Energy		**Yes**	**Yes**	
Impact	**Yes**		**Yes**	
Relationships	Limited			
Social life	Limited		Limited	
Cognition				
Quality of Life				
Planning				
Sleep				

Global scores only

Nicklin et al 2010a, 2010b

Fatigue causes: Cross-sectional correlations conflicting

Pain	NS - 0.68
Function	0.26- 0.56
Disease duration	NS - 0.17
Female	No & Yes
Depression	NS - 0.54
Sleep	NS - 0.58
Social Support	NS - 0.26

No associations
Inflammatory indices
Cortisol
Age
Anaemia

Belza 1993, 1995
Huyser 1998
Riemsma 1998
Rupp 2004
Treharne 2005
Pollard 2006
Hoogmoed 2010

Hewlett,, Arthritis Research UK Topical Reviews 2008

Bristol RA Fatigue Multidimensional Questionnaire (BRAF)

- Grounded in the conceptual model derived through qualitative studies
- Questionnaire developed through multistep process involving patients: explored patient perspective; drafted fatigue items in collaboration with patients; tested items for comprehension
- Cross sectional testing in 229 RA patients with fatigue
- Initial 45 items, reduced to 20 items using factor analysis
- Short VAS and NRS cover: fatigue severity, impact, and coping
- BRAF-MDQ (20 items) covers physical, cognitive, mental, and impact of fatigue

15 Nicklin J et al. AC&R 2010; 62: 1552–8.
16 Nicklin J et al. AC&R 2010; 62: 1559–68.

BRAF MDQ- Global fatigue plus 4 domains

Physical severity
NRS
Number of days
Length of episode
Physical energy

Living
Bath or shower
Dress yourself
Avoided making plans
Social life
Cancelled plans
Refused invitations
Work/other daily activities

Emotional
Less control of your life
Embarrassed
Upset
Down or depressed

Cognitive
Lacked mental energy
Forgotten things
Think clearly
Concentrate
Made mistakes

Nicklin et al 2010b

Validation of BRAF-MDQ

- Internal consistency (Cronbach's α = 0.932), criterion validity (correlation with other fatigue scales: r = 0.643–0.813), and construct validity (correlations with disability, mood, helplessness, and pain: r = 0.340–0.627)
- Global score correlated:
  - strongly with MAF, POMS and FACIT but not SF-36 vitality
  - moderately with depression, anxiety, helplessness, and disability
  - weakly correlated with pain
  - more strongly with emotions vs other instruments
- Evaluated in short term study of IM Steroids: global score reliable and sensitive to change, all subscores sensitive to change except coping
- BRAF incorporated into 4 large international RCTs in RA with TNF inhibitor
- BRAF being prospectively tested in 6 EULAR countries with RAID

Nicklin J et al.. AC&R 2010; 62: 1559–68.. Hewlett S in review and personal communication

Fatigue Scales Review

BRAF-MDQ & BRAF-NRS

Chalder Fatigue Questionnaire

Checklist Individual Strengths

Fatigue Severity Scale

FACIT (F)

Multi-dimensional Assessment of Fatigue

Multi-dimensional Fatigue Inventory

PEDsQol Multi-dimensional Fatigue Scale

Profile of Fatigue

SF-36 Vitality Subscale

VAS

Hewlett et al , Arthitis Care & Research 2011; http://onlinelibrary.wiley.com/doi/10.1002/acr.20579/pdf

Fatigue Summary

- Fatigue is an extremely common part of RA
- Fatigue is consistently rated as one of the most important symptoms of RA
- Fatigue can be considerably disabling
- There are multiple dimensions of RA fatigue
- Neither “Physical tiredness” nor “vitality” adequately reflects the domain
- Which of the available fatigue instruments is best for RA has yet to be determined
- Final validation of BRAF-NRS and BRAF MDQ are ongoing

Stiffness is a common feature of RA that impacts HRQL

- Morning RA symptoms > 1 hour is present in in 24-49% of RA patients
- Surveys and qualitative studies in 11 EU countries of 750 RA patients
- 92% of patients described impaired AM function as moderate to severe; 82% had significant impact on QoL
- AM symptoms include pain, impact on ADL, and stiffness

- Severe AM stiffness in recent-onset RA is a strong predictor of early retirement
- Although duration of AM stiffness may be assessed, severity of AM stiffness may be more responsive to change

Cutolo M. Scand J Rheumatol 2011; 40 Supp 25:17-22; daSilva JAP, Scand J Rheumatol 2011; 50 Supp 25: 6-11; Khan NA, J Rheumatol 2009; 36: 2435-42; Yazici Y, J Rheumatol 2004; 31: 1723-6; Westhoff G, Rheumatology 2008;47:980-4; Hazes JMW, J Rheumatol 1993; 20: 1138-42; Vliet Vlieland TPM, J Clin Wpidemiol 1997; 50: 757-63.

Morning Symptoms Have Significant Impact on Worklife

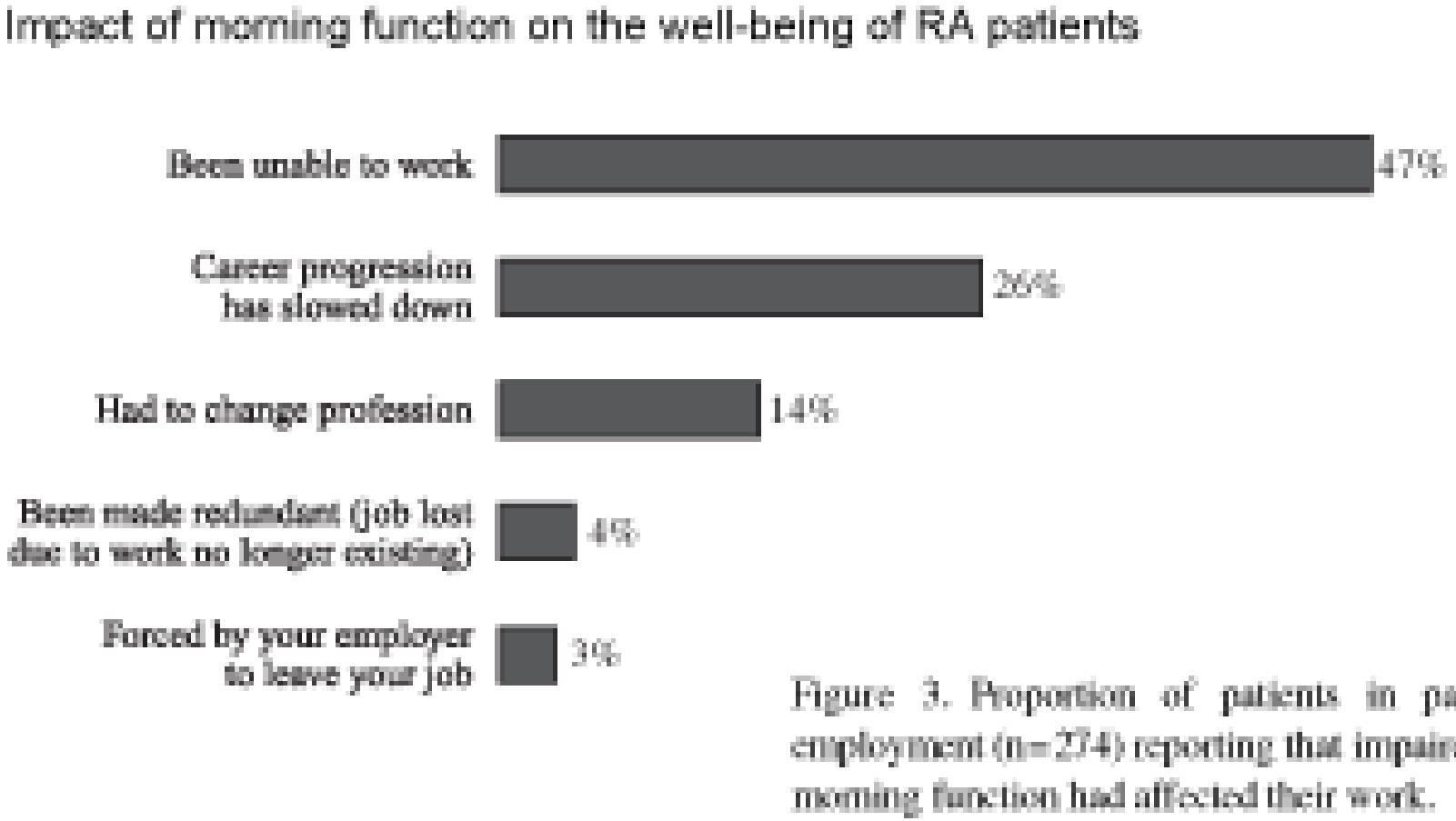


Figure 3. Proportion of patients in paid employment (n=274) reporting that impaired morning function had affected their work.

daSilvaJAP, Scand J Rheumatol 2011; 40 Suppl 125: 6-11

Stiffness in RA

- Morning stiffness was part of 1958 and 1987 Classification Criteria for RA, and part of prior RA remission criteria
- Most studies have focused on the Morning accentuation of stiffness
- Ways to assess stiffness have been variable:
  - Duration of morning stiffness, time to maximal improvement, time to resolution, severity of morning stiffness, severity of stiffness (general)
- Stiffness severity is more responsive, with less within patient variability, and better able to discriminate active vs inactive RA than stiffness duration
- RA patients use many different words to describe “stiffness”:
  - Limited movement, painful, tight, tense, aches, hurts, sore, rigid, stuck, inflexible, immobile, solid, fixed, locked up, like a board, resistance to movement
- Symptoms may vary day to day

Vliet Vlieland TPM, J Clin Epidemiol 1997;50:757–63. Hazes JMW J Rheumatol 1993;20:1138-4. Hazes JMW Br J Rheuym 1994;33:562-5. Rhind VM, Br J Rheumatol 1987;36:126-30. Lineker S, J Rheumatol 1999; 26: 1052-7.Sokka T; Scand J rheumatol 2011; 40 Supp 125;23-27.

Qualitative Studies of Stiffness

- 2 focus groups 10 patients with RA recruited from Johns Hopkins Arthritis Center

Age	**50.9 yr (range 29-64)**
Sex	**6 Female** **4 Male**
Race/Ethnicity	**8 White** **2 Black** **2 Hispanic**
RA Disease Duration	**11.5 yr (range 1-19)**
Patient Global Assess (100 mm VAS)	**52.5 (range 5-80)**
mHAQ	**0.6 (range 0-1.4)**
Stiffness past week (100 mm VAS)	**43.5 (range 5-80)**

- One-on-one interviews and cognitive debriefing of stiffness questions in 9 additional RA patients

Orbai, Smith, Bartlett, Bingham unpublished

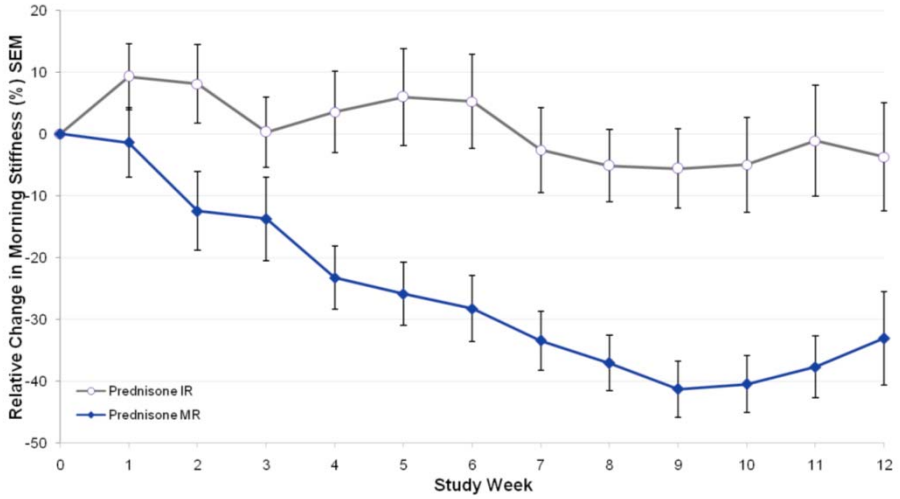
Preliminary Thematic Analysis

- Descriptions of stiffness
  - "Tin man", tightness, frozen, etc.
  - Pain-Stiffness Dyad
    - Intertwined for some, dissociable for others, stiffness>>pain in some
- Temporality
  - Worse in AM, after inactivity/rest, after use, worse in evening, all day, variability, difficult defining time
- Regionalization of symptoms
  - Joint stiffness, total body stiffness
- Impact
  - Functional ability and participation
- Alleviation and Coping
  - Heat, water, movement, massage, etc.

Orbai, Smith, Bartlett, Bingham unpublished

Recent RA clinical trials have shown reductions in AM Stiffness

Figure 2.5-6 **Mean relative change in duration of morning stiffness by week in study EMR 62215-003**



The reduction of morning stiffness in the Lodotra group was consistently higher than in the IR prednisone group. A difference of 10% for the Lodotra group was already apparent at week 2. Under continued treatment this difference increased and reached a plateau at about 30% to 40% from Week 7 onwards.

- Required patients to have > 45 min AM stiffness for inclusion
- Daily diaries to measure AM stiffness in joints (Y/N), time to resolution, and recurrence of stiffness
- Report relative change in AM stiffness between treatments

Buttgereit F et al, Lancet 2008, Buttgerit F Ann Rheum Dis 2012

Stiffness: Summary

- Stiffness has been identified and prioritized as an important symptom for many RA patients
- May have considerable impact on ADLs and participation

- No standardized method for assessment
- Traditional conceptualization of AM stiffness may be inadequate to capture the domain
- Stiffness intensity may be more sensitive and reliable than stiffness duration in response to pharmacological interventions

- Additional qualitative and quantitative studies are needed

Participation → The Ultimate Life Impact Measure

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- Different from physical function
- Different from activities of daily living
- Different from productivity

- RAID: Family life, ability to fill social roles, professional life, sexuality, being a burden to others
- RAPP-Pi: Enjoy life again, independence, valued life activities
- Flare: Participation, loss of independence

Participation

- Participation in social roles and valued life activities
- Part of WHO-ICF Framework to measure HRQL
- Encompasses work, leisure, social roles, family roles, valued activities, interactions with others
- Not only ability to perform role but satisfaction with ability
- Not an economic construct
- Not equivalent to presenteeism/absenteeism
- Best instruments are unclear
- Studies are ongoing in RA (RAID, Flare, PROMIS), but more research is required

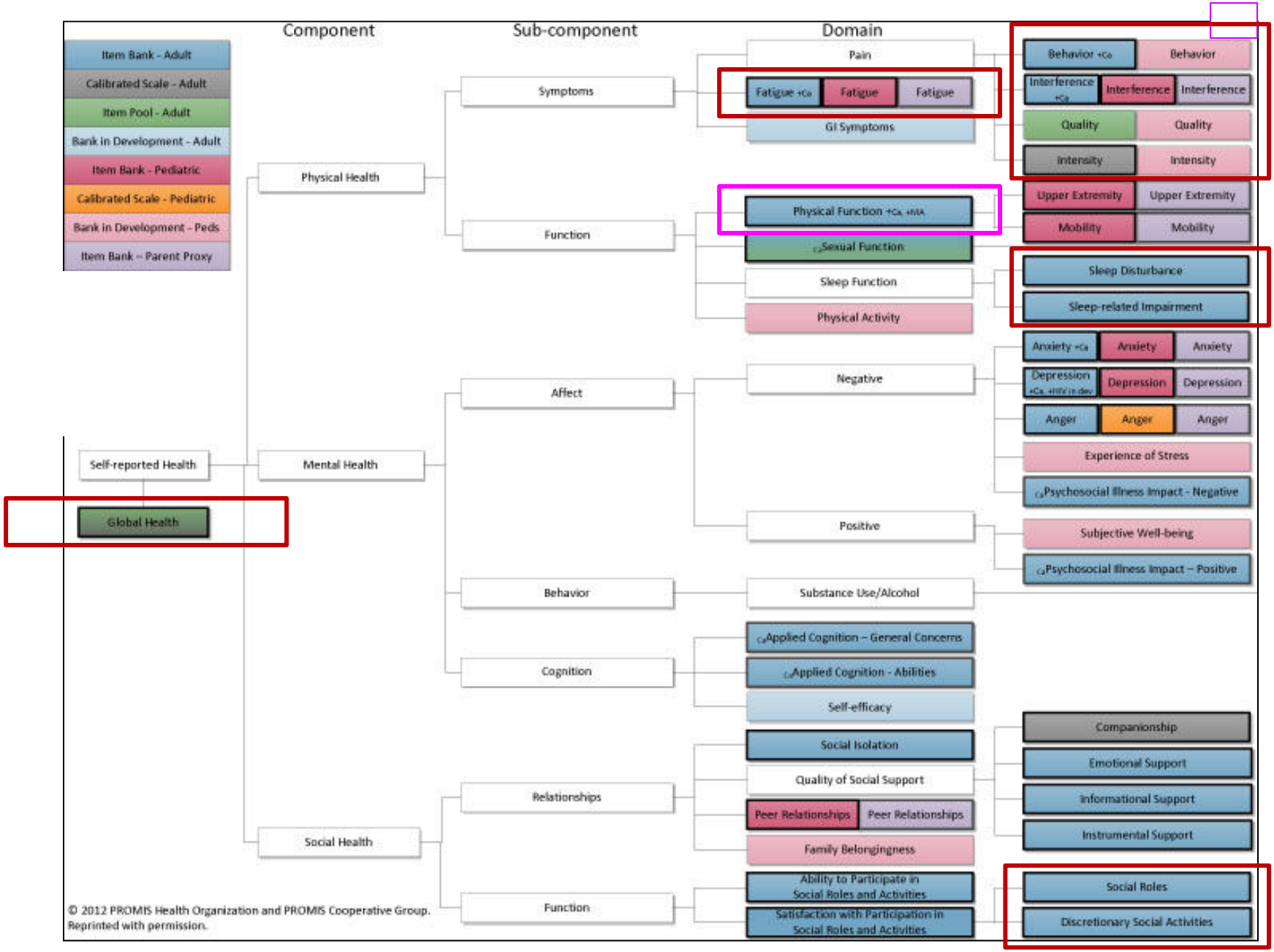
Sleep

- Identified in multiple studies as a domain of importance to patients
- Difficulty with sleep quality, and interference in daytime activities due to poor sleep
- Worsens with RA disease activity
- Recommended for further study by OMERACT
- Best instruments not determined
- Studies ongoing (RAID, Flare, PROMIS), but additional research is required

Emotional Health

- Emotional health/well-being is affected by RA
- Depression and depressive symptoms are common
- Anxiety and anger have also been identified by many patients
- Changes in cognition have also been described
- There are considerable individual contextual factors that influence emotional health in RA (e.g., personal, support, coping strategies, beliefs)
- Emotional health can be improved by RA-specific interventions
- Some elements of emotional health covered by SF36 MCS
- Studies ongoing to assess other instruments (RAID, PROMIS)

PROMIS Framework



PROMIS Includes Domains and Instruments that may Capture RA-relevant Symptoms

Domain	Instruments
• Global Health	• SF
• Pain Intensity	• SF
• Pain Impact/Interference	• SF/CAT
• Pain Behavior	• SF/CAT
• Physical Function	• SF/CAT
• Fatigue	• SF/CAT
• Sleep Disturbance	• SF/CAT
• Sleep-related Impairment	• SF/CAT
• Anxiety	• SF/CAT
• Depression	• SF/CAT
• Cognitive Abilities	• SF/CAT
• Social Roles	• SF/CAT
• Satisfaction with Participation	• SF/CAT

www.nihpromis.org

Developed in normative US population; RA disease-specific "norms" not established

Only physical function well studied in RA (and improves precision and range c/w legacy HAQ/SF36)

PROMIS does not include Stiffness

SF=Short forms, CAT=Computer Adaptive Testing

Example PROMIS Report

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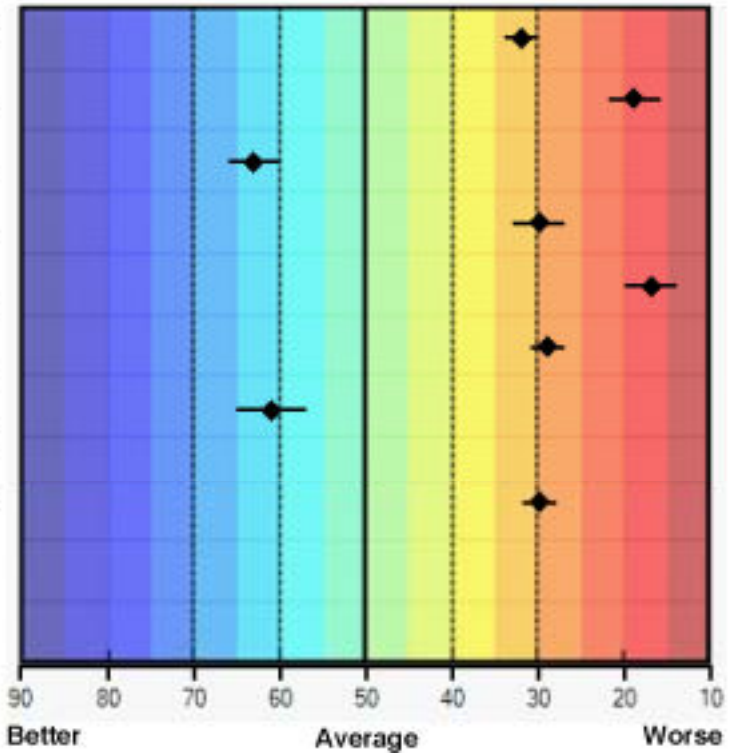
Your scores for the CATs you completed are shown below.

	Your Score	SE
Pain Interference	68	2
Fatigue	81	3
Sleep Disturbance	37	3
Sleep-Related Impairment	70	3
Depressive Symptoms/Sadness	83	3
Anxiety/Fear	71	2
Anger	39	4
Physical Function	30	2



Summary

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- Rheumatoid arthritis patients consistently identify a number of important domains of health not included within the existing RA core set (pain, function, global score)
- These domains include fatigue, stiffness, sleep, participation, and emotional health
- Appreciation of their impact is. in part, limited by the failure to routinely capture this information in clinical trials and clinical practice settings
- Instruments to assess some of these domains have been tested, and others are in development and/or undergoing validation
- Additional research is needed in these areas

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Thank You

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