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TITLE PAGE

Title: Uptake of the OMERACT-OARSI Hip and Knee Osteoarthritis Core Outcome Set: review of randomised controlled trials from 1997 to 2017.

Authors:

Toby O Smith PhD

Senior Researcher in Rehabilitation

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

Michael Mansfield MSc

Senior Lecturer in Physiotherapy

School of Health and Social Care, London South Bank University, London, UK

Gillian A Hawker PhD

Professor of Medicine

Department of Medicine, Faculty of Medicine, and Institute of Health Policy, Management, and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Canada

David J Hunter PhD

Florance and Cope Chair of Rheumatology Chair of Institute of Bone and Joint Research Professor of Medicine

Institute of Bone and Joint Research, Florance and Cope Professorial Dept of Rheumatology, School of Medicine, University of Sydney and Royal North Shore Hospital, Sydney, Australia

Lyn M March PhD

Liggins Professor of Rheumatology and Musculoskeletal Epidemiology Medicine

Institute of Bone and Joint Research, Florance and Cope Professorial Dept of Rheumatology, School of Medicine, University of Sydney and Royal North Shore Hospital, Sydney, Australia

Maarten Boers PhD

Professor of Clinical Epidemiology

Department of Epidemiology and Biostatistics, Amsterdam University Medical Centers, location VUmc, Amsterdam, The Netherlands

Beverley J Shea PhD

Adjunct Professor

Ottawa Hospital Research Institute, Ottawa, Canada

Robin Christensen PhD

Professor of Biostatistics and Clinical Epidemiology

Musculoskeletal Statistics Unit, the Parker Institute, Bispebjerg and Frederiksberg Hospital & Department of Rheumatology, Odense University Hospital, Denmark

Francis Guillemin PhD

Professor of Epidemiology & Public Health
Université de Lorraine, APEMAC, Nancy, France

Caroline B Terwee PhD

Associate Professor in Clinimetrics
Department of Epidemiology and Biostatistics, Amsterdam University Medical Centers, location
VUmc, Amsterdam, The Netherlands.

Paula R Williamson PhD

Professor of Medical Statistics
Institute of Translational Medicine, University of Liverpool, Liverpool, UK

Ewa M Roos PhD

Professor, Head of Research Unit
Center for Muscle and Joint Health, Department of Sports Science and Clinical Biomechanics,
University of Southern Denmark, Odense, Denmark

Richard F Loeser MD

Herman and Louise Smith Distinguished Professor of Medicine, Division of Rheumatology, Allergy &
Immunology
Division of Rheumatology, Allergy and Immunology, Thurston Arthritis Research Center, University of
North Carolina, Chapel Hill, USA

Thomas J Schnitzer PhD

Professor of Physical Medicine and Rehabilitation, Anesthesiology and Medicine (Rheumatology)
Northwestern University Feinberg School of Medicine, Department of Physical Medicine and
Rehabilitation, Chicago, USA

Margreet Kloppenburg PhD

Professor in Rheumatology
Departments of Rheumatology and Clinical Epidemiology, Leiden University Medical Centre, Leiden,
Netherlands

Tuhina Neogi PhD

Professor, Epidemiology
Sections of Clinical Epidemiology and Rheumatology, Boston University School of Medicine, Boston,
USA

Christoph H Ladel PhD

Clinical Biomarker & Diagnostics Lead
Merck Biopharma, Merck KGaA, Darmstadt, Germany

Gurdyal Kalsi MD

Chief Medical Officer, Senior Vice President of Clinical Development and Regulatory and Medical
Affairs
TissueGene, Inc., Rockville, MD, USA

Ulrike Kaiser PhD

Principal Investigator
University Pain Centre, University Hospital Carl Gustav Carus Dresden, Germany

Thomas Buttel MSc

Psychologist

Inner West Psychology, Sydney, Australia & Institute of Bone and Joint Research, Florance and Cope
Professorial Dept of Rheumatology, School of Medicine, University of Sydney and Royal North Shore
Hospital, Sydney, Australia

Anne E Ashford PhD

Emeritus Professor

School of Biological, Earth and Environmental Sciences, UNSW, Sydney, Australia

Ali Mobasher DPhil

Professor of Musculoskeletal Physiology

Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK & Department of
Regenerative Medicine, State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania

Nigel K Arden MD

Professor in Rheumatic Diseases

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of
Oxford, Oxford, UK

Alan Tennant PhD

Permanent Visiting Professor

Faculty of Humanities and Social Sciences, University of Lucerne, Lucerne, Switzerland

Marc C Hochberg MD

Professor of Medicine and Epidemiology and Public Health

Division of Rheumatology and Clinical Immunology, Department of Medicine and Division of
Gerontology, Department of Epidemiology and Public Health, University of Maryland School of
Medicine, Baltimore, USA

Maarten de Wit PhD

Visiting Fellow

Amsterdam University Medical Centre, Dept. Medical Humanities, Amsterdam Public Health (APH),
Amsterdam, Netherlands

Peter S Tugwell PhD

Professor of Medicine and Epidemiology & Community Medicine

Faculty of Medicine, University of Ottawa, Ottawa, Canada

Philip G Conaghan PhD

Professor of Musculoskeletal Medicine

Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, & NIHR Leeds
Biomedical Research Centre, Leeds, UK

Corresponding Author: Professor Philip Conaghan, Leeds Institute of Rheumatic and Musculoskeletal
Medicine, Chapel Allerton Hospital, Chapeltown Road, Leeds, LS4 7SA, United Kingdom. Email:
p.conaghan@leeds.ac.uk

ABSTRACT

Objective: To assess the uptake of the OMERACT-OARSI core outcome set (COS) domains in hip and/or knee osteoarthritis (OA) trials.

Methods: 382 trials of hip and/or knee OA were identified from the ClinicalTrial.gov registry from 1997 to 2017. Frequency of COS adoption was assessed by year and per 5-yearly phase.

Results: COS adoption decreased from 61% between 1997-2001 to 38% between 2012-2016. Pain (95%) and physical function (86%) were most consistently adopted. Patient global assessment (48%) was the principal missing domain.

Conclusion: Limited adoption of the COS Domains indicates that further consideration to improve implementation is required to improved uptake.

Keywords: OMERACT; Core outcome set; domain; adoption; trial registration

Word Count: 1498/1500

INTRODUCTION

Clinical trials seek to determine whether a treatment is effective and safe for patients by comparing their relative effects on outcomes chosen to identify benefit or harm.(1) These can be used to make decisions on whether the treatment under investigation should be recommended or not.(2) It is therefore essential that outcomes reported in trials are those which are needed by decision-makers, and reflect meaningful outcomes for patients, clinicians and all stakeholders involved in the care of these patients.(3)

In 1997 OMERACT-OARSI presented the core outcome set (COS) for people involved in trials with hip and knee osteoarthritis (OA). They reported that four domains should be measured and reported in all future clinical trials including patients with hip or knee OA.(4) These were: pain; physical function; patient global assessment; and with an extra conditionally recommended domain for studies with a follow-up period of a year or longer with putative structure-modifying OA drugs, joint imaging (such as x-rays or MRI scans). Whilst these recommendations have been in the public domain for 20 years, it remains unknown whether they have changed the selection of outcomes used in trials with this population during this period.

The purpose of this study was to assess the uptake of a COS for hip and knee OA, and explore if specific study characteristics are associated with the failure of COS uptake.

METHODS

We adopted Kirkham et al's (5) recommendations on the assessment of COS uptake. Through this, we searched the trials registry ClinicalTrials.gov on 6th July 2017 to identify all phase 3 or 4, drug or non-drug trials registered from January 1997 to July 2017, recruiting people with hip or knee OA. The following filters were applied to identify eligible trials: "conditions: osteoarthritis", "study type: interventional studies", and "phase: 3 and 4". Only Phase 3 and 4 trials were included to reflect the Phase 3 and 4 recommendations made in the original OMERACT-OARSI COS.(4) We excluded trials

which did not exclusively recruit people with OA, did not assess treatment benefit (i.e. effectiveness or efficacy) as endpoints (i.e. medication dosage or safety studies). We also excluded studies assessing outcomes following surgical intervention (principally joint replacement).

We extracted data on all planned trial outcomes and assessed whether the full OMERACT-OARSI hip and knee OA COS was adopted.⁽⁴⁾ These were the assessment of pain, physical function, patient global assessment and, with a conditional recommendation for trials with a 12 month or greater follow-up period and for putative structure modifying OA drugs, imaging outcomes. We also assessed the uptake of 'strongly recommended' domains including: health-related quality of life (HRQOL) and physician global assessment. We assessed the frequency of use of outcomes which were recommended as 'optional', including: stiffness, biologic markers, inflammation, performance-based function, flares, time to surgery, analgesic count. If a trial had registered a composite outcome, all individual outcomes were considered in the composite, even when not listed separately.

Data also collected included: year of trial registration, anatomic location of OA participants presented with (hip, knee or hip and/or knee), country of origin, sample size, duration of follow-up at end-point, the intervention type under investigation (drug or non-drug trial) and phase of the trial.

All 382 trial registrations were extracted by one reviewer (TS). An independent reviewer (MM) verified 10% of the data collected to ensure accuracy of extraction from the trial registry, following Kirkham et al's ⁽⁵⁾ approach. Disagreement between the reviewers was resolved through discussion. To assess the veracity of the ClinicalTrials.gov registry data, when a trial did not meet the full COS, with any of the core domains missing (n=230), the published full report was used to verify the data (n=74). When published reports were not available (n=156), the chief investigator or named contact on the trial registration was contacted via email to verify the data. Of these 14% (n=21) responded and provided additional data.

Data Analysis

We calculated the proportion of trials which reported each OA COS domain and the full domain set, and the percentage of core outcomes reported from the COS per year. These were assessed over the 20-year follow-up period to determine change over time.

Using a forced entry multivariate logistic regression model, we assessed the relationship between year of registration, sample size, country of origin, duration of follow-up interval, whether participants presented with isolated hip, isolated knee or hip and/or knee OA, phase of trial (Phase 3 or 4), whether it was a drug trial or non-drug trial and full COS domain uptake (yes/no). A forced entry method was

adopted to ensure that all variables were included in the model. Data were presented as odds ratios (OR) with 95% confidence intervals (CI). A two-sided p-value <0.05 was deemed as indicating statistical significance. Analyses were undertaken using Stata version 14.0 (StataCorp LLC, Texas, USA).

RESULTS

In total, 382 Phase 3 or 4 trials registered in Clinicaltrials.gov were eligible for analysis. The eligibility assessment and reasons for exclusion of trials are presented in Figure 1. Trial characteristics are presented in Supplementary Table 1.

The assessment of COS uptake is summarised in Table 1 and Figure 2. There was a decrease in the adoption of the full COS from 61% between 1997 to 2001 to 38% between 2012 to 2016. The adoption of the full COS has largely plateaued between 2002 to 2017, within the ranges of 38% to 54% (Table 1; Supplementary Table 2). Whilst trials have consistently assessed pain (over 90%; Table 1) and physical function (over 80%; Table 1), there has been greater variability for patient global assessment (67% to 38%). As Figure 2 illustrates, the assessment of patient global assessment was the principal domain for COS not being fully reported from 1997 to 2017.

On assessment of domains which were 'recommended' but not 'essential' by the 1997 OMERACT-OARSI COS,⁽⁴⁾ joint stiffness was most commonly assessed (58%) followed by HRQOL (26%) and analgesic consumption (27%). Least frequently assessed included swelling (7%), pain flares (2%) and time to surgery (3%) (Table 1).

On analysis of the factors which may be associated with a successful COS uptake, the phase of the trial was a significant factor, where Phase 3 trials were over twice as likely to have reported a full COS, compared to Phase 4 trials (OR: 2.32; 95% CI: 1.26 to 4.26; p=0.01). Drug trials were over three times as likely to have presented the full COS compared to non-drug trials (OR: 3.57; 95% CI: 1.12 to 5.37; p=0.03). The country of trial origin (p=0.99), year of registration (p=0.28), duration of the trial (p=0.07) and whether the trial recruited people with hip, knee or hip and knee OA (p=0.53) were not significant. Although statistically significant, there was no important difference in COS adoption based on sample size (OR: 1.00; 95% CI: 1.00 to 1.00; p<0.01).

DISCUSSION

This study has demonstrated that there has been limited uptake of the full OMERACT-OARSI COS domains in randomised controlled trials of hip and knee OA during the past 20 years. Whilst pain and physical function are consistently assessed, (over 90% and over 80% respectively), patient global assessment is less frequently evaluated and decreased from 67% to 38%, which is the principal reason for trials not satisfying the full COS uptake.

Of the three (conditionally four) components required to satisfy the COS, patient global assessment was the principal missing domain for trials not satisfying the full COS. There has been concern that patient global assessment scores may be influenced by social desirability bias.⁽⁶⁾ This may therefore be a reason for the reported lower adoption of patient global assessment measures. Nonetheless, OMERACT and others have highlighted the importance of patient-reported outcome measures to measure the patient's overall perceptions of their disease.⁽⁷⁾ Accordingly, the diminishing inclusion of patient global domain warrants an update of the COS to ensure its relevance for OA trials.

The results contrast with the Kirkham et al ⁽⁸⁾ analysis of the uptake of the rheumatoid arthritis COS where uptake had increased within a 14-year period (from 2002) to 81% of eligible trials. This was attributed to the introduction of consistent guidance provided by regulatory authorities including the Food and Drug Administration (FDA) ⁽⁹⁾ and European Medicines Agency (EMA).⁽¹⁰⁾ There is less consistency around COS domains in OA.⁽¹¹⁾ The OARSI-FDA Disease State Working Group¹² recommended the assessment of pain, function, radiological measures and other wider patient experiences of illness including fatigue, mood, sleep and HRQOL.⁽¹²⁾ The EMA guidelines recommend that pain, functional disability and structural damage should be assessed, but patient global assessment is recommended rather than mandatory.⁽¹³⁾ Some of this discordance may account for lack of uptake, and therefore future work may be undertaken to standardise recommendations across regulatory authorities.

Trials were evaluated using their ClinicalTrials.gov registration, as recommended by Kirkham et al ⁽⁵⁾ to provide a more efficient means of assessing COS uptake compared to reviewing final trial reports or publications.^(5,14) However, a disadvantage to the adopted approach was that we did not review additional registries such as the World Health Organization International Clinical Trials Registry Platform (ICTRP) or the Netherlands Trial Registry. However, since ClinicalTrials.gov demonstrates

international coverage (Supplementary Table 1), we feel that the results were representative of trials on this population.

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Conflicts of Interest: No author declares a conflict of interest in relation to this paper.

Ethical approval: No ethical approval was sought for this study design.

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Figure 1: Flow-chart of identification of trial registrations from ClinicalTrials.gov database

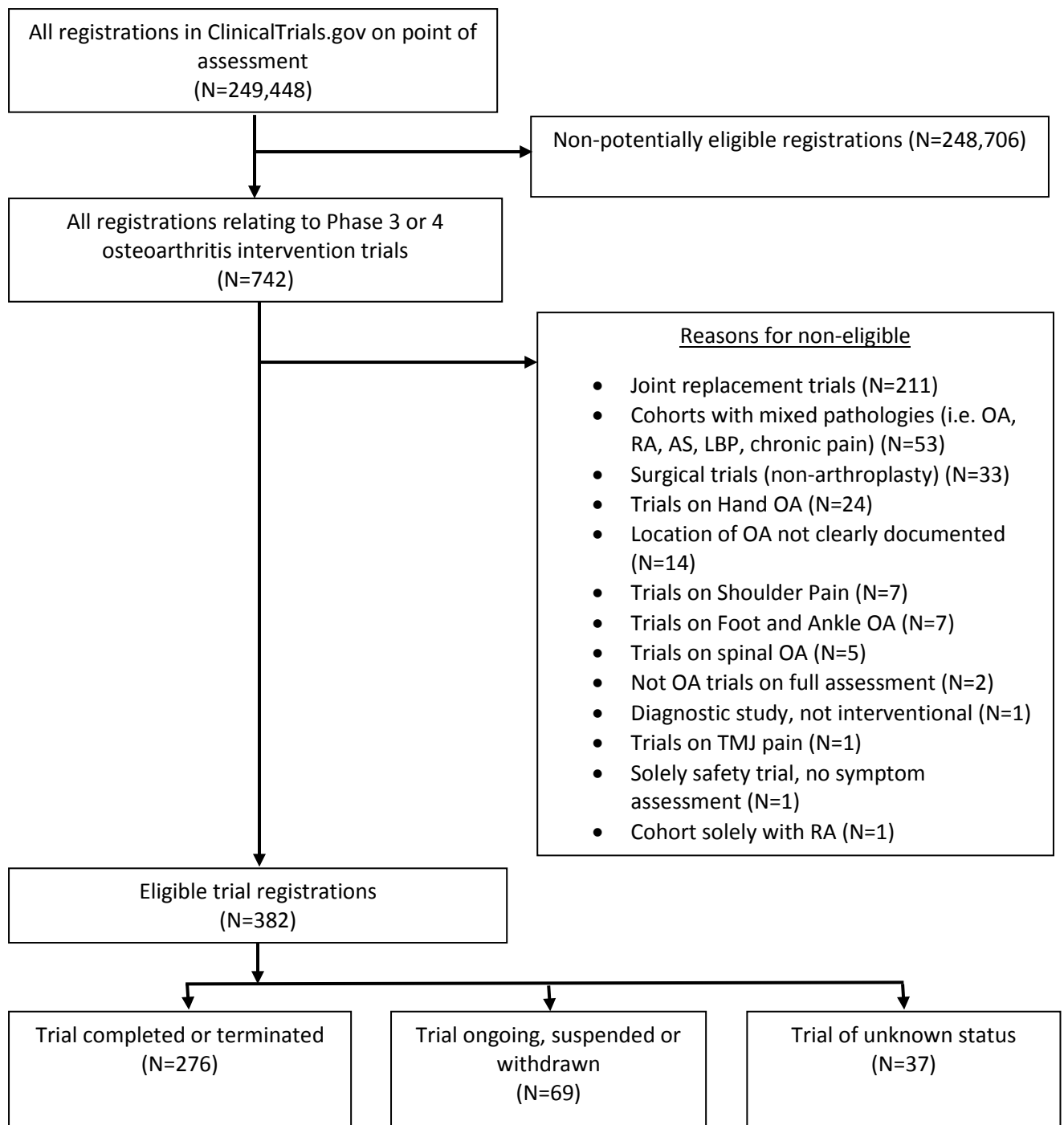


Figure 2: Graph of uptake of core domain and individual domains for the osteoarthritis core outcome set from 1997 to 2017.

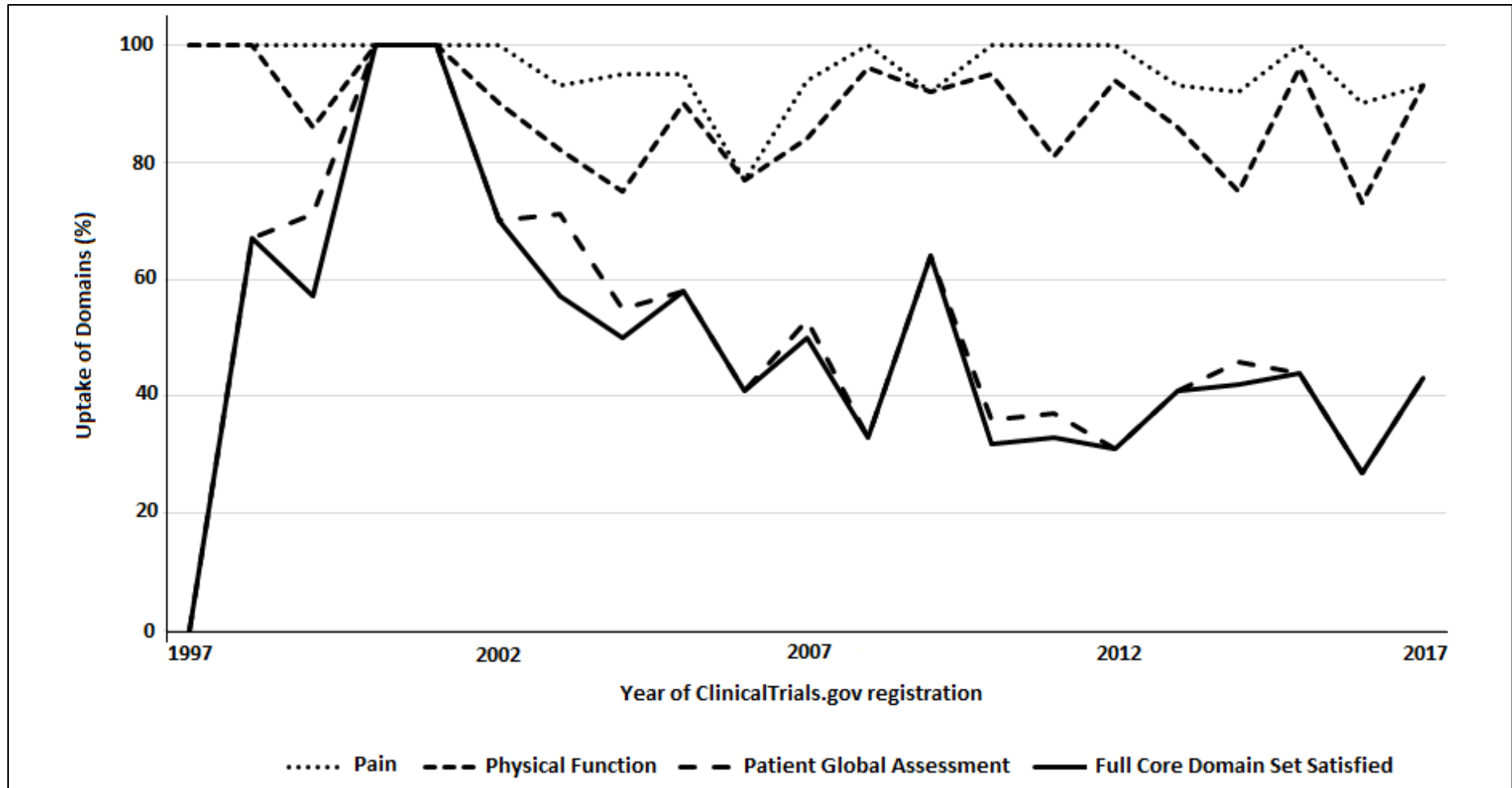


Table 1: Percentage frequency of domains reported and complete adoption of the Core Outcome Set in included trial registrations.

Domain	Percentage Total Frequency (N=382)	Percentage Frequency by Year				
		1997-2001 (N=18)	2002-2006 (N=94)	2007-2011 (N=133)	2012-2016 (N=123)	2017 (N=14)
Core Domain						
Pain	94.8	100	91.5	96.9	94.4	92.9
Physical function	86.1	94.4	81.9	89.2	84.1	92.9
Patient global assessment	47.6	66.7	59.6	45.4	38.1	42.9
Imaging*	75.0	71.4	40.0	79.2	89.5	85.7
All core domains measured	45.3	61.1	54.3	43.1	38.1	50.0
Recommended Domains						
HRQOL	26.2	27.8	12.8	39.1	27.6	14.3
Clinician global assessment	23.0	44.4	36.2	16.5	20.3	14.3
Optional Domains						
Stiffness	58.1	66.7	58.5	64.7	52.0	35.7
Biological markers (i.e. relevant blood tests)	18.8	22.2	17.0	23.3	15.4	7.1
Swelling	7.1	16.7	3.2	6.8	8.1	7.1
Performance Assessment	14.7	27.8	11.7	15.0	16.3	7.1
Pain flares	1.6	5.6	3.2	1.5	0.8	0.0
Time to surgery	2.6	16.7	0.0	0.0	4.1	7.1
Analgesic consumption	27.0	50.0	29.8	24.8	22.8	21.4

* Imaging is a required core outcome set domain for trials of 12 month or greater follow-up in trials of structure modifying osteoarthritis drugs (Total N=68).

APPENDIX: Supplementary Table 1: Characteristics of included trials registered on ClinicalTrials.gov

Characteristic	Number (%) of trials (N=382)
Location of Osteoarthritis	
Hip	17 (4.5)
Knee	299 (78.3)
Hip and Knee	66 (17.3)
Trial Phase	
3	253 (66.2)
4	129 (33.8)
Intervention Type	
Drug Trial	348 (91.1)
Non-Drug Trial	34 (8.9)
Trial duration	
Mean duration (weeks; SD)	27.2 (46.0)
<6 months	254 (66.5)
6-12 months	95 (24.9)
>12 months	29 (7.6)
Not documented	4 (1.0)
Planned sample size	
Mean sample size	359.5 (537.1)
<100	100 (26.2)
100-500	194 (50.8)
>500	88 (23.0)
Trial status	
Complete	259 (67.8)
Recruiting	42 (11.0)
Terminated	17 (4.5)
Not yet recruiting	11 (2.9)
Active, not recruiting	7 (1.8)
Withdrawn	7 (1.8)
Enrolling by invitation	2 (0.5)
Unknown status	37 (9.7)
Principal continent of registration	
Europe	95 (24.9)
Asia	80 (20.9)
North America	177 (46.3)
South America	22 (5.8)
Australasia	8 (2.1)
Africa	0 (0.0)
Antarctica	0 (0.0)
Year of Registration	
1997-2001	18 (4.7)
2002-2006	94 (24.6)
2007-2011	130 (34.0)
2012-2016	126 (33.0)
2017	14 (3.7)

APPENDIX: Supplementary Table 2: Frequency of domains reported and complete adoption of the Core Outcome Set in included trial registrations by year.

Domain	Frequency (%)																				
	1997 (N=3)	1998 (N=3)	1999 (N=7)	2000 (N=4)	2001 (N=1)	2002 (N=10)	2003 (N=28)	2004 (N=20)	2005 (N=19)	2006 (N=17)	2007 (N=32)	2008 (N=24)	2009 (N=25)	2010 (N=22)	2011 (N=27)	2012 (N=16)	2013 (N=29)	2014 (N=24)	2015 (N=27)	2016 (N=30)	2017 (N=14)
Core Domain																					
Pain	3 (100)	3 (100)	7 (100)	4 (100)	1 (100)	10 (100)	26 (93)	19 (95)	18 (95)	13 (77)	30 (94)	24 (100)	23 (92)	22 (100)	27 (100)	16 (100)	27 (93)	22 (92)	27 (100)	27 (90)	13 (93)
Physical function	3 (100)	3 (100)	6 (86)	4 (100)	1 (100)	9 (90)	23 (82)	15 (75)	17 (90)	13 (77)	27 (84)	23 (96)	23 (92)	21 (95)	22 (81)	15 (94)	25 (86)	18 (75)	26 (96)	22 (73)	13 (93)
Patient global assessment	0 (0)	2 (67)	5 (71)	4 (100)	1 (100)	7 (70)	20 (71)	11 (55)	11 (58)	7 (41)	17 (53)	8 (33)	16 (64)	8 (36)	10 (37)	5 (31)	12 (41)	11 (46)	12 (44)	8 (27)	6 (43)
Imaging*	3 (100)	N/A	2 (100)	N/A	N/A	0 (0)	0 (0)	2 (67)	0 (0)	2 (100)	4 (100)	5 (71)	1 (33)	3 (43)	2 (33)	1 (33)	1 (25)	1 (100)	1 (33)	4 (57)	6 (86)
All core domains measured*	3 (100)	2 (67)	4 (57)	4 (100)	1 (100)	7 (70)	16 (57)	10 (50)	11 (58)	7 (41)	16 (50)	8 (33)	16 (64)	7 (32)	9 (33)	5 (31)	12 (41)	10 (42)	12 (44)	9 (30)	7 (50)
Recommended Domains																					
HRQOL	1(33)	2 (67)	1 (14)	1 (25)	0 (0)	1 (10)	3 (11)	0 (0)	4 (21)	4 (24)	7 (22)	12 (50)	11 (44)	7 (32)	11 (41)	5 (31)	7 (24)	7 (29)	6 (22)	8 (27)	2 (14)
Clinician global assessment	0 (0)	1 (33)	5 (71)	1 (25)	1 (100)	2 (20)	13 (46)	8 (29)	7 (37)	4 (24)	6 (19)	1 (4)	5 (20)	5 (23)	5 (19)	6 (38)	5 (17)	5 (21)	2 (7)	4 (13)	2 (14)
Optional Domains																					
Stiffness	1(33)	1 (33)	5 (71)	4 (100)	1 (100)	8 (80)	16 (57)	14 (50)	10 (53)	7 (41)	22 (69)	17 (71)	18 (72)	13 (59)	11 (41)	9 (56)	16 (55)	12 (50)	17 (63)	15 (50)	5 (36)
Biological markers (i.e. relevant blood tests)	0 (0)	1 (33)	1 (14)	1 (25)	1 (100)	1 (10)	8 (29)	3 (11)	2 (11)	2 (12)	6 (19)	6 (25)	7 (28)	6 (27)	5 (19)	1 (6)	5 (17)	3 (3)	5 (19)	7 (23)	1 (7)
Swelling	0 (0)	1 (33)	1 (14)	1 (25)	0 (0)	0 (0)	1 (4)	1 (4)	1 (5)	0 (0)	1 (3)	4 (17)	1 (4)	2 (9)	2 (7)	0 (0)	2 (7)	2 (8)	2 (7)	4 (13)	1 (7)
Performance Assessment	0 (0)	1 (33)	2 (29)	1 (25)	1 (100)	2 (20)	1 (4)	3 (11)	5 (26)	0 (0)	7 (22)	5 (21)	3 (12)	3 (14)	2 (7)	3 (19)	7 (24)	3 (13)	2 (7)	4 (13)	1 (7)
Pain flares	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	2 (11)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Time to surgery	2(67)	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (10)	0 (0)	1 (4)	2 (7)	1 (7)
Analgesic consumption	2(67)	1 (33)	3 (43)	2 (50)	1 (100)	3 (30)	7 (25)	6 (21)	6 (32)	6 (35)	9 (28)	6 (25)	5 (20)	6 (27)	8 (30)	4 (25)	9 (31)	4 (17)	5 (19)	7 (23)	3 (21)
Non-Recommended Domains																					
Adverse events	1(33)	2 (67)	2 (29)	3 (75)	1 (100)	7 (70)	14 (50)	10 (36)	5 (26)	4 (24)	11 (34)	15 (63)	15 (60)	10 (46)	8 (30)	7 (44)	14 (48)	9 (38)	12 (44)	11 (37)	7 (50)
Treatment adherence	1(33)	1 (33)	2 (29)	2 (50)	1 (100)	2 (20)	9 (32)	6 (21)	5 (26)	0 (0)	5 (16)	9 (38)	7 (28)	4 (18)	4 (15)	2 (13)	7 (24)	1 (4)	2 (7)	4 (13)	2 (14)
Physical examination	0 (0)	0 (0)	1 (14)	1 (25)	0 (0)	1 (10)	8 (29)	3 (11)	1 (5)	4 (24)	1 (3)	7 (29)	6 (24)	8 (36)	1 (4)	1 (6)	3 (10)	5 (21)	5 (19)	5 (17)	3 (21)
Vital signs (e.g. BP/HR)	0 (0)	0 (0)	1 (14)	0 (0)	0 (0)	1 (10)	8 (29)	2 (7)	4 (21)	3 (18)	1 (3)	4 (17)	7 (28)	5 (23)	2 (7)	2 (13)	3 (10)	2 (8)	5 (19)	4 (13)	1 (7)
Work productivity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	1 (6)	1 (3)	0 (0)	1 (4)	0 (0)	0 (0)	1 (3)	0 (0)	1 (4)	1 (3)	0 (0)	0 (0)
Treatment response	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	1 (10)	3 (11)	5 (18)	4 (21)	2 (12)	6 (19)	2 (8)	7 (28)	5 (23)	4 (15)	1 (6)	5 (17)	3 (13)	5 (19)	5 (17)	5 (36)
Sleep	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	2 (20)	5 (18)	1 (4)	0 (0)	4 (24)	3 (9)	1 (4)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	4 (15)	0 (0)	0 (0)
Mood and mental wellbeing	0 (0)	0 (0)	1 (14)	1 (25)	0 (0)	0 (0)	2 (7)	0 (0)	0 (0)	1 (6)	2 (6)	3 (13)	5 (20)	1 (5)	2 (7)	2 (13)	2 (7)	1 (4)	2 (7)	2 (7)	0 (0)
Cost and economic evaluation	1 (33)	1 (33)	2 (29)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	1 (6)	1 (3)	2 (8)	0 (0)	1 (5)	1 (4)	0 (0)	0 (0)	0 (0)	1 (4)	1 (3)	0 (0)
Biomechanical / kinematic assessment	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	1 (4)	0 (0)	1 (6)	0 (0)	3 (13)	0 (0)	0 (0)	0 (0)	1 (6)	2 (7)	1 (4)	0 (0)	0 (0)	0 (0)
Patient reported health status	0 (0)	0 (0)	1 (14)	0 (0.0)	0 (0)	1 (10)	1 (4)	0 (0)	1 (5)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
Falls	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)
Fatigue	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cognitive function	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Time to treatment response (pain)	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0)	0 (0)	0 (0)	1 (5)	1 (5)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Patient preference (to other treatment)	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Coping and self-efficacy	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

N/A – not applicable as respective trials did not meet the threshold to require an imaging outcome in accordance with OMERACT recommendations (Bellamy, 1997).