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Original article

Outcomes assessed in trials of gout and accordance with OMERACT-proposed domains: a systematic literature review

Filipe Araújo[1,2], Inês Cordeiro[3], Sofia Ramiro[3,4], Louise Falzon[5], Jaime C. Branco[1,6] and Rachelle Buchbinder[7,8]

Abstract

Objective. The aim of this study was to systematically review outcome domains and measurement tools used in gout trials and their accordance with the preliminary OMERACT gout recommendations published in 2005.

Methods. Randomized controlled trials (RCTs) and quasi-RCTs investigating any intervention for gout published up to February 2013 were included. Recruitment start dates and all measured outcomes were extracted. Risk of bias (RoB) was assessed with the Cochrane Collaboration tool. Numbers of OMERACT domains were compared for trials at low *vs* unclear/high RoB and for recruitment start date before 2005 or 2005 and later.

Results. Of 9784 articles screened, 38 acute and 30 chronic gout trials were included. Mean (S.D.) number of OMERACT outcomes was 2.9 (1.1) (out of 5) and 2.5 (1.2) (out of 9) for acute and chronic gout trials, respectively. Health-related quality of life, participation and joint damage imaging were not assessed in any trial. Tools used to measure individual domains varied widely. There were no differences in the number of OMERACT outcomes reported in acute or chronic gout trials recruiting before 2005 *vs* 2005 or later [mean (S.D.): 3.0 (1.1) *vs* 3.5 (1.3), $P = 0.859$ and 2.7 (1.1) *vs* 2.8 (1.4), $P = 0.960$, respectively]. While both acute and chronic trials at low RoB reported more OMERACT domains than trials at unclear/high RoB, these differences were not significant. Industry-funded trials and trials performed by OMERACT investigators reported more OMERACT outcome domains.

Conclusion. We found no appreciable impact of the OMERACT recommendations for gout trials to date.

Key words: gout, outcomes research, patient perspective.

Introduction

Use of various outcomes, measured in a non-standardized manner, can hamper efforts to pool results and make comparisons between trials. The OMERACT initiative was developed to address this issue, defining and validating outcome domains and measures to be used in clinical trials of rheumatic diseases [1, 2].

Since the second half of the twentieth century, numerous clinical trials have been undertaken to investigate the efficacy and safety of interventions aimed at treating gout flares and lowering serum uric acid (sUA), and these trials have included a wide range of outcomes. The OMERACT Gout Special Interest Group first proposed a core set of domains to be included in gout trials in 2005. Five domains were defined for acute gout trials: pain,

[1]Rheumatology Department, Hospital de Egas Moniz, Centro Hospitalar de Lisboa Ocidental, [2]Institute of Microbiology, Faculdade de Medicina da Universidade de Lisboa, Lisboa, [3]Rheumatology Department, Hospital Garcia de Orta, Almada, Portugal, [4]Department of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [5]Center for Behavioral Cardiovascular Health, Columbia University Medical Center, NY, USA, [6]CEDOC, Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Lisboa, Portugal, [7]Monash Department of Clinical Epidemiology, Cabrini Hospital and [8]Department of Epidemiology and Preventive Medicine, School of Public Health & Preventive Medicine, Monash University, Melbourne, Australia

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Correspondence to: Filipe Araújo, Rheumatology Department, Hospital de Egas Moniz, Centro Hospitalar de Lisboa Ocidental, Rua da Junqueira, No. 126, 1349-019 Lisboa, Portugal.
E-mail: flipar@msn.com

inflammation, patient global assessment, function of the target joint, and safety; and nine domains were defined for chronic gout trials: serum urate, gout flare recurrence, tophus regression, joint damage imaging, health-related quality of life, musculoskeletal function, patient global assessment, work participation, and safety and tolerability [3]. These domains were revised and ratified by OMERACT in 2009 according to the evidence found in literature reviews and expert opinion. For acute gout trials, the only change was that inflammation was replaced by joint swelling and joint tenderness. For chronic gout trials, pain was added, work participation and joint damage imaging were removed, and function, gout flare recurrence and tophus regression were renamed as activity limitations, acute gout attack and tophus burden, respectively [4–7]. Measurement of safety and tolerability, though not part of the revised outcomes of 2009, were considered obligatory in all studies investigating new products for gout [6].

While it is generally assumed that rheumatic disease trialists would be guided by OMERACT recommendations regarding outcome measurement [7], there has been no assessment of compliance with these recommendations, either for gout or for any other rheumatic conditions for which recommendations have been developed.

The purpose of the present study was to systematically review which outcome domains, outcome measures and corresponding measurement tools have been reported in trials of gout to date, and to assess their accordance with the 2005 preliminary OMERACT core set of domains.

Methods

Inclusion criteria

We included all randomized controlled trials (RCTs) and quasi-randomized controlled trials (CCTs) investigating any intervention in adults (>18 years of age) with gout (PICOT is available as supplementary material, available at *Rheumatology* Online). Only published reports were included. Post hoc analyses, open-label extensions and trials concerning participants with hyperuricaemia without gout were excluded.

Search strategy

MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials databases were searched from inception to 18 February 2013. No language restriction was applied to the search strategy, but papers without an English, Portuguese, Spanish or French translation were excluded. Systematic reviews of interventions for gout and the reference lists of included studies were screened to identify any additional studies. The list of search terms is available as supplementary material, available at *Rheumatology* Online.

Trial selection, data extraction and assessment of risk of bias

Titles and abstracts were independently assessed for inclusion suitability by two authors (F.A. and I.C.), and all potentially relevant papers were assessed by full-text review. Selected studies were classified into acute or chronic gout trials according to their different features such as type of intervention (treatment of flare or lowering of sUA), outcomes assessed (for instance, pain/inflammation or sUA-related outcomes) and trial duration ($\leqslant$2 or >2 months of follow-up). Details about the interventions, study duration, number of participants included and year of recruitment (prior to 2005 or 2005 or later), as well as all outcomes, measurement tools and respective units were extracted using a standardized data extraction form. Outcomes were categorized as either OMERACT-proposed outcome domains for acute or chronic gout or non-OMERACT domains [3].

As a reference standard, we used the 2005 domains rather than those published in 2009. The 2005 domains are similar and representative of those published in 2009, and using 2009 as the reference year for patient recruitment would impair any analysis due to the low number of trials before and during 2009. The 2005 preliminary domains were also used instead of the 2009 definitive ones to try to minimize the effect of the implementation gap between publication of guidelines and their application in clinical trial design.

Risk of bias (RoB) of included trials was assessed using the Cochrane Risk of Bias Assessment Tool [8, 9]. The following items were evaluated: random sequence generation, allocation concealment, blinding of participants, care provider and outcome assessor for each outcome measure, incomplete outcome data, selectiveoutcome reporting and other potential sources of bias. Each criterion was rated as low, high or unclear (either lack of information or uncertainty over the potential for bias) RoB. An overall judgement of the RoB of the trial was made and trials were categorized into low RoB or high/unclear RoB. Whenever there was uncertainty or disagreement regarding trial selection or classification, data extraction or RoB appraisal, the decision was taken after discussion with co-authors (S.R. or R.B.).

Data analysis

We compared the number of OMERACT outcomes included in trials according to overall RoB (low RoB *vs* unclear or high RoB) and according to recruitment date [<2005 (prior to OMERACT preliminary core set of domains) *vs* $\geqslant$2005]. We also sought whether trials performed by investigators affiliated to the OMERACT gout committee or funded by the pharmaceutical industry assessed more OMERACT outcome domains. All analyses were performed using the Mann–Whitney U-test. Finally, we also evaluated the proportional use of the different measures employed to assess each OMERACT domain throughout time by means of graphs computed with Stata SE version 12 (Statacorp, College Station, TX, USA).

Results

Results of the search

Of 9784 articles that were screened, 70 studies were excluded because no translation could be obtained

(papers in Chinese, Japanese, German, Russian, Slovak, Hungarian, Polish, Croatian and Danish) (Fig. 1). Other reasons for exclusion were: duplicate studies (555 publications), wrong study population (7473 publications) and wrong study type (1620 publications). Two of the included trials were obtained by hand search. In total, 67 articles [10–76] corresponding to 68 trials (one article contained two distinct trials) with a total of 9741 participants fulfilled our inclusion criteria; one trial was published in the 1960s, six trials in the 1970s, 13 trials in the 1980s, 11 trials in the 1990s, 26 trials in the 2000s and 11 trials in 2010 or later.

The characteristics of the 68 included trials are summarized in Table 1. Of these, 38 acute gout trials (35 RCTs, 3 CCTs) evaluated diverse interventions [10–15, 17, 19, 21–46, 71, 72, 75]. NSAIDs (23 trials) and complementary medicine (5 trials) were the most common interventions studied. Only four trials started recruiting participants from 2005 [33, 39, 41, 75].

The 30 chronic gout trials (28 RCTs, 2 CCTs) also included a range of interventions, most commonly allopurinol alone (seven trials) or in combination with other interventions (seven trials), febuxostat (four trials) and uricosuric agents (four trials) [16, 20, 47–70, 73, 74, 76]. Eight trials started recruiting participants from 2005 [33, 47, 50, 59, 63, 73, 74, 76].

Outcomes assessed in acute gout trials

Each acute gout trial assessed a mean (S.D.) 2.9 (1.1) OMERACT outcome domains (out of five possible). Only two trials (5%) assessed all five proposed domains [34, 46]. Most trials included measures of pain (79%), inflammation (71%) and safety (87%). Table 2 lists the number of acute gout trials that reported each OMERACT outcome domain, as well as the measures, tools and units used to assess them. For the domain pain, overall pain was most commonly measured, but tools varied widely from VAS, Likert, verbal and/or facial pain scales. None of the trials used a dichotomous measure of pain. There were 20 different measures of inflammation across trials, including both clinical (joint tenderness, swelling and/or erythema) and laboratory markers (ESR, CRP, white cell count). Safety was measured most commonly as the proportion of participants with adverse events (AEs) (74%), number of AEs (50%) and withdrawal due to serious AE (34%). Fewer than a third of trials ($n = 11$, 29%) reported patient

Fig. 1 Flowchart with the search results.

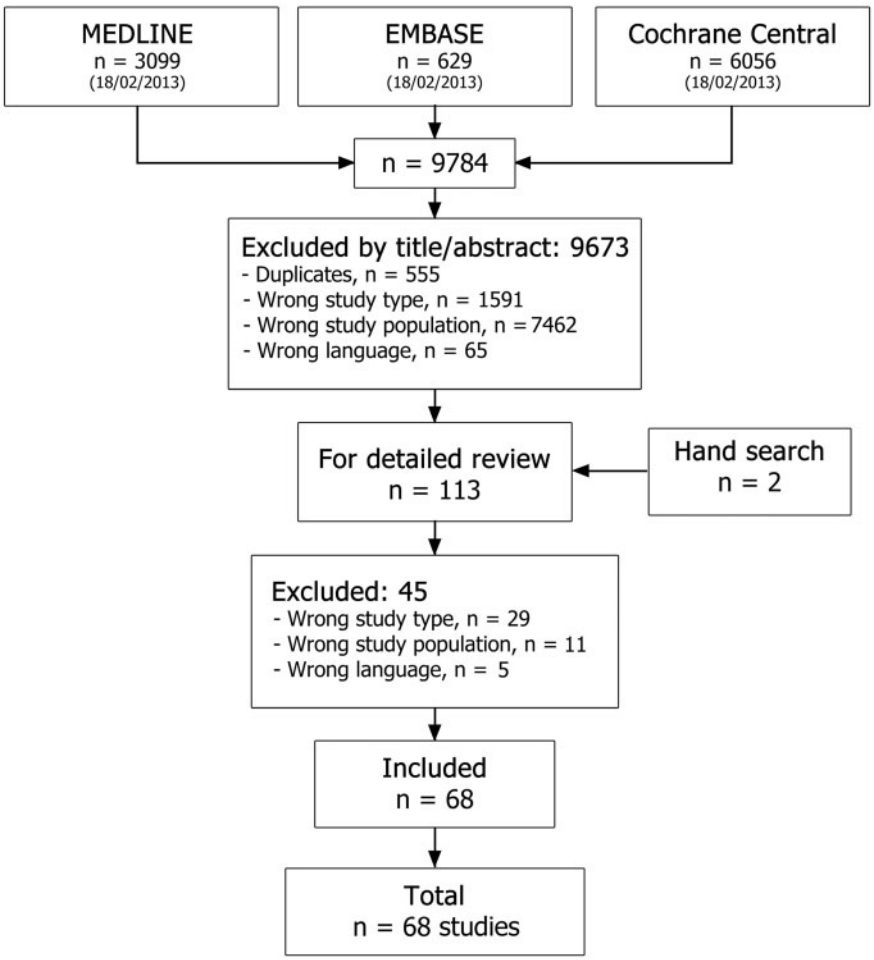


Table 1 Characteristics of the 68 gout trials included in the review

Trial intervention	Number of trials	RCTs, *n* (%)	Recruitment after publication of OMERACT guidelines, *n* (%)	Total number of participants enrolled, mean (S.D.)	Trial duration[a]
Acute gout trials					
NSAIDs	23	21 (91)	1 (4)	1826 (75, 91)	1–28
Colchicine	2	2 (100)	1 (50)	228 (114, 100)	2–7
Glucocorticoids/ACTH	3	2 (66)	0 (0)	126 (42, 30)	30–365
Canakinumab	2	2 (100)	2 (100)	400 (NA, NA)	56
Complementary medicine[b]	5	5 (100)	0 (0)	589 (118, 49)	6–30
Drug combinations[c]	2	2 (100)	0 (0)	109 (55, 50)	7–14
Allopurinol + colchicine + NSAIDs[d]	1	1 (100)	0 (0)	25 (NA, NA)	10
Chronic gout trials					
Allopurinol	7	5 (71)	1 (14)	456 (65, 47)	2–24
Allopurinol + colchicine	3	3 (100)	0 (0)	292 (97, 81)	6–24
Allopurinol + other[e]	4	4 (100)	3 (75)	769 (192, 186)	1–6
Uricosuric agents	1	1 (100)	0 (0)	93 (NA, NA)	7
Uricosurics + other[f]	3	1 (33)	0 (0)	92 (31, 8)	5–6
Febuxostat	4	4 (100)	1 (25)	4253 (1063, 889)	5.6–28
Pegloticase	3	2 (67)	1 (33)	174 (58, 45)	1–6
Complementary medicine[b]	1	1 (100)	0 (0)	26 (NA, NA)	1
Surgery	1	0 (0.0)	0 (0)	28 (NA, NA)	29
Diet	2	1 (50)	1 (50)	173 (87, 47)	1–3
Patient education	1	0 (0)	1 (100)	82 (NA, NA)	24

[a]Range is given in days for acute gout trials and in months for chronic gout trials. [b]Complementary medicine included rebixiao granules, modified simiao tang, weicao capsule, tongfengding capsule and electroacupuncture for acute gout trials, and danggui-nian-tong-tang in chronic gout trials. [c]Drug combinations correspond to colchicine + oral prednisone + local ice, oral prednisolone + paracetamol. [d]Trial assessing the influence of early treatment with allopurinol in acute gout flares. [e]Allopurinol + other corresponds to allopurinol + canakinumab, rilonacept or benzbromarone. [f]Uricosurics + other corresponds to probenecid + losartan or fenofibrate. ACTH: adrenocorticotropic hormone, NA: not applicable.

global assessment; in all cases, it was measured as patient-reported response to treatment. Function was also poorly represented (three trials, 8%). Gout flare recurrence was the most frequently reported non-OMERACT domain in acute gout trials, while 12 trials (32%) measured serum urate normalization.

Outcomes assessed in chronic gout trials

Each chronic gout trial assessed a mean (S.D.) of 2.5 (1.2) OMERACT outcome domains (out of nine possible). No trial assessed all nine proposed domains. Table 3 lists the number of chronic gout trials that reported each OMERACT outcome domain, as well as the measures, tools and units used to assess them. The most frequently reported outcome was serum urate ($n = 24$, 80%), with a preference for reporting the mean sUA changes per treatment group instead of using dichotomous targets (like achievement of <6, 5 or 4 mg/dl). Gout flare recurrence was measured in 21 trials (70%), although there was a wide range of tools used, most commonly number of participants with one or more flares ($n = 13$, 43%), number of flares per treatment group ($n = 10$, 33%) and number of flares per participant ($n = 9$, 30%). Safety and tolerability was assessed in the majority of trials ($n = 22$, 73%). Tophus regression was only reported in three trials (10%); measures included reduction in tophus area, complete tophi resolution and change in number of tophi (although the instruments used were not clarified). Only two trials included patient global assessment, and function was only assessed in one trial (using the HAQ). Participation, health-related quality of life and joint damage imaging were not measured in any of the trials. Renal function, a non-OMERACT domain, was measured in 10 trials (33%).

Proportional use of outcome measures over time

The proportional use over time of the efficacy and safety domains of the included trials is presented in Fig. 2. In acute gout trials, duration of pain, used most commonly in the 1970s, was replaced by overall pain as the main pain measure in later decades, with almost 90% of trials using it in 2010. For inflammation, inflammatory serum markers have become the most frequently reported measures since the late 1990s, while for safety, proportion of participants with AEs has been replaced over time by the number of AEs, severity of AEs and withdrawals due to AEs. In chronic gout trials, for measurement of gout flare recurrence, flares per treatment group has been replaced by number of participants experiencing $\geqslant 1$ flare and mean number of flares per participant. Since 2009, mean reduction in sUA has gradually been replaced by the proportion of participants achieving a target level of sUA, most commonly sUA < 6 mg/dl.

Table 2 Outcome domains, measures and tools in acute gout trials

Outcome domains *n* (%) trials	Measures		*n* (%) Number of trials, *n* = 38	Measuring tools and units
OMERACT outcome domains for acute gout				
Pain, 30 (79%)	Overall pain		28 (74)	VAS (0–10 cm and 0–100 mm), Likert scales (various), Keele verbal scale, Wong–Baker face scale
	Rest pain		3 (8)	Likert scales (4 or 5 point)
	Pain with movement		3 (8)	Likert scales (4 or 5 point)
	Duration of pain		3 (8)	Hours and days
	Time to achieve <50% of baseline pain score		2 (5)	Hours and days
Inflammation, 27 (71%)	Joint tenderness	Tenderness	16 (42)	Likert scales (3-, 4- and 5-point)
		Duration of tenderness	2 (5)	Days
	Joint swelling	Swelling	17 (45)	Likert scales (3-, 4- and 5-point)
		Duration of joint swelling	3 (8)	Days
	Joint erythema	Erythema	11 (29)	Likert scales (3- and 5-point); categorical scale (absent/mild/moderate/severe)
		Duration of joint erythema	2 (5)	Days
	Inflammatory markers	ESR	5 (13)	mm/h
		CRP	4 (11)	mg/l
		White blood cell count	3 (8)	Cells/mm^3 and 10^9 cells/l
	Other measures used		14 (39)	Joint global inflammation, joint hotness, duration of joint hotness, joint stiffness, no. of participants with >50% reduction in erythema, no. of participants with >50% reduction in tenderness, no. of participants with >50% reduction in hotness, change in joint circumference, change in affected limb volume, volume of aspirated synovial fluid, change in serum Amyloid A, beta-2 microglobulin levels and synovial fluid white blood cell count
Patient global assessment, 11 (29%)	Patient global assessment of response to treatment		11 (29)	3-, 4- and 5-point verbal scales; 5-point Likert scale
Function/activity limitation, 3 (8%)	Global disability		3 (8)	VAS (0–100 mm), HAQ-DI (0–3), SF-36 (0–100), EQ-5D (−0.59 to 1)
	Walking disability		1 (3)	VAS (0–100 mm)
Safety, 33 (87%)	Proportion of participants with AEs		28 (74)	—
	Number of AEs		19 (50)	—
	Proportion of participants who withdrew due to serious AEs		13 (34)	—
	Severity of AEs		13 (34)	No. of participants with severe AE; total no. of severe AE; organ/system affected by severe AE
	Organ/system affected by AE		11 (29)	—
	Other measures used		21 (55)	AE-related mortality, AE judged as related to study drug, infectious AE, intolerance/toxic/allergic reactions, cancer and immunogenicity
Non-OMERACT outcome domains for acute gout				
Gout flare recurrence, 16 (42%)	Flare recurrence		7 (18)	Time to flare recurrence; no. of participants with flare recurrence; no. of rebound attacks
	Need for rescue medication		6 (16)	No. of patients; type of rescue medication
	Mean duration of flare		3 (8)	Days (since start of treatment)
	Other measures used		10 (26)	No. of participants with ⩾1 flare, time needed to flare resolution, comparison of current flare drug with previous flare drugs, no. of participants that needed to repeat treatment and no. of participants that had to switch treatment drug

(continued)

Table 2 Continued

Outcome domains *n* (%) trials	Measures	*n* (%) Number of trials, *n* = 38	Measuring tools and units
Serum urate normalization, 12 (32%)	sUA	12 (32)	mg/dl, mmol/l and μmol/l
Renal function, 5 (13%)	Serum creatinine	3 (8)	mg/dl and μmol/l
	Creatinine clearance	2 (6)	ml/min/1.73 m^2
	Other measures used	2 (5)	Change in serum urea levels, change in 24-h urinary pH and in 24-h proteinuria
Joint range of motion, 5 (13%)	Physician-assessed movement	5 (13)	Likert scales (4- and 5-point)

Domains are categorized by whether or not they have been proposed by OMERACT. HAQ-DI: HAQ disability index; SF-36: short-form 36 items; EQ-5D: European quality of life 5 dimensions; AE: adverse event; sUA: serum uric acid; VAS: visual analogue scale.

OMERACT outcome domains according to recruitment date, RoB, author affiliation to OMERACT and trial funding

The mean number of reported OMERACT domains did not differ between trials that began participant recruitment before 2005 or from 2005 onwards [acute gout trials: mean (S.D.) 3.0 (1.1) *vs* 3.5 (1.3), $P = 0.859$; chronic gout trials: mean (S.D.) 2.7 (1.1) *vs* 2.8 (1.4), $P = 0.960$] (Table 4). RoB was deemed low overall for 16 (42%) acute gout trials and 10 (33%) chronic gout trials (see online supplementary Table S1, available at *Rheumatology* Online). Although trials at low RoB tended to report slightly more OMERACT outcome domains than high or unclear RoB trials, these differences were not statistically significant [acute gout trials: mean (S.D.) 3.4 (1.0) *vs* 2.7 (1.2), $P = 0.082$; chronic gout trials: mean (S.D.) 3.1 (1.2) *vs* 2.5 (1.1), $P = 0.153$] (Table 4).

We found significantly more OMERACT-proposed domains in chronic gout trials performed by clinical trialists affiliated to OMERACT compared with those involving trialists not involved with OMERACT [mean (S.D.) 3.4 (1.0) *vs* 1.9 (0.9), $P = 0.001$]. In acute gout trials, clinical trialists affiliated to OMERACT also assessed more OMERACT domains, although this difference was not statistically significant [mean (S.D.) 3.5 (1.0) *vs* 2.9 (1.2), $P = 0.282$]. Compared with non-sponsored trials, those funded by pharmaceutical companies also included a significantly higher number of OMERACT outcome domains [acute gout trials: mean (S.D.) 3.6 (1.2) *vs* 2.1 (0.8), $P = 0.001$; chronic gout trials: mean (S.D.) 3.1 (1.1) *vs* 2.2 (0.9), $P = 0.02$].

Discussion

We found that both acute and chronic gout trials included a wide range of outcome domains, and there was also a wide variation in how these domains were measured. Overall, acute gout trials reported a mean 2.9 out of the 5 outcome domains proposed by OMERACT, while fewer preliminary domains proposed by OMERACT were included in chronic gout trials (mean 2.5 of 9). Only two trials assessed all five domains for acute gout, while no trial assessed the nine proposed domains for chronic gout. We found no differences in the mean number of reported OMERACT domains in trials that commenced recruitment before 2005 or from 2005 onwards, suggesting that there has been no appreciable impact of the OMERACT-recommended domains to date, although comparatively fewer trials commenced after 2005. In acute gout trials, the most frequently appraised domains were safety, pain and inflammation. Serum urate, safety and gout flare recurrence were the most common domains in chronic gout trials. In spite of the importance of patient-reported domains, function and disability, patient global assessment and health-related quality of life were underrepresented, especially in chronic gout trials. These results are in keeping with a smaller review (nine acute and five chronic RCTs) reported by Taylor *et al*. [77]. They identified pain intensity in the index joint, and physician and patient assessment of treatment response as the most frequent domains included in acute gout trials, while gout flare and serum urate were the most common in chronic gout trials. They also noted a lack of assessment of activity limitation and health-related quality of life.

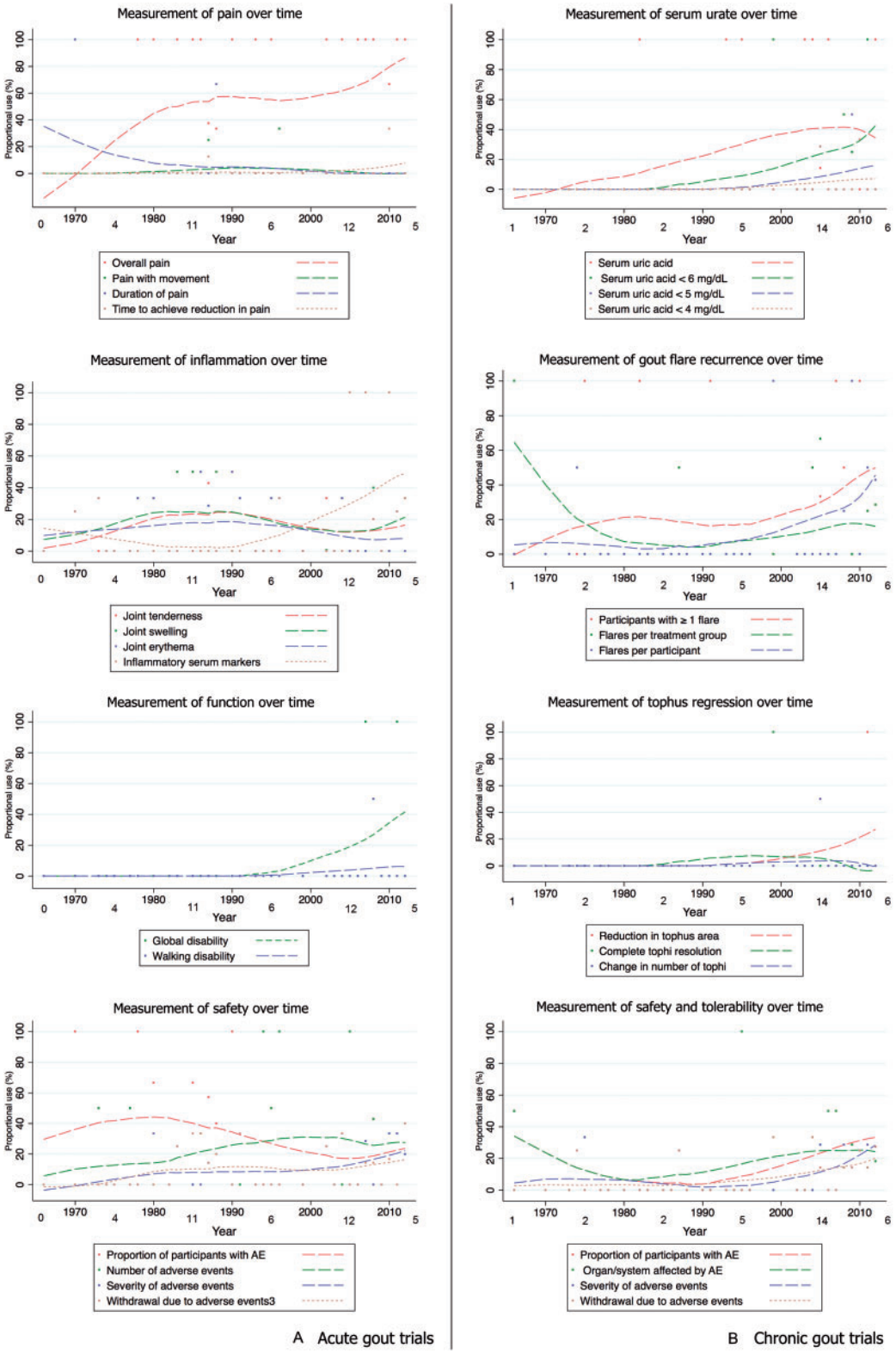
Standardization of endpoints has been a longstanding priority in rheumatology, not only for the OMERACT initiative [78], but also for scientific societies like the European League Against Rheumatism, the ACR [79] and the Assessment of SpondyloArthritis International Society [80–82]. Although it is generally assumed that OMERACT-recommended core sets of domains would be adopted as they became available [7], we were unable to identify any previous studies that have sought objective evidence of this. Our review did not find any significant differences between use of OMERACT outcomes before and after publication of the proposed domains for acute and chronic gout. This apparent absence of impact may be related to a lack of power, as only 12 of the 68 trials started participant recruitment after 2005. In addition, the greater number of OMERACT outcome domains included among trials funded by industry and/or including trialists involved in the OMERACT initiative suggests that progress is being made. We also found that, in recent years, there was stabilization towards the

Table 3 Outcome domains, measures and tools in chronic gout trials

Outcome domains, *n* (%) trials	Measures	*n* (%) trials, *n* = 30	Measuring tools and units
OMERACT outcomes for chronic gout			
Serum urate, 24 (80%)	sUA	19 (63)	mg/dl, mmol/l and μmol/l
	sUA < 6 mg/dl	9 (30)	—
	sUA < 5 mg/dl	5 (17)	—
	sUA < 4 mg/dl	3 (10)	—
	Other measures used	12 (40)	sUA < 6.5 mg/dl, sUA < 6 mg/dl among participants with renal impairment and mean sUA per treatment group
Gout flare recurrence, 21 (70%)	Participants experiencing ⩾ 1 flare	13 (43)	—
	Flares per treatment group	10 (33)	—
	Flares per participant	9 (30)	—
	Other measures used	6 (20)	Timing of flares, time to achieve reduction in mean no. of flares, mean duration of flare, amount of rescue medication taken per flare, time spent with pain VAS ⩾ 5, amount of total rescue medication taken throughout the study and dose of treatment drug needed to obtain same efficacy as active comparator
Tophus regression, 3 (10%)	Reduction in tophus area	2 (7)	Percentage reduction in tophus area
	Complete tophi resolution	1 (3)	No. of patients
	Change in number of tophi	1 (3)	—
Patient global assessment, 2 (7%)	Patient global assessment of response to treatment	2 (7)	Two-point verbal scale
Musculoskeletal function, 1 (3%)	Health assessment questionnaire	1 (3)	—
Work participation, 0 (0%)	—	0	—
Joint damage imaging, 0 (0%)	—	0	—
Health-related Quality of life, 0 (0%)	—	0	—
Safety and tolerability, 22 (73%)	Proportion of participants with AE	19 (63)	—
	Organ/system affected by AE	17 (57)	—
	Proportion of participants who withdrew due to serious AE	16 (53)	—
	Severity of AEs	14 (47)	No. of participants with severe AE; total no. of severe AE; organ/system affected by severe AE; withdrawal due to severe AE
	Number of AEs	11 (37)	—
	Other measures used	20 (67)	AE-related mortality, infectious AE, intolerance/toxic/allergic reactions, cancer and immunogenicity
Non-OMERACT outcomes			
Renal function, 10 (33%)	Creatinine clearance	5 (17)	ml/min/1.73 m^2
	Serum creatinine	2 (7)	mg/dl
	Other measures used	10 (33)	Change in serum urea, change in urinary creatinine, change in 24-h proteinuria, change in urinary pH, change in ammonium excretion, change in titrable acid excretion, change in net acid excretion, change in urate clearance, change in oxypurine clearance, change in urate clearance/creatinine clearance ratio, change in urinary uric acid/urinary creatinine ratio, urine volume and urinary level of *N*-acetylglucosaminidase
Pain, 5 (17%)	Overall pain	3 (10)	VAS (0–10 cm and 0–100 mm); 0–4-point Likert scale
	Duration of pain	1 (3)	Days

Domains are categorized by whether or not they have been proposed by OMERACT. AE: adverse event; sUA: serum uric acid; VAS: visual analogue scale.

Fig. 2 Proportional use over time of outcome measures



(**A**) Acute outcome domains: pain, inflammation, function and safety; (**B**) chronic outcome domains: serum urate, gout flare recurrence, tophus regression and safety and tolerability. Domains that are not represented either have only one outcome measure (patient global assessment in acute trials and musculoskeletal function in chronic trials) or were not assessed in any trial (work participation, joint damage imaging and HR-QoL in chronic trials). The numbers between the dates represent the number of acute or chronic gout trials published in that decade.

Table 4 Outcome domains and accordance with OMERACT recommendations

	Trials, *n* (%)	Number of outcomes, mean (S.D.)	*P*-value
Acute gout ($n = 38$)			
Before OMERACT	33 (87)[a]	3.0 (1.1)	0.859
After OMERACT	4 (11)[a]	3.5 (1.3)	
High or unclear risk of bias	22 (58)	2.7 (1.2)	0.082
Low risk of bias	16 (42)	3.4 (1.0)	
OMERACT trialists	6 (16)	3.5 (1.0)	0.282
Non-OMERACT trialists	32 (84)	2.9 (1.2)	
Pharmaceutical funding	16 (42)[b]	3.6 (1.2)	0.001
Non-pharmaceutical funding	15 (40)[b]	2.1 (0.8)	
Chronic gout ($n = 30$)			
Before OMERACT	21 (70)[a]	2.7 (1.1)	0.960
After OMERACT	8 (27)[a]	2.8 (1.4)	
High or unclear risk of bias	20 (67)	2.5 (1.1)	0.153
Low risk of bias	10 (33)	3.1 (1.2)	
OMERACT trialists	12 (40)	3.4 (1.0)	0.001
Non-OMERACT trialists	18 (60)	1.9 (0.9)	
Pharmaceutical funding	14 (47)[b]	3.1 (1.1)	0.02
Non-pharmaceutical funding	10 (33)[b]	2.2 (0.9)	

Comparison of mean number of OMERACT outcome domains assessed in gout trials before and after publication of the OMERACT preliminary domains, and also according to risk of bias, clinical trialist's affiliation with OMERACT, and trial funding. [a]In one trial of acute gout and one trial of chronic gout there was no available information regarding recruitment date, and [b]in seven acute gout and six chronic gout trials there was no available information regarding sponsoring. OMERACT: Outcome Measures in Rheumatology Clinical Trials.

assessment of three to four OMERACT domains per trial, as opposed to the significant variability prior to 2005 (one to five domains in acute trials and one to four in chronic trials). As regulating authorities become more aware of the importance of standardization of procedures in clinical research, it is also likely that the OMERACT gout recommendations will be adopted. For example, in 2012, the European Medicines Agency released a concept paper on the need for guidelines on clinical investigation of medicinal products for the treatment of gout and recommended that patient-reported outcomes in chronic gout, as ratified at the OMERACT 10 meeting, should be used as clinically meaningful endpoints [83].

We observed substantial heterogeneity in measures used to assess different outcome domains across trials. Since 2005, the OMERACT Gout Special Interest Group has continued its efforts to define and validate a core set of outcome domains, as well as how best these should be measured. For example, in acute gout trials, pain assessed by a 5-point Likert scale has been endorsed by OMERACT, as well as response to treatment as a measure of patient global assessment [84]. Both were fairly represented in acute gout trials captured in this review (Table 2). For chronic gout, preference was given by OMERACT to reporting the number of participants who achieve a target of 6 mg/dl instead of continuous measures [77], while in our review, only nine trials (30%) reported sUA outcome in this way. We only found one chronic gout trial that assessed function. This trial assessed function with the HAQ, which has now been endorsed by OMERACT as a valid measure of function and activity limitation for chronic gout trials [84]. Despite the growing interest in the study of health-related quality of life in gout patients, no chronic gout trial assessed this domain in our review. A recent work by Chandratre *et al.* [85] has recognized the negative impact of gout on health-related quality of life and has demonstrated good clinimetric properties of the HAQ disability index (HAQ-DI) and short-form 36 (SF-36) for measuring it.

None of the included chronic gout trials assessed radiographic damage. While a radiographic damage index was recommended for use in trials of chronic gout because urate-lowering therapies may reduce structural damage [2], and although a modified Sharp–van der Heijde scoring system has been validated for that purpose [86], radiographic damage was not endorsed as a mandatory outcome [3].

Measures of safety varied widely across all gout trials, and many chronic gout trials measured renal function, most likely due to concerns about renal safety for urate-lowering therapies and the elevated risk of chronic kidney disease associated with persistent hyperuricaemia. Although OMERACT did not explicitly include renal assessment as an individual outcome domain for chronic gout trials, it is implicitly included within the safety domain.

This appears to be the first published study assessing compliance with OMERACT-proposed domains. Strengths of our study include the comprehensive literature search, which yielded a high number of gout trials and an even higher number of extracted outcomes. We believe our strategy allowed us to capture practically all the RCTs

and CCTs of gout present in the main electronic databases from the 1960s to the present day, contributing to the reliability of the results. The main limitation of our study relates to the difficulty we encountered in categorizing some of the extracted outcomes into the predefined OMERACT domains, since hundreds of different instruments and units were found and some of these presented a high level of ambiguity. As previously noted, the majority of trials (56, 82%) started participant recruitment after 2005, limiting our ability to draw firm conclusions about the impact of the OMERACT-proposed domains so far.

In summary, the demonstration of a significant variation in outcome domains and how these are measured across trials supports the development of a core set of outcomes for both acute and chronic gout trials. Further efforts are needed to encourage the uptake of the OMERACT recommendations in future trials, although there is some indirect evidence of progressive adoption of the preliminary core set of domains. This review confirmed that non-patient reported measures are still preferred over patient-reported outcomes. To truly understand burden of disease and treatment impact, it is of the utmost importance that authorities also strive for the implementation of patient-related domains, such as patient global assessment, function and disability and health-related quality of life.

Rheumatology key messages

- There was significant heterogeneity in outcome domains, measures and tools used in trials of gout.
- Patient-reported outcomes were underrepresented compared with non-patient-reported outcomes in gout trials.
- To date, OMERACT recommendations for gout trials have not made an appreciable impact.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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