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Outcome reporting in randomized trials in gout: A systematic scoping review from the OMERACT gout working group assessing the uptake of the core outcome set

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ABSTRACT

Objective: The selection and reporting of core outcome measures in clinical trials is essential for patients, researchers, and healthcare providers for clinical research to have an impact on healthcare. In this systematic scoping review, we aimed to quantify the extent to which gout clinical trials are collecting and reporting data in accordance with the core outcome domains from Outcome Measures in Rheumatology (OMERACT) published in 2009 applicable for both acute and chronic trials and evaluate the reporting according to the core domains before and after the 2009 OMERACT endorsement.

Methods: We searched multiple databases PubMed, EMBASE, the Cochrane Library including the Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews (CDSR) and www.clinicaltrials.gov for randomized controlled trials (RCTs) allocating people with gout versus an active pharmacological gout treatment or a control comparator (no date limitation). We extracted the data in accordance with the core outcome sets, focusing individually on core outcome domains and the core outcome measurements for acute and chronic trials, respectively. In this study 'Acute trials' reflect studies that describe interventions for short term management of gout flares, and 'chronic trials' describe interventions for long-term urate lowering therapy in the management of gout.

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Results: From 8,522 records identified in the database search, 134 full text papers were reviewed, and 71 trials were included, of which 36 were acute and 35 were chronic. Only 3 of 36 (8%) acute trials reported all five core domains and none of the 35 included chronic trials reported all 7 core domains. In the acute trials, twenty-seven unique measurement instruments across the 5 core domains were identified. For chronic trials there were 31 unique measurement instruments used across the 7 core domains. Serum urate was reported in 100% of the chronic trials and gout flares in 80%. However, other core domains were reported in <30% of chronic trials. In particular the patient-important domains such as HR-QOL, patient global assessment and activity limitations were rarely reported. A broad variety of different measurement instruments were used to assess each endorsed core domain, a minority of trials used the OMERACT endorsed instruments. For acute trials, the number reporting on all core domains was consistently low and no change was detected before and after the endorsement of the core domains in 2009. None of the included chronic trials reported on all 7 endorsed core domains at any time.

Conclusion: In this study we found a low adherence with the intended endorsed (i.e., core) outcome domains for acute and chronic gout studies which represents a poor uptake of the global OMERACT efforts for the minimum of what should be measured in clinical trials. In addition, there is a significant variation in *how* the OMERACT endorsed outcome domains have been measured. This systematic review demonstrates the need for continuous encouragement among gout researchers to adhere to OMERACT core domains as well as further guidance on outcome measurements reporting.

Registration: Prospero: CRD42019151316

Introduction

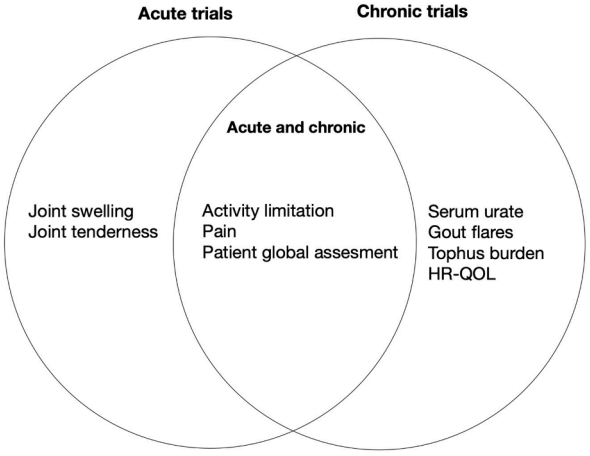
The Outcome Measures in Rheumatology (OMERACT) initiative has worked since 1992 to develop, improve and endorse standardized core outcome sets for collecting and reporting data in clinical trials of rheumatic diseases[1,2]. The intent of a core outcome set for each individual disease is to create a uniform approach that facilitates comparison and evidence synthesis of data from different trials for a more complete understanding of the effects of interventions and the body of evidence across trials[3]. Appropriate core outcome sets are essential to ensure that a specific minimum set of outcomes is measured. As such, patients, researchers, healthcare professionals and other key-stakeholders should be involved in the selection and endorsement of the core outcome set to ensure they have a relevant impact on healthcare[4].

An OMERACT core outcome set constitutes two related but partially independent components: The *what* to measure is known as the core outcome domain set, and the core outcome measurement set describes *how* to measure each of the core outcome domains, describing the measurement instrument or tools used to measure the core outcome domain[5]. Measurement instruments can take a variety of forms: "The tool can be a single question, a questionnaire, a score obtained through a physical examination, a laboratory measurement, a score obtained through observation of an image, and so on"[6,7]. Thus, endorsed outcome domains (the *What* to measure) need a corresponding standardized and accurate measurement instrument (the *How* to measure) for a core outcome set to be complete.

In 2008, the OMERACT Gout Special Interest Group (SIG) proposed core outcome domains for acute (gout flare) and chronic (urate lowering therapy) studies at the OMERACT 8 meeting[8]. They conducted a modified Delphi exercise at OMERACT 9[9] and the core outcome domains for acute and chronic studies in gout were endorsed in 2009[10]. Currently most, but not all the endorsed gout core outcome domains have an endorsed measurement instrument (Fig. 1)[11,12]. The endorsement of instruments for acute studies was at OMERACT 11 (2012)[13]. The patient-reported core outcome domains in chronic gout were endorsed at OMERACT 9 and 10. The core outcome set for acute and chronic studies is nevertheless not completed. For acute studies, the activity limitations domain does not have an endorsed instrument and for chronic studies, flares and tophus burden lack endorsed instruments.

In addition to the work by OMERACT in defining outcome domains and measurement instruments in gout[11] The Gout and Crystal Arthritis Network (G-CAN) have defined definitions of core disease elements in gout[14]. Combined these two key pieces of work provide a powerful mechanism for ensuring reporting of clinical trials is uniform.

Despite the work of OMERACT on defining core outcome domains and core outcome measurement set (the instruments) in rheumatic



Domain	Instrument
Joint swelling	4-point Likert
Joint tenderness	4-point Likert
Activity limitation.	Acute trials: Not endorsed Chronic trials: HAQ-DI
Pain	Acute trials: VAS, 5-point Likert Chronic trials: VAS, numeric scale
Patient global assesment	Acute trials: VAS Chronic trials: VAS
Serum urate	Serum urate
Gout flares	Not endorsed
Tophus burden	Not endorsed
HR-QOL	SF-36

HR-QOL: Health Related Quality of Life, VAS: Visual Analog Scale, SF-36: 36 item Short Form survey.

Fig. 1. Core Outcome Domains for Acute and Chronic trials and the Endorsed Measurement Instruments.

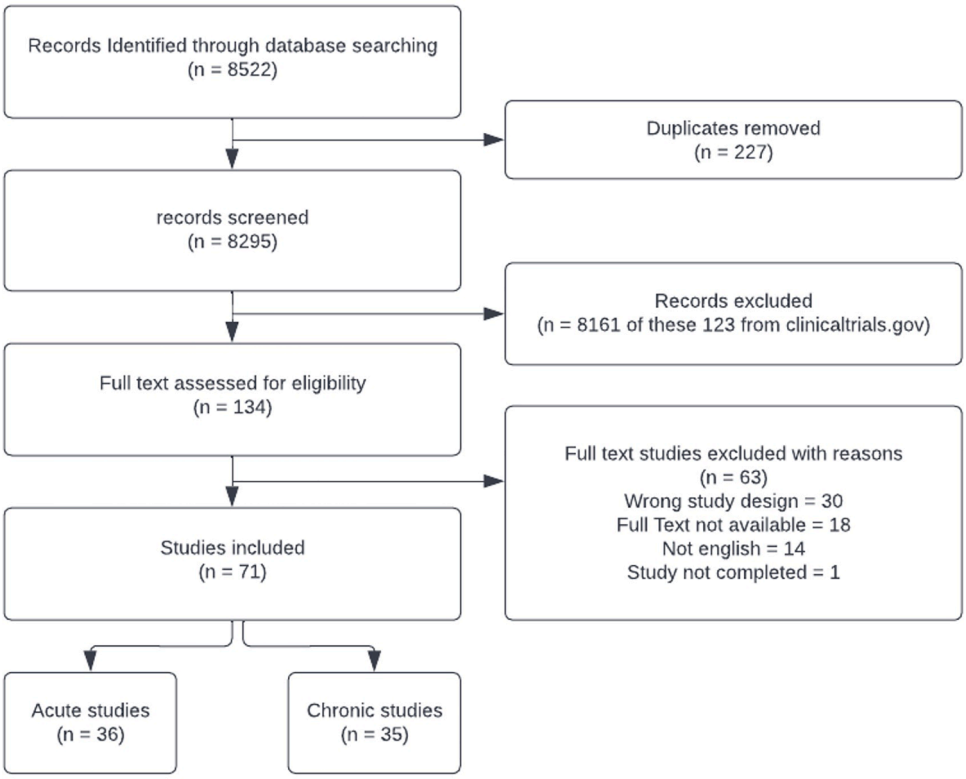


Fig. 2. Flowchart of Randomized Trials Included in the Systematic Review.

diseases, the use and reporting of these in trials of rheumatologic diseases has been variable[15,16,17]. We conducted this systematic scoping literature review[18] to evaluate the application of the endorsed core outcome domains and measurement instruments[10-12,19] in the clinical setting of gout trials by:

1) Quantifying the extent to which gout trials are collecting and reporting data in accordance with the OMERACT acute and chronic core outcome domains and core outcome measurement set for gout.
2) Evaluating the uptake and reporting of the core outcome domains for gout before and after the endorsement of the 2009 OMERACT for acute and chronic studies.

Methods

Protocol and registration

Trial selection, assessments of eligibility criteria, data extraction, and statistical analysis methods, were performed based on a pre-specified protocol. The protocol was prepared according to the recommendations given in PRISMA-P[20], and registered on PROSPERO: CRD42019151316. The study did not require specific ethics approval since it is based on analysis of already published trials.

Information sources and search strategy

We searched the following electronic databases: PubMed, EMBASE, the Cochrane Library including the Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews (CDSR). In addition, www.clinicaltrials.gov was searched for ongoing studies. The pre-specified literature search strategy was made by instructions and with assistance from a team of research librarians from Lister Hill Library of the Health Sciences, Birmingham, Alabama, USA, and is provided in the PROSPERO protocol. The final literature search was conducted on January 18, 2021.

Eligibility criteria

We included randomized controlled trials (RCTs) randomly allocating people with gout to an active pharmacological gout treatment or a control comparator. This included current recommended treatments for a gout flare and urate lowering therapy, as well as emerging therapies[21,22]. Studies of flare prevention when initiating urate lowering therapy were excluded since there are no specific core outcome domains and measurement set for this specific subset of trials. Non-pharmacologic interventions were only included if they were applied as a comparator (control) group. Participants enrolled in the RCTs had to be ≥18 years of age. There was no time limit on trial duration or year of publication.

Definitions

The Gout, Hyperuricemia and Crystal Associated Disease Network (G-CAN) have published a consensus statement regarding definitions for disease elements in gout. Eleven definitions were agreed upon and the previously used term ‘acute gout’ was replaced by ‘gout flare’. G-CAN has also recommended against the term ‘chronic gout’[14]. In this paper, we refer to ‘acute trials’ to reflect studies that describe

Table 1
Summary of the 71 Included Trials

Trials	Acute (36)	Chronic (35)
Number of participants in the trials (median, range)	89 (18-456)	189 (12-6198)
Trial duration (median, range)	7 (1-365) Days	6 (0,25-43) Months
Age median Quartiles (Q0, Q1,Q3,Q4)	53 (44,51,58,70)	53 (43,50,57,71)
Male %	78	88
Trial registration year (n, median, range)	n= 15	n= 24
	2009	2011
	(2004-2018)	(2002-2014)
Trial publication year (median, range)	2003	2016
	(1970-2020)	(1966-2020)
Year of publication	**No. (%)**	**No. (%)**
-1999	17 (47)	5 (14)
2000-2009	6 (17)	5 (14)
2010-2020	13 (36)	25 (72)
Acute trials Intervention by drug class		
NSAIDs	21 (58)	
Glucocorticoids/ ACTH	6 (17)	
Colchicine	3 (8)	
Interleukin-1 receptor antagonist/inhibitor	5 (14)	
NSAID + Glucocorticoids	1 (3)	
Chronic trials Intervention by drug class		
Allopurinol		5 (14)
Febuxostat		17 (49)
Probenecid		1 (3)
Benzbromarone*		4 (11)
Lesinurad		5 (14)
Verinurad*		2 (6)
Pegloticase		1 (3)

* Alone or in combination

interventions for short term management of gout flares, and 'chronic trials' that describe interventions for long-term urate lowering therapy in the management of gout.

Trial selection

Results of the literature were reviewed independently by two authors (MM and AN): Titles and abstracts were reviewed and if further information was required to assess eligibility criteria, the full text was obtained. According to the PRISMA principles[20], eligibility of the full-text papers was judged independently by the same two reviewers with disagreements resolved by a third independent reviewer (LKS).

Data collection process and data items

Covidence online software was used to manage the records retrieved from searches of electronic databases. A customized data extraction form was created in Microsoft Excel to capture the information available for each individual trial. The 2009 core outcome domains for gout were used as the reference standard[10] for assessment of the uptake of the gout core outcome domains in all included trials.

Data from the included trials was extracted by one author (MM) and verified by another author (AN). Discrepancies were resolved through discussion until consensus was reached. For each trial the following data were collected: author, year of trial registration (clinical trial registry), year of publication, gout diagnosis criteria, trial duration, number of participants randomized, % male, number of study arms, intervention drug, comparator drug, drug dose and all core outcome domains and core outcome measurement tools described either in the trial. Data were analyzed/interpreted descriptively.

Assessment of uptake of the gout core outcome domains

From the extracted data, the proportion of studies that reported data

Table 2
OMERACT Endorsed Core Outcome Domains for the 71 Included Acute and Chronic Trials

	Acute trials (n =36)			**Chronic trials (n = 35)**		
Domain	No. (%)	No. Instruments	No. reported with *endorsed* instruments (%)	No. (%)	No. Instruments	No. reported with *endorsed* instruments (%)
Joint swelling	21 (58)	7	11 (30)			N.A.
Joint tenderness	18 (50)	5	6 (17)			N.A.
Activity limitation	8 (22)	4	*	2 (6)	2	0 (0)
Pain	32 (89)	8	8 (22)	4(11)	3	4 (11)
Patient global assessment	14 (39)	4	1 (3)	0 (0)	0	0
Serum urate	N.A.			35 (100)	10	26 (74)
Flares	N.A.			28 (80)	9	*
Tophi	N.A.			10 (29)	6	*
HR-QOL	N.A.			1 (3)	1	1 (3)
Uptake all domains	3 (8)			0 (0)		

* No endorsed outcome measurement instrument, N.A.: Not applicable.

Table 3
Core Outcome Domains and Core Outcome Measurements in Included trials (acute and chronic).

Outcome domains acute trials			Outcome domain for acute and chronic trials				Outcome domain for chronic trials		
Domain (N=number of trials that reported on the domain)	**Name of measurement instrument**	**Number of trials using measurement instrument N (%)z**	**Domain** (N=number of trials that reported on the domain)	**Name of measurement instrument**	**Number of trials using measurement instrument N (%)***	**Number of trials using measurement instrument N (%)****	**Domain** (N=number of trials that reported on the domain)	**Name of measurement**	**Number of trials using measurement instrument N (%)**
Joint swelling (N=20)	Mean (3 or 4 point Likert)***	8 (40)	**Activity limitation** (N=8) for acute trials*(N=2) Chronic trials**	HAQ Baseline	2 (25)	2 (100)***	**Serum Urate** (N=35)	SU <6 g/dl or 0.36 mmol/L	23 (66)
	Mean change (4- or 5-point Likert)***	5 (25)		Limitation of function 4- or 5-point Likert	4 (50)	0 (0)		Mean % change SU	16 (44)
	% Change from baseline (4- or 5-point Likert)***	5 (25)		Composite measure defined by the study group	3 (38)	0 (0)		SU <5 g/dL OR 0.30 mmol/L	14 (40)
	% Per group with the value 1,2,3,4	2 (10)		Reduction in HAQ from baseline	0 (0)	0 (0)		SU <4 g/dl	6 (17)
	Mean number of days with swelling	2 (10)		HAQ Final visit	0 (0)	0 (0)		Mean change	6 (17)
	% Reduction in number of swollen joints	1 (5)	**Pain** (N=31) for acute studies (N=4) Chronic studies	Mean change (VAS 0-10, 0-100 or VAS not specified	10 (32)	2 (50)***		SU<3 g/dl	1 (3)
	Reduction in score (5-point Likert - absolute numbers)	1 (5)		Mean change (4,5,6 point Likert)***	10 (32)	0 (0)		SU 0.31-0.36 mmol/L	1 (3)
Joint tenderness (N=18)	Mean (3 or 4 point Likert)***	10 (56)		% Change from baseline (VAS 0-100 or 4- or 5-point Likert)***	8 (26)	0 (0)		Baseline value	34 (94)
	% Change from baseline (4- or 5-point Likert)***	4 (22)		Mean pain score (4,5,6 point Likert)***	7 (23)	0 (0)		Final visit value	24 (69)
	Mean change (4- or 5-point Likert)***	2 (11)		Mean pain score (VAS 0-10 or 0-100)	2 (6)	2 (50)***		SU <8 g/dl	1 (3)
	% Per group with the value 1,2,3,4	2 (11)		Mean time to pain relief (hours or days)	3 (10)	0 (0)	**Gout flares** (N=28)	Flares pr. group (%)	21 (75)
	Reduction in score (5-point Likert)	1 (6)		Mean reduction in days with pain score > 5 (VAS 0-10)	1 (3)	0 (0)		Proportion of pt. per group with >1 flare	5 (18)
				Responder/non-responder (50% reduction)	1 (3)	1 (25)		Mean gout flare rate	4 (14)
			Patient global assessment (N=14) for acute studies (N=0) for chronic studies	Mean 4- or 5-point Likert	11 (79)	0 (0)		Number of gout flares per Group	3 (11)
				Mean (VAS 0-10)	1 (7)***	0 (0)		Proportion of pt. per group with 1 flare	1 (4)
				Mean change	2 (14)	0 (0)		Proportion of pt. per group with ^{3} 2 gout flares	1 (4)

(*continued on next page*)

Table 3 (*continued*)

Outcome domains acute trials			Outcome domain for acute and chronic trials				Outcome domain for chronic trials		
Domain (N=number of trials that reported on the domain)	**Name of measurement instrument**	**Number of trials using measurement instrument N (%)z**	**Domain** (N=number of trials that reported on the domain)	**Name of measurement instrument**	**Number of trials using measurement instrument N (%)***	**Number of trials using measurement instrument N (%)****	**Domain** (N=number of trials that reported on the domain)	**Name of measurement**	**Number of trials using measurement instrument N (%)**
				% Per group with the value 1,2,3,4	2 (14)	0 (0)		Proportion of pt. per group with > 2 gout flares	1 (4)
								Flares per patient year per group	1 (4)
								Average flare per patient per group	1 (4)
							Tophi (N=10)	% Complete Tophus resolution	6 (60)
								% Reduction in tophus area	2 (20)
								Complete or partial tophus resolution of > 1	2 (20)
								Change in number of tophi	1 (10)
								Mean % decrease in number of tophi	1 (10)
								Median change in number of tophi pr. Patient	1 (10)
							HR-QOL (N=1)***	SF-36 physical component Summary score	1 (100)

* Acute trials,
** Chronic trials,
*** Endorsed outcome measurement instrument.

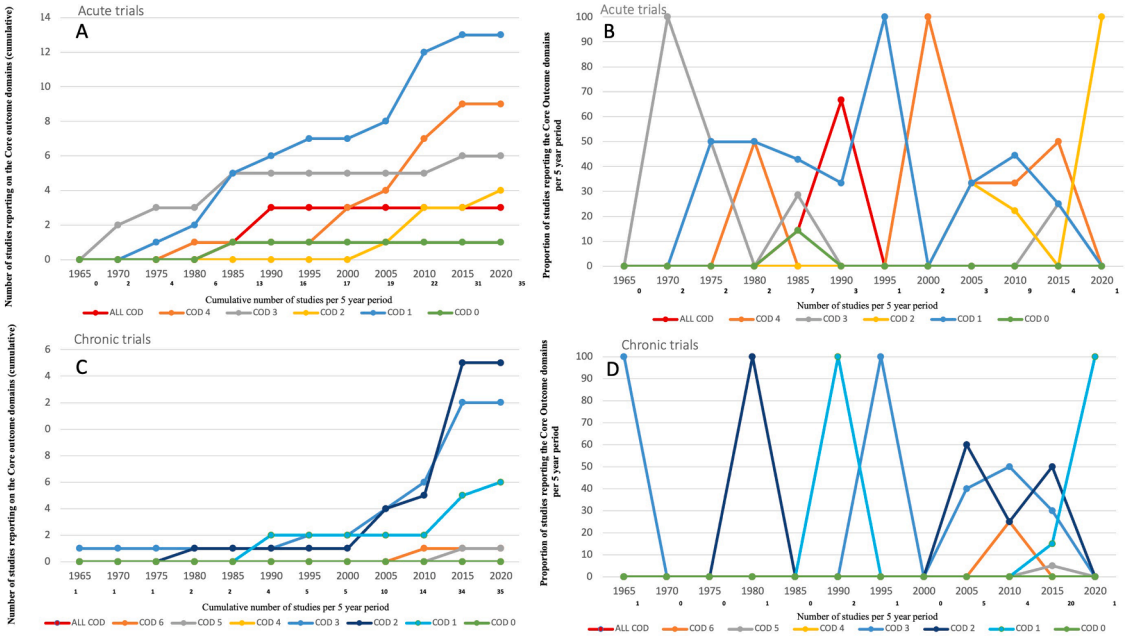


Fig. 3. Reporting on Core Outcome Domains (COD): Cumulative number of studies per year 5 year period reporting of the COD for studies of acute (A) and chronic (C) gout and proportion of studies per 5-year period reporting of the COD for studies of acute (B) and chronic (D) gout

on each of the core outcome domains and the applicable measurement tool was calculated for acute and chronic trials. The percentages of trials that reported data on the gout core outcome set (acute and chronic) results were assessed in the publications. The 2009 endorsed core outcome domains was used as the reference standard.

For assessment of the impact of the 2009 core outcome domains, we used the cumulative reporting over time of the 5 core outcome domains endorsed for acute studies of gout flares and the 7 core outcome domains endorsed for chronic studies of gout. Statistical analysis and graphs were done in Excel 16.6.

Results

Trial selection

As illustrated in Fig. 2, the overall literature search identified 8,522 papers, with 8,295 being screened on title and abstract after removal of duplicates. After screening 134 full text records were reviewed and 71 papers were included for analysis. The 71 eligible papers covered 36 acute trials and 35 chronic trials.

Study characteristics

The included trials were published between 1966 and 2020 with 40 (56%) of these being published from 2009 onwards. The detailed characteristics of the trials included are available in supplementary materials (Appendix Table 1). There were five types of interventions for acute trials and seven interventions under investigation for chronic trials -alone or in combination. Trials were divided into acute (gout flare) trials and chronic (urate lowering therapy) trials by intervention drug (Table 1). Furthermore, 3 of these studies were pharmacokinetic studies (Appendix Table 1).

Use of core outcome domains

Pain, joint swelling and joint tenderness was reported in $\geq$ 50% of acute trials, whereas the patient reported core outcome domains, patient global assessment and activity limitation was reported less frequent (39% and 22%). Twenty-seven unique measurement instruments across the 5 core outcome domains were identified in the acute trials. A minority of studies used the OMERACT endorsed outcome measurement instrument (Table 2).

Serum urate was reported in 100% of the chronic trials and gout flares in 80%. However, the other core outcome domains were reported in <30% of chronic trials. In particular the patient reported outcomes HR-QOL, patient global and activity limitation a rarely reported. Across the 7 core outcome domains, 31 unique measurement instruments were used (Table 3).

A wide variety of measurement instruments were used to assess each endorsed core outcome domains, (Table 3).

The uptake of core outcome domains in clinical gout trials is unfortunately low. In Fig. 3 the number of studies reporting on core outcome domains (cumulative) per year for studies of acute (**3A**) and chronic (**3C**) is shown. For acute trials, the number of studies reporting on all 5 core outcome domains is consistently low and no change is detected before and after the endorsement in 2009. None of the included chronic trials reported on the full core outcome domain set before or after the core outcome domain endorsement and even though the number of chronic gout studies more than doubled from 14 to 35 after 2009, the total number of reported core outcome domains did not double. In Fig. 3 (**B** and **D**) the proportion of acute and chronic studies reporting of core outcome domains per 5 year period can be seen and the reporting of core outcome domains per 5 year period was not convincingly increased after 2009.

Discussion

In this study we found overall low uptake and reporting of the endorsed core outcome domains for both acute and chronic trials in gout. Furthermore, there was a wide variation in *how* the OMERACT endorsed core outcome domains were measured. Trials after 2009, when the core outcome domains were endorsed by OMERACT, had a similar low reporting of domains.

Despite the endorsement in 2009 few if any studies report all the core outcome domains. Of particular concern, the patient reported core outcome domains are widely under-represented in both the acute and chronic trials. In the included acute trials activity limitation and patient global assessment were only reported in 22% and a 39% of the included

trials respectively. For chronic trials functional disability, health related quality of life, patient global assessment and pain were either not reported or reported in 10% or less of the included trials. The lack of reporting of these domains accentuates the importance of having patient research partners with gout included in the process in the design of RCTs, as well as other key stakeholder to further ensure patient-reported outcomes are measured and reported. FDA acknowledges patient reported outcomes when assessing new drugs[23] and a stringent demand from regulators/drug approval instances, of reporting the endorsed core outcome domains in all phase 3 registered trials, would prompt the reporting of core outcome domains as a minimum in all trials.

A wide range of instruments was used for the reporting of the core outcome domains in acute and chronic trials (Appendix Table 2), consistent with previous findings from Hughes et al [15] and Araujo et al. [24] For example, across all trials reported on SU, only 74 % reported with the ACR/EULAR[25,26] recommended SU target of < 6mg/dl and SU was reported in 10 different ways. The advantages of a more uniform way of reporting SU are that it allows for comparisons across trials to be made. The reporting should preferably include at least one measurement between baseline and end of trial as advocated for by Stamp et al.[16] Furthermore, the dichotomous reporting (SU<6 mg/dl) could be challenged since important details (distribution and means) are lost when SU is not reported as a continuous variable. This emphasizes the importance of adequate outcome reporting in clinical trials of gout and the need for endorsed outcome measurement instruments. It is also important to note that the development of the core outcome set for gout clinical trials is not yet completed. For acute studies, the activity limitations domain does not have an endorsed instrument and for chronic studies, the gout flares and tophus burden do not have endorsed instruments. Currently gout flares are most often reported as "patient reported" meaning there may be subjectivity and uncertainty margins that are difficult to interpret in a clinical trial setting. Regarding tophi, different approaches have been undertaken measuring with calipers, imaging (plain radiographs, Magnetic Resonance imaging (MRI), Computed Tomography (CT), Ultrasonographic measurement (US), Dual Energy Computed Tomography (DECT). Agreement has not been reached in OMERACT setting regarding a suitable instrument, however US seems promising.[27]

It is disappointing that the implementation and impact of the gout core outcome domains has yet to be seen more than 10 years after the OMERACT endorsement. In comparison, rheumatoid arthritis (RA) has a high uptake of core outcome domains, which may be attributed to the endorsement of the core outcome domains for RA by the FDA and European Medicine Agency (EMA) as implied by Kirkham et al.[28]. Possible barriers for implementation in gout include lack of awareness and understanding of core outcome domains, insufficient patient research partner inclusion in study design, and lack of validated outcome measurement instruments. To date both the FDA and medical journals have accepted SU as the primary outcome measure for chronic trials. However, there is increasing importance placed on patient reported outcomes such as the gout flare as the primary outcome. The lack of an OMERACT validated and endorsed flare definition is therefore problematic and requires attention. A flare definition has been agreed upon by Gaffo et al. and it seems relevant to consolidate this flare definition in the OMERACT core outcome measurement set in clinical trials in gout. Interestingly the first study of ULT using flare as the primary outcome has been published in 2022 and used the Gaffo flare definition[29].

A limitation to this study is the fact that clinical studies are time consuming and a considerable timespan (years) from trial registry to final publication of trial results is inherent and the implementation of core outcome domains might be significantly delayed.

It is important to note that when indexing trials into acute and chronic by intervention drug/primary treatment, studies of flare prevention when initiating urate lowering therapy were not appropriate to include within the acute studies category given they were not treating a specific flare. The use of the endorsed core outcome domains for chronic trials is more appropriate for these trials and is recommended for use in future trials of prophylaxis.

Conclusion

In this study we found a low adherence with the intended endorsed core outcome domains for acute and chronic gout studies which represents a poor uptake of the global OMERACT efforts. Significant variation in *how* the OMERACT endorsed outcome domains have been measured has been demonstrated and the core outcome domain set for gout clinical trials is not yet fully completed. Trials investigating the effect of flare prophylaxis when initiating urate lowering therapy represents a subgroup for which there currently is no core outcome domain set. This systematic review demonstrates the need for improved adherence to OMERACT core domains as well as further guidance on outcome measurements during clinical trial development.

Authors' contributions

MBM, LS and RC conceived of the study, and participated in its design and helped to draft the protocol manuscript. All authors edited the manuscript and read and approved the final version.

Data sharing

Data is accessible by reasonable request. If any research group would like to access the data that will be possible if laws and regulations is followed. If any research group would like to reuse data, an affiliation/co-authorship will be acquired.

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Appendix Table 1. Included studies

AUTHOR	YEAR TRIAL REGISTERED	YEAR PUBLISHED	GOUT DEFINITON	TRIAL DURATION	NUMBER RANDOMISED	% MALE	NO. STUDY ARMS	INTERVENTION DRUG + GROUPS	DAILY DOSE	NO. RANDOMISED TO INTERVENTION	COMPARATOR DRUG	DAILY DOSE	NO. RANDOMISED TO COMPARATOR	OUTCOE DOMAINS REPORTED (%)
ACUTE TRIALS (Intervention by drug class)														
Douglas[30]		1970	ϒ	14 Days	26	88	2	Flufenamic acid	400-1200mg	11	Phenylbutazone	400-1200mg	14	3/5 (60)
Smyth[31]		1973	ϒ	nr	31	87	2	Indomethacin	150-200mg	16	Phenylbutazone	600-800mg	15	3/5 (60)
Ruotsi[32]		1978	ϒ	10 days	18	61	2	Proquazone	300mg	9	Indomethacin	50mg	9	3/5 (60)
Weiner[33]		1979	ϒ	4 days	30	100	2	Fenoprofen	3-3.6mg	15	Phenylbutazone	400-700mg	15	1/5 (20)
Reardon[34]		1980	ϒ	10 days	24	91	2	Feprazone	600-800mg	11	Phenylbutazone	600-800mg	13	1/5 (20)
Eberl[35]		1983	ϒ	7 days	20	100	2	Meclofenalate sodium	100-600mg	10	Indomethacin	150mg	10	4/5 (80)
Butler[36]		1985	ϒ	12 days	33	nr	2	Flurbiprofen	200-400mg	nr	Phenylbutazone	400-800mg	nr	0/5 (0)
Tumrasvin[37]		1985	ϒ	7 days	34	100	2	Piroxicam	40mg	17	Piroxicam	10-40mg	17	3/5 (60)
Lomen[38]		1986	ϒ	5 days	35	nr	2	Flurbiprofen	200-400mg	14	Indomethacin	100-200mg	21	3/5 (60)
Ahern[39]		1987	ϒ	48 hours	43	93	2	Colchicine	0.5-1mg	22	Placebo	nr	21	1/5 (20)
Fraser[40]		1987	ϒ	28 days	93	nr	2	Azapropazone	600-1200mg	46	Indomethacin	100-200mg	47	0/5 (0)
Altman[41]		1988	ARA 1977*	7 days	59	92	2	Ketoprofen	100mg	29	Indomethacin	150mg	30	5/5 (100)
Axelrod[42]		1988	ϒ	12 months	100	100	2	ACTH**	40 IU	50	Indomethacin	400mg	50	1/5 (20)
Lederman[43]		1990	ϒ	7 days	60	97	2	Etodolac	900mg	29	Naproxen	1500mg	31	5/5 (100)
Maccagno[44]		1991	ϒ	7 days	61	77	2	Etodolac	600mg	31	Naproxen	1000mg	30	5/5 (100)
Alloway[45]		1993	ϒ	30 days	27	100	2	Triamcinolone	60mg	14	Indomethacin	100mg	13	1/5 (20)
Shrestha[46]		1995	ARA 1977*	24 hours	20	95	2	Ketorolac tromethamine	60mg	10	Indomethacin	50mg	10	1/5 (20)
Schumacher[47]		2002	ARA 1977*	8 days	150	95	2	Eterocoxib	120mg	75	Indomethacin	150mg	75	4/5 (80)
Rubin[48]		2004	ARA 1977*	8	189	93	2	Eterocoxib	120mg	103	Indomethacin	150mg	86	4/5 (80)
Cheng[49]		2004	ARA 1977*	7 days	62	86	3	Rofecoxib Meloxicam	50mg 7.5mg	20 21	Diclofenac	75mg	21	2/5 (40)
Man[50]		2007	ϒ	5 days	90	83	2	Prednisolone + Paracetamol	30mg 4g	44	Indomethacin + Diclofenac +Paracetamol	50mg 75mg 4g	46	1/5 (20)
Willburger[51]	2004	2007	ARA 1977*	7 days	235	69	2	Lumiracoxic	400mg	118	Indomethacin	150mg	117	4/5 (80)
Janssen[52]	2005	2008	ϒ	5 days	120	89	2	Prednisolone +placebo	35 nr	60	Naproxen + Placebo	500mg nr	60	2/5 (40)
Terkeltaub[53]	2007	2010	ARA 1977*	3 days	185	95	3	Colchicine Colchicine	1.8mg 4.8mg	74 52	Placebo	nr	58	1/5 (20)
So[54] Schlesinger [55]	2008	2010*** 2011***	ARA 1977*	8 weeks	200	93	6	1)Canakinumab 2)Canakinumab 3)Canakinumab 4)Canakinumab 5)Canakinumab	10mg 25mg 50mg 90mg 150mg	28 29 29 29 28	Triamcinolone	40mg	57	3/5 (40)
Schlesinger[56]	2010	2012	ARA 1977*	12 weeks	230	91	2	Canakinumab	150 mg	115	Triamcinolone	40mg	115	4/5 (80)
β-RELIEVED I					226	91	2	Canakinumab	150mg	112	acetonide	40mg		4/5 (80)
β-RELIEVED-II											Triamcinolone acetonide		114	
Schumacher[57]	2007	2012	ARA 1977*	8 days	402	91	4	1)Celecoxib 2)Celecoxib 3)Celecoxib	100mg 200-400mg 400-800mg	101 99 99	Indomethacin	150mg	103	3/5 (60)
LI[58]	2009	2013	ARA 1977*	5 Days	178	93	2	Eterocoxib	120mg	89	Indomethacin	150mg	89	4/5 (80)

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AUTHOR	YEAR TRIAL REGISTERED	YEAR PUBLISHED	GOUT DEFINITON	TRIAL DURATION	NUMBER RANDOMISED	% MALE	NO. STUDY ARMS	INTERVENTION DRUG + GROUPS	DAILY DOSE	NO. RANDOMISED TO INTERVENTION	COMPARATOR DRUG	DAILY DOSE	NO. RANDOMISED TO COMPARATOR	OUTCOE DOMAINS REPORTED (%)
Terkeltaub[59]	2009	2013)	ARA 1977*	12 days	225	93	3	1)Rilonacept + indomethacin 2)Rilonacept + placebo	320mg 75-150mg 320mg nr	74 75	Placebo+Indomethacin	nr 75-150mg	76	1/5 (20)
Zhang[60]	2010	2014	ARA 1977*	7 days	60	97	2	Betamethasone	7mg one dose only	30	Diclofenac	150mg	30	4/5 (80)
Rainer[61]	2015	2016	ϒ	5 days	416	74	2	Prednisone	30mg	208	Indomethacin	75-150mg	208	3/5 (60)
Xu[62]	2014	2016	ARA 1977*	4 days	132	99	3	1) Prednisone+Allopurinol+Aspirin 2)Eterocoxib + Allopurinol+ Aspirin	35mg nr 120mg nr	41 46	Indomethacin +Allopurinol+ Aspirin	150mg nr	45	4/5 (80)
Janssen[63]	2015	2019	ϒ	5 days	88	94	2	Anakinra + ULT (Febuxostat, Allopurinol or Benzbromarone in unknown dose)	100mg nr	43	Placebo +ULT (Febuxostat, Allopurinol or Benzbromarone in unknown dose)	nr	45	4/5 (80)
Roddy[64] (CONTACT)	2013	2019	ϒ	7 days	399	87	2	Colchicine	1.5mg	199	Naproxen	750mg	200	1/5 (20)
Ren[65]	2018	2020	ACR/ EULAR 2015	7 days	90	64	3	1)Diclofenac gel CQGB+ 2)Loxoprofen	nr 30g 180mg	30 30	Loxoprofen	180mg	30	2/5 (40)
CHRONIC TRIALS (Intervention by drug class)														
Scott[66]		1966	ϒ	10-23 months	37	100	2	Probenecid		17	Allopurinol	300-600mg	20	3/7 (43)
Gibson[67]		1982	ϒ	24 months	59	98	2	Allopurinol + Colchicine	200mg 0.5mg	26	Colchicine	0.5 mg	33	2/7 (29)
Ohue[68]		1991	ARA 1977	48 months	46	98	2	Benzbromarone	25mg	23	Allopurinol	200mg	23	1 (14)
Müller[69]		1993	ϒ	7 days⊕	14	100	2	Allopurinol +Benzbromarone	200mg 40mg	Nr	Allopurinol	200mg	nr	1 (14)
Perez-Ruiz[70]		1999	ARA 1977	9-12 months	37	84	2	Benzbromarone	100-200mg	17	Allopurinol	100-300mg	19	3/7 (43)
Becker[71]		2005	ARA 1977	28 Days	153	87	4	1)Febuxostat 2)Febuxostat 3)Febuxostat	40mg 80mg 120mg	37 40 38	Placebo	nr	38	2/7 (29)
Becker[72] FACT	2002	2005	ARA 1977	12 months	762	96	3	1)Febuxostat 2)Febuxostat	80mg 120mg	257 251	Allopurinol	300mg	254	3/7 (43)
Schumacher[73] APEX	2005	2008	ARA 1977	28 weeks	1072	94	5	1)Febuxostat 2)Febuxostat 3)Febuxostat 4) Allopurinol	80mg 120mg 240mg 300mg	267 269 134 268	Placebo	nr	134	3/7 (43)
Reinders[74]	2007	2009	ϒ	4 months	65	82	2	Allopurinol	300-600mg	36	Benzbromarone	100-200mg	29	2/7 (29)
Reinders[75]	2007	2009	ARA 1977	2 months	62	95	2	Benzbromarone + Allopurinol	200mg 400mg	27	Probenecid + Allopurinol	2000mg 400mg	35	2/7 (29)
Becker[76] CONFIRMS	2007	2010	ARA 1977	6 months	2269	94	3	1)Febuxostat 2) Febuxostat	40mg 80mg	757 756	Allopurinol	200-300mg	755	2/7 (29)
Sundy[77]	2006	2011	ARA 1977	6 months	109	73	3	1)Pegloticase	8mg BW	44	Placebo	nr	22	6/7 (86)
GOUT 1		2011	ARA 1977		116	80	3	2)Pegloticase	8mg FW	43			24	Pooled data
Sundy GOUT 2								1)Pegloticase 2) Pegloticase	8mg BW 8mg FW	46 46				Gout 1+2

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AUTHOR	YEAR TRIAL REGISTERED	YEAR PUBLISHED	GOUT DEFINITON	TRIAL DURATION	NUMBER RANDOMISED	% MALE	NO. STUDY ARMS	INTERVENTION DRUG + GROUPS	DAILY DOSE	NO. RANDOMISED TO INTERVENTION	COMPARATOR DRUG	DAILY DOSE	NO. RANDOMISED TO COMPARATOR	OUTCOE DOMAINS REPORTED (%)
Taylor[78]	2011	2012	ARA 1977	10 days⊕	57	100	2	Allopurinol	300mg	31	Placebo	nr	26	3/7 (43)
Huang[79]		2014	ARA 1977	28 weeks	516	97	3	1)Febuxostat 2)Febuxostat	40mg 80mg	172 172	Allopurinol	300mg	172	3/7 (43)
Hill[80]	2013	2015		28 Days	37	99	2	Allopurinol	100-200mg	16	Placebo		19	2/7 (29)
Perez-Ruiz[81]	2009	2015	ARA 1977	28 days	227	98	4	1)Lesinurad + Allopurinol 2)Lesinurad + Allopurinol 3)Lesinurad + Allopurinol	200mg 200-600mg 200-400mg 200-600mg 200-600mg 200-600mg	46 42 48	Placebo + Allopurinol	200-600mg	72	2/7 (29)
Xu[82]	2011	2015	ARA 1977	24 weeks	504	96	3	1)Febuxostat 2)Febuxostat	40mg 80	168 168	Allopurinol	300mg	168	2/7 (29)
Yu[83]	2012	2016	ARA 1977	12 weeks	109	97	2	Febuxostat	80mg	54	Allopurinol	300mg	55	2/7 (29)
Bardin[84] CLEAR 2	2013	2017	ARA 1977	12 months	610	96	3	1)Lesinurad +Allopurinol 2)Lesinurad +Allopurinol	200mg 200-900mg 400mg 200-900mg	204 200	Placebo + Allopurinol	nr 150mg	206	3/7 (43)
Dalbeth[85]	2010	2017	ARA 1977	24 months	314	92	2	Febuxostat	40-80mg	157	Placebo	nr	157	2/7 (29)
Dalbeth[86] CRYSTAL	2012	2017	ARA 1977	12 months	330	95	3	1)Lesinurad + Febuxostat 2)Lesinurad + Febuxostat	200mg 80mg 400mg 80mg	106 109	placebo + Febuxostat	nr 80mg	109	3/7 (43)
Stamp[87]	2011	2017	ARA 1977	12 months	183	87	2	Allopurinol (dose escalation until SU<6mg/dl)	100-600mg	90	Allopurinol,(same dose throughout the study)	100-600mg	93	5/7 (71)
Saag[88] CLEAR 1	2012	2017	ARA 1977	12 months	607	94	3	1)Lesinurad + Allopurinol 2)Lesinurad +Allopurinol	200mg 200-800mg 400mg 200-800mg	201 201	Placebo +Allopurinol	nr 200-800mg	201	3/7 (43)
Tausche[89]	2012	2017	ARA 1977	6 months	214	91	2	Lesinurad	400mg	107	Placebo	nr	107	2/7 (29)
Fitz-Patrick[90]	2013	2018	ARA 1977	24 weeks	172	93	4	1)Verinurad 2)Verinurad 3)Verinurad	5mg 5-10mg 5-12.5mg	42 43 44	Placebo	nr	42	2/7 (29)
Gunawardhana [91]	2014	2018	ARA 1977	3 months	189	71	5	1)Febuxostat 2)Febuxostat 3)Febuxostat 4)Febuxostat	40mg IR 40mg XR 80mg IR 80mgXR	37 39 37 38	Placebo	nr	38	2/7 (29)
Kankam[92]	2014	2018	ARA 1977	7 days⊕	12	100	2	Verinurad	10mg	6	Allopurinol	300mg	6	1 (14)
Wang[93]	NR	2018	ARA 1977	6 months	160	55	2	Febuxostat	80mg	80	Allopurinol	300mg	80	2/7 (29)

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AUTHOR	YEAR TRIAL REGISTERED	YEAR PUBLISHED	GOUT DEFINITON	TRIAL DURATION	NUMBER RANDOMISED	% MALE	NO. STUDY ARMS	INTERVENTION DRUG + GROUPS	DAILY DOSE	NO. RANDOMISED TO INTERVENTION	COMPARATOR DRUG	DAILY DOSE	NO. RANDOMISED TO COMPARATOR	OUTCOE DOMAINS REPORTED (%)
White[94] CARES	2010	2018	ARA 1977	32months (median follow up)	6198	84	2	Febuxostat	40-80mg	3098	Allopurinol	300-600mg	3092	2/7 (29)
Yamanaka[95]	2012	2018	ARA 1977*	12 weeks	255	100	3	1)Febuxostat 2)Febuxostat +Colchicine	10-40mg 40mg 0.5mg	101 102	Febuxostat	40mg	52	2/7 (29)
Hao[96]	NR	2018	ϒ	8 weeks	80	76	2	Febuxostat	40mg	40	Allopurinol	300mg	40	1 (14)
Liang[97]	NR	2019	ARA 1977	12 weeks	240	100	2	Febuxostat	20mg	120	Benzbromarone	25mg	120	2/7 (29)
Saag[98]	2014	2019	ARA 1977	3 months	1790	88	5	1)Febuxostat 40mg IR 2)Febuxostat 40mg XR 3)Febuxostat 80mg IR 4)Febuxostat 80mg XR	357 355 357 357	Placebo	nr	357	2/7 (29)
Huang[99]	NR	2019	ϒ	24 weeks	156	nr	2	Febuxostat	80mg	78	Placebo	nr	78	1 (14)
Mackenzie[100]	2011	2020	ϒ	1324 days (median)	6128	85	2	Febuxostat	80-120mg	3063	Allopurinol	100-900mg	3065	1 (14)

**American Rheumatism Association* 1977 Gout criteria ϒ Physician diagnosed gout. ** AdrenoCorticoTrophHormone ***Identical study (NCT00798369) results published in two papers, nr: not recorded ULT: Urate lowering therapy, CQGB: Compound Qingbi granules external application SD: Single dose, BW: Biweekly, FW: four weekly. NR = Not Registered/Not available. ⊕ Pharmacokinetic/dynamic tr

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