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Post-hoc analysis of two gout remission definitions in a two-year randomized controlled trial of nurse-led versus usual gout care

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ABSTRACT

Objective: To compare the performance of the 2016 preliminary gout remission definition and a simplified gout remission definition in a clinical trial of nurse-led gout care.

Methods: Data from a 2-year parallel arm, non-blinded, randomised controlled trial of 517 community-derived people with gout were analyzed. Participants were assigned 1:1 to receive nurse-led care or general practitioner usual care. Remission was defined using the 2016 preliminary gout remission definition and a simplified gout remission definition without patient reported outcomes. Binary logistic regression was used to compare intervention groups. General linear models were used to compare Gout Impact Scale (GIS) scores between those in remission and those not in remission using either definition.

Results: Participants in the nurse-led care group were more likely to achieve remission using either definition; at Year 2 the odds ratio was 7.92 [95 % CI 4.86–12.92] using the 2016 preliminary definition and 11.88 [95 % CI 7.49–18.84] using the simplified definition. For all participants, the 2016 preliminary definition was fulfilled by 9.9 % at Year 1 and 28.4 % at Year 2, $p < 0.001$ and the simplified definition was fulfilled by 17.6 % at Year 1 and 42.7 % at Year 2, $p < 0.001$. People in remission using either definition had better gout outcomes assessed using the GIS, including greater control over their gout.

Conclusion: Both definitions discriminated between the intervention groups and showed high construct validity. The simplified definition identified more people as being in gout remission at Year 1 and Year 2. The simplified definition is a feasible and valid option for defining gout remission.

Introduction

Gout is a disease of monosodium urate (MSU) crystal deposition resulting from elevated levels of urate and characterised by intermittent episodes of acute inflammatory arthritis (gout flares). In the setting of persistent hyperuricemia, gout flares become more frequent and severe, and chronic synovitis, tophi and joint damage may also develop [1]. Gout is associated with poor health outcomes [2-4] and reduced health related quality of life [5-7].

In the setting of chronic rheumatic disease, remission, which has been described as "either a complete absence of disease activity or a level of disease activity so low it is not troublesome to the patient" [8], is a desired outcome, including for people with gout [9]. In 2016, a preliminary definition of gout remission was established using Delphi and

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1000Minds consensus exercises of rheumatologists, other health professionals, and gout researchers [10]. The preliminary definition required all of the following conditions to be achieved over the relevant time-period (preferably twelve months): absence of gout flares, serum urate <0.36 mmol/l, absence of tophi, pain due to gout <2 on a 10 point Likert scale or 10 cm visual analogue scale, and patient global assessment of gout disease activity <2 on a 10 point Likert scale or 10 cm visual analogue scale [10]. It should be noted that being in the state of gout remission using this definition associates with low MSU crystal burden [11], but may not reflect complete clearance of crystals [12].

At the time of development of the 2016 preliminary remission definition, the participating health professionals and researchers raised uncertainty about the use of the patient-reported outcome measures, particularly due to the lack of specificity for gout and the potential for recall bias [10]. In a subsequent qualitative study interviewing people with gout about their views of gout remission, patients also indicated overlap and potential redundancy of the patient-reported outcome measures if absence of gout flares was included in the remission definition [9]. In response to these findings, we have developed and tested a simplified gout remission definition that utilizes the same domains as the 2016 preliminary definition, but does not include the patient reported outcomes [9]. In a previous study, we reported that low baseline dual energy CT MSU crystal volume associates with remission according to both the 2016 preliminary definition and the simplified definition following two years of intensive urate-lowering therapy [13]. We have also reported that gout remission using the simplified definition associates with favourable perceptions of gout consequences, identity, and concern using a gout-specific brief illness perception questionnaire (BIPQ) [14].

To date, discrimination of the remission definitions between intervention groups has not been demonstrated in a clinical trial of urate-lowering therapy. Therefore, we compared the performance of the 2016 preliminary gout remission definition and the simplified gout remission definition by evaluating their discrimination between intervention groups, sensitivity to change over time, and construct validity, in a community-based clinical trial of nurse-led treat-to-target gout care versus usual general practitioner care.

Patients and methods

This paper reports an analysis of a 2-year parallel arm, non-blind, randomised controlled trial of 517 people with gout recruited from 56 East Midlands general practices around the Nottingham area. The full methods and results of the trial have been reported previously [15].

In brief, all participants had gout according to the 1977 American Rheumatism Association gout classification criteria [16]. Ethical approval was obtained from East Midlands Nottingham Research Ethics Committee (12/EM/0044) and all participants provided written informed consent. Participants were assigned 1:1 to receive nurse-led care or usual general practitioner care. Participants in the nurse-led care group received an education intervention, had regular follow-up and measurement of serum urate levels, individualised advice on management of a gout flare, and escalation of urate-lowering therapy using a treat-to-target approach, consistent with British and international gout management rheumatology society guidelines [17]. Participants in the usual care group received a gout information booklet from Arthritis Research UK and continued with their general practice management. Allopurinol was used as first line therapy for both groups. At Year 2, nurse-led care led to more participants within the serum urate target, higher use of urate-lowering therapy, fewer gout flares, fewer tophi, and better patient reported outcomes [15].

Measurements

Participant demographics including age, sex, gout history and patient reported outcomes were recorded at the baseline visit. Frequency of gout flares during Year 1 and Year 2 was determined by data recorded in gout flare diaries. Serum urate, subcutaneous tophus count, patient global assessment of gout disease activity on a 10-point Likert scale, and pain due to gout on a 10-point Likert scale were also assessed at Year 1 and Year 2.

The Gout Impact Scale (GIS) of the Gout Assessment Questionnaire 2.0 (GAQ2.0), is a validated gout-specific quality of life instrument that is more sensitive to gout characteristics than general HRQoL instruments [18]. The GIS items included in this analysis were measured at the Year 2 visit and were pre-specified: 1) I am worried that I will have a gout attack within the next year; 2) I am afraid that my gout will get worse over time; 3) I feel anxious that my gout will interfere with my future activities; 4) I worry that I will not be able to continue to enjoy my leisure activities as a result of my gout; 5) It is difficult to plan ahead for events or activities because I may have a gout attack; 6) My current medications do not work well to prevent gout attacks from happening; and 7) I have control over my gout. Items pertaining to gout medication side effects and symptoms during gout flares were not included. Response options were completed on a five-point ordinal scale (e.g. strongly agree, agree, not certain, disagree, strongly disagree). Each item was converted to a 0 to 100 score, with higher scores indicating worse condition/greater gout impact.

Gout remission definitions

Gout remission, defined using the 2016 preliminary definition (absence of gout flares, absence of tophus, serum urate <0.36 mmol/l, pain due to gout < 2 on a 10-point Likert scale, patient global assessment of gout disease activity < 2 on a 10-point Likert scale [10]) and using the simplified definition (absence of gout flares, absence of tophus, serum urate <0.36 mmol/l), was assessed at Year 1 and Year 2. In the clinical trial, serum urate, pain due to gout, and patient global assessment of gout disease activity were only measured at the baseline, Year 1 and Year 2 visits. Supplementary Table 1 shows the variables, cut-points and study visits for each gout remission definition used in the analysis.

Statistical analysis

Demographics and clinical features were summarised using standard descriptive statistics including mean, standard deviation (SD), median, interquartile range (IQR), count, and percent, as appropriate. Comparison of proportions between those fulfilling the 2016 preliminary definition and the simplified definition at Year 1 and Year 2 were analysed using McNemar's test for paired data. Additionally, comparison of individual domain fulfilment between intervention groups at Year 1 and Year 2, were analysed using Pearson's Chi square test for independent groups. Binary logistic regression was used to measure the association between these remission definitions and intervention group. Generalised linear mixed models were used to compare remission across intervention groups over time. General linear models were used to compare GIS scores between those in remission and those not in remission using either definition at Year 2, controlling for baseline GIS scores and intervention groups. Missing data were addressed through multiple imputation using the 'Fully Conditional Specification' (FCS) algorithm with predictive mean matching (PMM) in SPSS. Statistical analysis was performed using SPSS software version 28 and GraphPad Prism software version 9.3.1. $p < 0.05$ was used to denote statistical significance.

Results

Clinical features

Clinical features of the 517 study participants are shown in Table 1. Most participants were male, with a mean age of 63 years and mean disease duration of 12 years. At baseline, the mean number of gout flares in the past year was four, the mean serum urate concentration was 0.44

Table 1
Clinical characteristics and treatment during the trial.

	Overall $N = 517$	Nurse-led care group $N = 255$	Usual care group $N = 262$
Age at baseline visit, years [mean(SD)]	63 (11)	62 (11)	64 (12)
Sex, n (%)			
Male	461 (89 %)	229 (90 %)	232 (89 %)
Female	56 (11 %)	26 (10 %)	30 (11 %)
Ethnicity, n (%)			
Black/Caribbean	5 (1 %)	2 (0.8 %)	3 (1 %)
Other	11 (2 %)	7 (3 %)	4 (1.5 %)
White	501 (97 %)	246 (96 %)	255 (97 %)
Disease duration at baseline visit, years [mean (SD)]	12 (10)	12 (10)	13 (11)
BMI at baseline visit, kg/m^2 [mean (SD)]	30 (5)	30 (5)	30 (5)
Baseline serum urate, mmol/L [mean (SD)]	0.44 (0.10)	0.44 (0.10)	0.44 (0.10)
Baseline number of gout flares [mean (SD)]	4 (5)	4 (3)	4 (3)
Baseline patient global assessment of gout disease activity, 10-point Likert scale [mean (SD)]	4 (3)	5 (3)	4 (3)
Baseline pain, 10-point Likert scale [mean (SD)]	4 (3)	4 (3)	4 (3)
Baseline tophus count [median (IQR)]	2 (2-3)	2 (1-4)	2 (1-3)
Baseline presence of tophus, n (%)	58 (11 %)	35 (14 %)	23 (9 %)
Allopurinol dose at baseline study visit, mg/day [mean (SD)]	227 (101)	226 (95)	228 (107)
Use of urate lowering therapy at baseline visit	203 (39 %)	101 (40 %)	102 (39 %)
Use of urate lowering therapy at Year 1 visit, n (%)	341 (66 %)	232 (91 %)	109 (42 %)
Use of urate lowering therapy at Year 2 visit, n (%)	355 (69 %)	237 (93 %)	118 (45 %)
Baseline GIS scores*			
I am worried that I will have a gout attack within the next year	70.59 (68.15–73.05)	72.23 (68.74–75.73)	68.97 (65.53–74.40)
I am afraid that my gout will get worse over time	70.19 (67.99–72.39)	71.25 (68.11–74.38)	69.14 (66.04–72.23)
I feel anxious that my gout will interfere with my future activities	70.30 (67.99–72.61)	72.04 (68.75–75.33)	68.56 (65.31–71.80)
I worry that I will not be able to continue to enjoy my leisure activities as a result of my gout	69.59 (67.25–71.92)	71.64 (68.31–74.97)	67.53 (64.25–70.81)
It is difficult to plan ahead for events or activities because I may have a gout attack	40.99 (38.37–43.62)	43.18 (39.45–46.91)	38.80 (35.12–42.49)
My current medications do not work well to prevent gout attacks from happening	46.01 (43.45–48.57)	46.10 (42.45–49.75)	45.91 (42.32–49.51)
I have control over my gout	51.39 (49.00–53.77)	53.35 (49.95–56.75)	49.43 (46.08–52.77)

*100 = worse condition/greater gout impact; 0= better condition/less gout impact.
Data in groups are mean (SD) or (95 % CI) or median (IQR).

mmol/L and 11 % of participants had subcutaneous tophi. At baseline the mean pain score and patient global assessment score were both 4 on a 10-point Likert scale (Table 1). At baseline, 39 % of participants were on urate-lowering therapy, and for those on allopurinol, the mean dose was 227 mg/day. At Year 1 the percentage of all participants on urate-lowering therapy was 66 % and at Year 2, 69 % (Table 1). Baseline GIS scores did not differ significantly between the nurse-led and usual care group (Table 1).

Intervention group differences using the two gout remission definitions

Rates of remission for the two groups at each time point are shown in Table 2 and Fig. 1. Participants in the nurse-led care group were more likely to be in remission using either gout remission definition at Year 1 or Year 2, compared to those in the usual care group. Using the 2016 preliminary definition, the odds ratio for remission in the nurse-led care group was 2.54 [95 % CI 1.33–4.87] at Year 1 and 7.92 [95 % CI 4.86–12.92] at Year 2 (Table 2). Using the simplified definition the odds ratio for remission in the nurse-led care group was 2.24 [95 % CI 1.31–3.80] at Year 1 and 11.88 [95 % CI 7.49–18.84] at Year 2 (Table 2).

There were significant differences between Year 1 and Year 2 for the nurse-led care group but not the usual care group using either definition (nurse-led care group $p < 0.001$ for both definitions and $p > 0.05$ for usual care group, Fig. 1).

Intervention group differences in gout remission domains

At Year 1, fewer participants in the nurse-led care group fulfilled the gout flares domain, $p = 0.004$, but there were more participants in the nurse-led care group that fulfilled the serum urate domain (91.0 % in the nurse-led care group and 28.6 % in the usual care group, $p < 0.001$) (Supplementary Figure 1). At Year 1, there were no significant differences in the other remission domains between the nurse-led care group and usual care group. At Year 2, similar findings were observed for the serum urate domain (91.4 % in the nurse-led care group and 28.6 % in the usual care group, $p < 0.001$). However, at Year 2, there were more participants in the nurse-led care group who also fulfilled the gout flares domain, $p < 0.001$, the tophus domain, $p = 0.009$, the pain due to gout domain, $p < 0.001$ and the patient global assessment of gout disease activity domain, $p = 0.002$.

Gout remission at year 1 and year 2 using the two gout remission definitions

For all study participants, the 2016 preliminary definition was fulfilled by 9.9 % at Year 1 and 28.4 % at Year 2, $p < 0.001$ and the simplified definition was fulfilled by 17.6 % of all participants at Year 1 and 42.7 % at Year 2, $p < 0.001$ (Fig. 2). At both time points, more participants were defined as being in remission using the simplified

Table 2
Proportion of participants in remission by intervention group.

	Nurse-led care group $N = 255$	Usual care group $N = 262$	*OR [95 % CI]	p-value
Preliminary gout remission definition				
Year 1	36 (14.1 %)	15 (5.7 %)	2.54 [1.33–4.87]	0.005
Year 2	120 (47.1 %)	27 (10.3 %)	7.92 [4.86–12.92]	<0.001
Simplified gout remission definition				
Year 1	59 (23.1 %)	32 (12.2 %)	2.24 [1.31–3.80]	0.003
Year 2	178 (69.8 %)	43 (16.3 %)	11.88 [7.49–18.84]	<0.001

*Participants in usual care group were used as the reference.

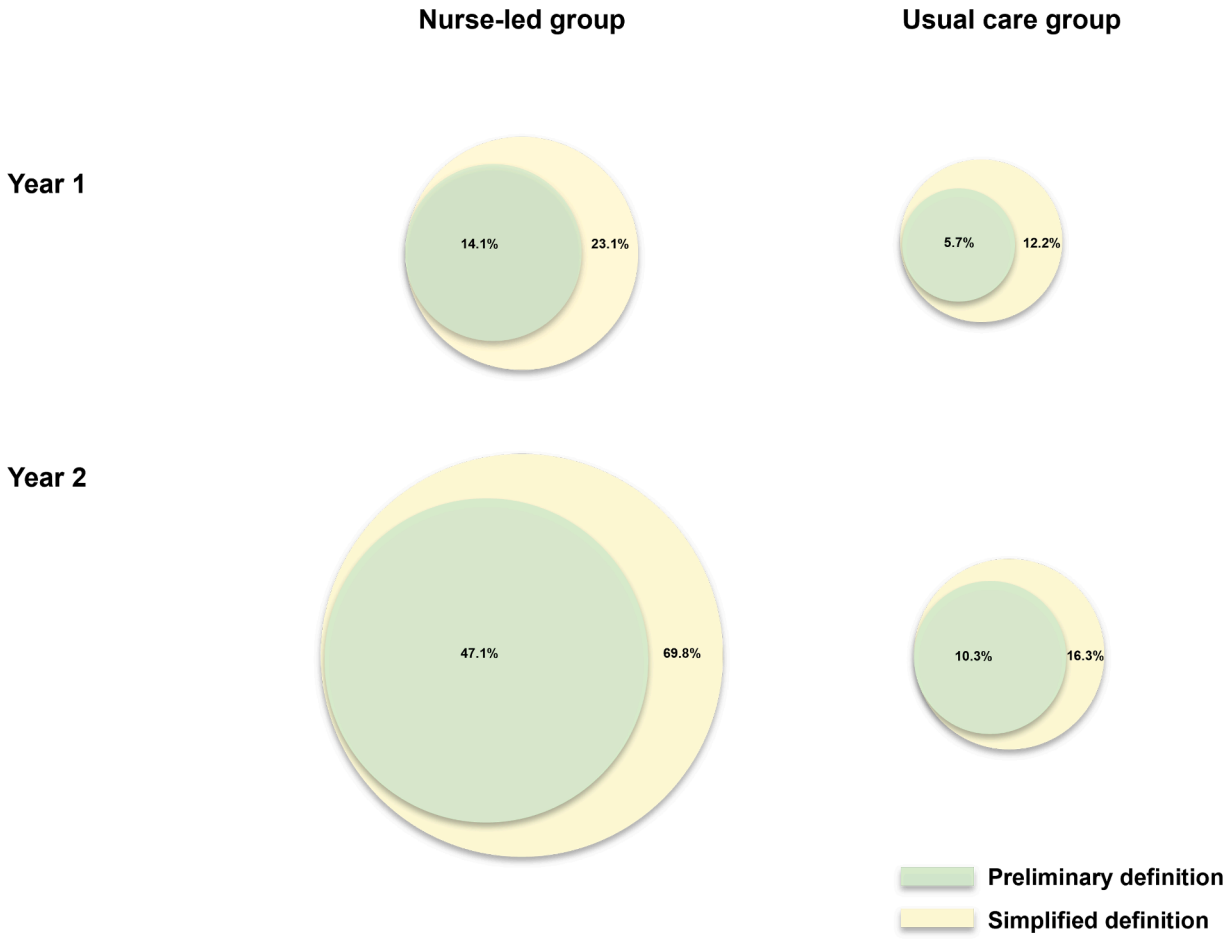

Fig. 1. Percentage of participants fulfilling the preliminary gout remission definition and simplified gout remission definition across the nurse-led and usual care group at Year 1 and Year 2. The area of the circles are proportional to the percentages.

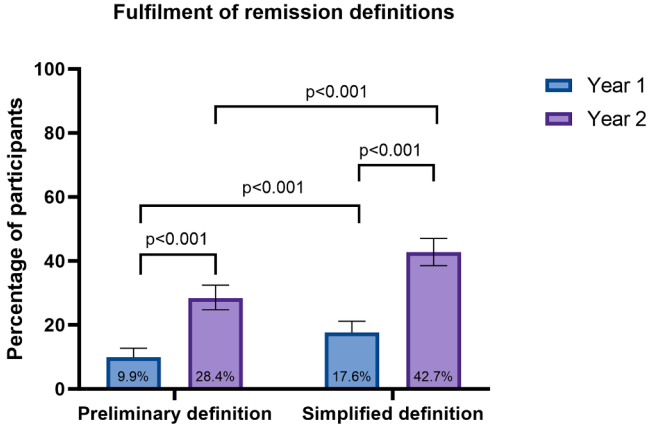

Fig. 2. Fulfilment of gout remission definitions at Year 1 and Year 2 for all study participants.

definition compared with the 2016 preliminary definition ($p < 0.001$ for Year 1 and Year 2) (Fig. 2, Supplementary Table 2).

Gout impact scale scores according to remission status using the two gout remission definitions

There was no difference between baseline GIS scores for those in remission and those not in remission at Year 2 according to the 2016 preliminary definition (Supplementary Table 3) or the simplified definition (Supplementary Table 4). At Year 2, participants in gout remission had better GIS scores when remission was defined using the 2016 preliminary definition (Table 3) and the simplified definition (Table 4). This was observed for all tested GIS items, specifically: worry about future gout attacks, gout disease progression and its interference in future activities, efficacy of gout medication, and control over gout.

Discussion

Gout remission has been defined using the 2016 preliminary gout remission definition and a subsequent simplified gout remission definition that utilises fewer domains. In this analysis we compared the performance of these definitions by evaluating their discrimination between intervention groups, sensitivity to change over time, and construct validity using the GIS. Both definitions performed similarly when discriminating between the nurse-led care group and usual care group, the simplified definition identified more people as being in remission at both Year 1 and Year 2, and both definitions showed high construct validity.

Participants in the nurse-led care group were more likely to be in gout remission using either definition at both Year 1 and Year 2. It is noteworthy that, at Year 1, relatively few participants were in remission. Participants in the nurse-led group were less likely to fulfil the gout flares domain in the first year, consistent with an increase of gout flares that is well recognized in the early stages of urate-lowering therapy [19-21]. The differences in remission status between the nurse-led and usual care groups at Year 1 were primarily due to differences in the serum urate domain. During development of the 2016 remission

Table 3
A comparison of gout impact scale scores at last follow-up between those fulfilling the 2016 preliminary definition and those not at year two.

	Overall *N* = 517 Mean [95 % CI]	Fulfilling criteria *N* = 147 Mean [95 % CI]	Not fulfilling criteria *N* = 370 Mean [95 % CI]	Mean difference [95 % CI]	p-value
I am worried that I will have a gout attack within the next year	41.90 [38.63–45.21]	33.69 [27.94–39.44]	50.15 [47.14–53.16]	−16.46 [−22.82 to -10.10]	<0.001
I am afraid that my gout will get worse over time	43.89 [41.34–46.45]	39.85 [35.41–44.29]	47.94 [45.00–50.88]	- 8.09 [−13.09 to -2.04]	0.004
I feel anxious that my gout will interfere with my future activities	42.74 [40.09–45.39]	36.03 [31.43–40.63]	49.46 [46.41–52.50]	−13.43 [−19.15 to -7.70]	<0.001
I worry that I will not be able to continue to enjoy my leisure activities as a result of my gout	41.75 [39.05–44.46]	33.70 [28.99–38.40]	49.81 [46.71–52.92]	−16.12 [−21.97 to -10.27]	<0.001
It is difficult to plan ahead for events or activities because I may have a gout attack	26.24 [23.92–28.55]	21.94 [17.88–26.01]	30.53 [27.86–33.19]	−8.58 [−13.58 to -3.58]	0.002
My current medications do not work well to prevent gout attacks from happening	22.02 [19.61–24.41]	15.76 [11.62–19.91]	28.27 [25.52–31.02]	−12.51 [−17.68 to -7.34]	<0.001
I have control over my gout	29.08 [26.34–31.81]	24.15 [19.39–28.91]	33.99 [30.85–37.14]	−9.85 [−15.74 to -3.95]	<0.001

100 = worse condition/greater gout impact; 0= better condition/less gout impact.

Table 4
A comparison of gout impact scale scores at last follow-up between those fulfilling the simplified definition and those not at year two.

	Overall *N* = 517 Mean [95 % CI]	Fulfilling criteria *N* = 221 Mean [95 % CI]	Not fulfilling criteria *N* = 296 Mean [95 % CI]	Mean difference [95 % CI]	p-value
I am worried that I will have a gout attack within the next year	44 0.18 [41.64–46.72]	37.94 [33.71–42.17]	50.42 [46.58–54.26]	−12.48 [−18.65 to -6.31]	<0.001
I am afraid that my gout will get worse over time	45.10 [42.73–47.47]	41.85 [37.95–45.76]	48.35 [44.80–51.90]	−6.50 [−12.23 to -0.76]	0.03
I feel anxious that my gout will interfere with my future activities	44.89 [42.40–47.38]	41.06 [36.95–45.18]	48.71 [44.97–52.46]	−7.65 [−13.65 to -1.63]	0.013
I worry that I will not be able to continue to enjoy my leisure activities as a result of my gout	44.32 [41.75–46.89]	39.59 [35.34–43.83]	49.05 [45.20–52.90]	−9.46 [−15.75 to -3.29]	0.003
It is difficult to plan ahead for events or activities because I may have a gout attack	27.59 [25.44–29.74]	24.90 [21.32–28.48]	30.28 [27.02–33.53]	−5.38 [−10.58 to -0.17]	0.04
My current medications do not work well to prevent gout attacks from happening	24.01 [21.76–26.26]	20.21 [16.46–23.97]	27.80 [24.38–31.23]	−7.59 [−13.11 to -2.07]	0.008
I have control over my gout	30.46 [27.93–32.99]	25.53 [21.33–29.73]	35.39 [31.59–39.19]	−9.87 [−16.01 to -3.72]	0.002

100 = worse condition/greater gout impact; 0= better condition/less gout impact.

definition, there was strong endorsement (98 %) for inclusion of the serum urate domain within the definition, reflecting the importance of long-term serum urate lowering in dissolution of MSU crystals [10]. In subsequent qualitative research, patients with well-controlled gout (who were all taking urate-lowering therapy) also supported inclusion of serum urate within the remission criteria [9]. At Year 2, all remission domains were improved in the nurse-led care group, with much larger differences in remission outcomes between the nurse-led and usual care groups. These findings highlight the benefits of assessing remission status as a measure that captures control of both serum urate control and clinical outcomes of importance when using urate-lowering therapy. These findings also indicate that achievement of remission or improvement in some individual domains, particularly the tophi domain, may require longer timeframes, potentially extending beyond 2 years.

In both groups and at both time-points tested, the simplified definition identified more participants as being in remission than the 2016 preliminary definition. This is consistent with another study in which both the preliminary gout remission definition and simplified gout remission definition were assessed [13]. Collectively, these findings show that the simplified definition has higher sensitivity for gout remission. It is possible that the simplified remission definition incorrectly classifies some participants as being in remission, and that the patient-reported outcome measures capture aspects of the gout experience that are not reflected in the three other domains (serum urate, gout flares, tophus). However, the observations that both definitions have similar construct validity with both the gout-specific brief illness perceptions questionnaire [14] and the GIS scores (including greater control over gout) provide reassurance about the validity of the simplified definition. It is also possible that the 2016 preliminary remission criteria incorrectly classifies some participants as not being in remission, and that additional, more subjective domains do not reflect a gout-specific disease state. The very low thresholds for the patient-reported domains in the 2016 preliminary definition may be excessively restrictive. The simplified remission definition utilises fewer domains than the 2016 preliminary definition and consists of variables regularly measured in long term gout clinical trials and easily measured in clinical practice [22, 23]. In contrast, measurement of patient reported outcomes such as pain and patient global assessment of disease activity are rarely assessed in long term gout clinical trials, even after their inclusion in the OMERACT core outcome domain set [24,25]. Furthermore, even when included, pain and patient global assessment questionnaires utilised in gout research are rarely worded to be specific to gout [26], which increases the possibility that non-gout pain or other symptoms may be misattributed to gout or reflect chronic joint damage which is less amenable to therapy. Future steps in agreeing on a final gout remission criteria

would include further validation of the simplified criteria in other RCTs, particularly those with longer study follow-up, including in people with severe disease, and a consensus process to endorse the simplified definition to be adopted as the standard definition for gout remission.

This study was strengthened by the use of prospectively collected data with a parallel-arm randomised design, the measurement of the OMERACT core outcome domains for long-term gout studies, and the availability of the gout specific instrument, GIS, for the assessment of gout related HRQoL. Another strength was recruitment of participants from a primary care setting which allowed comprehensive evaluation of the two remission definitions across a range of disease severity and increases applicability to the general population with gout. A potential limitation is the low prevalence of people with tophaceous gout, which may limit generalisability to specialist rheumatologist care. A further limitation of the study was the measurement of gout flare, serum urate, tophus, pain, and patient global assessment outcomes only at the baseline, Year 1 and Year 2 time points. If remission had been assessed using outcomes collected at least twice over 12-month periods (as stated in the published 2016 preliminary gout remission definition [10]), the proportion of participants fulfilling either remission definition may have been even lower.

In summary, both remission definitions performed well in discriminating between the nurse-led care group and usual care group. The simplified definition identified more people as being in remission at Year 1 and Year 2, and also showed high construct validity using a gout specific health related quality of life instrument. The simplified definition is a feasible, sensitive, and valid option for defining gout remission.

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CRediT authorship contribution statement

Adwoa Dansoa Tabi-Amponsah: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Michael Doherty:** Writing – review & editing, Project administration, Investigation, Data curation. **Aliya Sarmanova:** Writing – review & editing, Data curation. **Weiya Zhang:** Writing – review & editing, Project administration, Investigation, Data curation. **Sarah Stewart:** Writing – review & editing, Supervision, Methodology, Conceptualization. **William J Taylor:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Lisa K Stamp:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Nicola Dalbeth:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

Nicola Dalbeth has received consulting or speaker fees from AstraZeneca, Dyve Biosciences, Horizon, Selecta, Arthrosi, JW Pharmaceutical Corporation, PK Med, LG Chem, JPI, PTC Therapeutics, Protalix, outside the submitted work. Lisa Stamp has received royalties from Up-to-Date and consulting fees from Pharmac NZ. Aliya Sarmanova was affiliated with the Nottingham University at the time of the study conduct and is currently affiliated with Roche Diagnostics International, Clinical Development and Medical Affairs. The other authors have no conflicting interests to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152555.

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