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Evaluation of continued 2-monthly or annual urate monitoring in gout: an extension of the GoutSMART randomised controlled feasibility trial

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Abstract

Aim: Improved outcomes for patients with gout are associated with reduced urate levels and many guidelines recommend regular urate monitoring. There is no consensus on how frequently monitoring should be performed, and so we have used a supported self-management approach which incorporates urate self-testing to evaluate 2-monthly urate monitoring compared to annual monitoring.

Methods: This study was an extension of a 12-month feasibility trial in 60 gout patients randomised 2:1 to support gout self-management or usual care. Participants exiting the self-management arm were offered 2-monthly urate monitoring, with usual care participants offered annual monitoring. Additional participants were randomised 1:1 to either arm. All participants were offered initial dose titration to a urate target of 0.3 mmol/L. The primary outcome was the proportion of participants with urate ≤ 0.36 mmol/L at 24 months with an intention-to-treat analysis.

Results: Between September 2020, and September 2021, 67 patients were enrolled. The mean age was 55.5 (SD 14.0) years. 61 (91%) self-reported as cisgender male, 5 (7.5%) as cisgender female and 1 (1.5%) as transgender female. 62 (92.5%) were White, 4 (6.0%) were Asian and 1 (1.5%) was Black. 40 participants were allocated to 2-monthly monitoring (including 10 new participants), and 27 participants to annual monitoring (including 12 new participants). The primary study outcome of urate ≤ 0.36 mmol/L at 24 months was achieved by 38 (95%) 2-monthly monitoring participants, compared to 17 (62.9%) annual monitoring participants (risk difference 0.32 [95% CI 0.13 to 0.52]; p = 0.0021). 5 (7.5%) participants withdrew with 4 allocated to annual monitoring. 2 annual monitoring participants died.

Conclusions: 2-monthly monitoring of urate is associated with improved maintenance of urate targets after 2 years compared to annual monitoring, a result influenced by an increased withdrawal rate amongst annual monitoring participants. Further trials evaluating the cost-effectiveness and optimal frequency of urate monitoring are now needed (ClinicalTrials.gov identifier: NCT03274063).

Keywords

Gout, urate monitoring, self-management, treat-to-target, point-of-care

Introduction

Gout is the most common cause of inflammatory arthritis with a rising incidence and resultant disability worldwide [1]. Improved clinical outcomes in gout are associated with reduced urate levels leading rheumatology specialist guidelines to adopt a treat-to-target urate approach and to recommend ongoing urate monitoring [2–4]. With adequate doses of urate lowering therapy most patients achieve target urate levels [5, 6], however maintaining adherence to therapy is recognised as a challenge globally [7], with medication adherence known to be worse in gout than in other chronic diseases [8]. Monitoring urate levels should help address this problem, however no evaluation of urate monitoring strategies has been performed, and in view of this, there is no evidence base to guide recommendations on the frequency of such monitoring, nor consensus that monitoring is justified at all [9].

Self-management is recommended in many chronic health conditions and with sufficient support can replicate the results observed in clinical trials [10]. Point-of-care urate meters are reliable and have been shown to guide clinical decision making in gout [11, 12]. We have developed a supported self-management approach to gout which uses a smartphone app (GoutSMART) to prompt patients to record a diary of their own urate levels and flares, and communicates these results directly to their healthcare team facilitating interpretation of results and direct management advice. We have shown that this approach is well tolerated and results in much higher attainment of urate targets than usual care [13]. We have completed a 2 year extension of this trial in which we compared the clinical outcomes for patients continuing to perform urate monitoring on a 2-monthly basis with annual urate monitoring.

Materials and methods

Study design

This was an extension of a randomised controlled feasibility trial conducted at one secondary care hospital site, the Western General Hospital, NHS Lothian, Edinburgh. In the feasibility trial participants were randomly allocated 2:1 to supported self-management or usual care. All participants completing the feasibility trial were invited to take part in a 2 year extension with participants from the self-management arm allocated to continued 2-monthly urate monitoring, and usual care participants allocated to annual monitoring. The 2-monthly monitoring frequency was selected in consultation with Lothian patient partners to ensure confidence in performing urate self-testing was maintained without testing becoming overly intrusive. Additional participants to the extension study were randomly allocated 1:1 to either arm. All participants provided written informed consent. Ethical approval was obtained from South East Scotland Research Ethics Committee (Reference 18/SS/0031) and NHS Lothian Caldicott Guardian. The extension trial protocol has been uploaded with the results of the feasibility trial on ClinicalTrials.gov, NCT03274063.

Participants

Details of the baseline characteristics of feasibility trial participants have been published previously [13]. Inclusion criteria were age ≥ 18, diagnosis of gout satisfying ACR criteria, physician recommendation of initiation/escalation of urate lowering therapy, possession of a smart phone, and serum urate > 0.36 mmol/L. Exclusion criteria were previous adverse reactions to either allopurinol or febuxostat, patients on maximum dose of either therapy, severe renal failure (eGFR < 30) or established liver disease, or prescription of azathioprine or mercapto-purine. Additional participants to the extension trial were recruited following referral to Lothian rheumatology service and satisfied the same criteria however all participants were already taking urate lowering therapy and there was no requirement for an elevated baseline urate.

Intervention

All participants were provided with a BeneCheck Plus hand-held urate meter and shown how to use it. All participants installed the GoutSMART mobile phone application which allowed direct communication with the study team and prompted participants to record urate, flare and quality-of-life diaries. Any participant with a baseline urate > 0.3 mmol/L was prompted through the app to self-test urate levels every 2 weeks and had urate lowering therapy titrated remotely by the study team to achieve urate target. Participants from the self-management arm of the feasibility trial were prompted to perform ongoing urate testing every 2 months, however usual care participants received urate self-testing prompts on an annual basis only. Additional participants in the extension study were randomly allocated 1:1 to either 2-monthly or annual monitoring. Urate lowering therapy de-escalation was permitted in the 2-monthly monitoring arm once remission had been achieved which was defined as cessation of flares and attainment of target urate for at least 12 months, as well as resolution of tophi. In these participants allopurinol was reduced in 100 mg decrements with 2 weekly urate self-testing until a urate in the range of 0.3–0.36 mmol/L had been achieved when no further decrease was advised, or the urate exceeded 0.36 mmol/L in which case the dose was adjusted back up. Flare and quality of life diaries were completed prospectively using the GoutSMART app which functions primarily as a healthcare diary and is not considered to fall within the definition of a medical device, with informal advice to this effect received from the Medicines and Healthcare Products Regulatory Authority.

Outcomes

The primary outcome was the proportion of participants achieving urate levels ≤ 0.36 mmol/L at 104 weeks. Planned secondary outcomes assessed at weeks 52 and 104 included proportion of participants achieving target urate ≤ 0.36 mmol/L, flare frequency, presence of tophi, medication compliance, proportion of patients maintaining urate target after dose reduction, number of medical attendances. Hospital care records were reviewed to identify serious adverse events. Adjudication of flares was performed at 12 and 24 month visits following the criteria of Gaffo et al. [14]. Quality of life scores were recorded using the EQ-5D-5L questionnaire. Permission was granted by all participants to perform record linkage with community prescribing data.

Sample size calculation

We assumed that 90% of participants in the 2-monthly monitoring arm of the study would remain adherent to therapy, compared with only 50% in the annual monitoring arm. These figures are conservative compared to 95% compliance reported in closely monitored patients by Doherty et al. [6] and the 36.8% medicine possession ratio reported in usual care by Briesacher et al. [8]. A sample size of 20 in each allocation yields 81% power, and 30 in each treatment allocation 94% power to detect such a difference. Due to observed drop outs from the feasibility trial and restrictions in recruiting participants during the COVID pandemic, we recruited additional participants in the extension phase of the study to ensure sufficient power was achieved.

Randomisation and blinding

Participants were allocated using a randomisation tool built into the GoutSMART app. Blinding of participants, and of those delivering the intervention or interpreting the data was not possible due to the nature of the intervention.

Patient participation

The self-monitoring approach has been developed in collaboration with a panel of NHS Lothian gout patients with qualitative feedback from participants in the feasibility trial used to improve the user experience.

Analysis

Categorical, continuous and discrete outcomes were analysed as previously described [13]. For the primary study outcome an intention to treat analysis was performed with dropouts from the study assumed to have failed to meet urate target. For secondary outcomes a nominal significance threshold of $p < 0.05$ was taken, however no correction for multiple testing has been performed so these results should be considered exploratory.

Results

Study recruitment

Recruitment ran from 20th September 2020 until 22nd September 2021, and the study concluded with the final study visit on 29th September 2023. The allocation and progression of participants through the study are summarised in Figure 1 with 67/77 (87%) of screened patients entering the study. The mean age of 9 patients excluded from the study was 53.7 (SD 12.7) years which is 1.8 years younger than participants, and all were male.

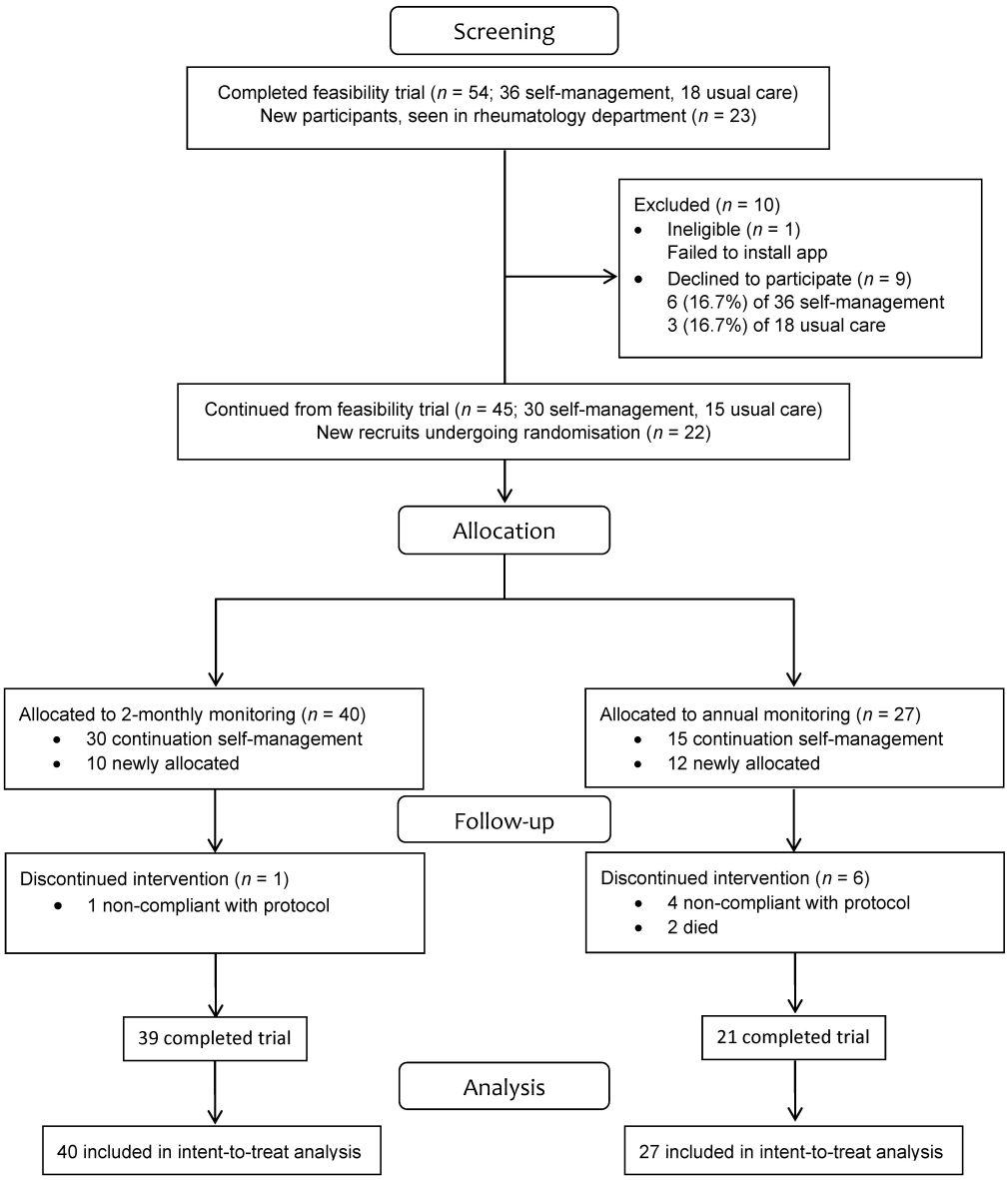

Figure 1. Consort diagram for participation in the study

Baseline characteristics

The groups were balanced at baseline with respect to age, gender, and the presence of tophi (Table 1). All participants were prescribed urate lowering therapy with the 2-monthly monitoring arm prescribed a mean dose of 410 (SD 170) mg allopurinol daily compared to a mean dose of 322 (SD 125) mg allopurinol daily in the annual monitoring arm, similarly the baseline urate was lower in the 2-monthly arm at 0.28 (SD 0.075) mmol/L compared to 0.37 (SD 0.12) mmol/L. Reflecting the tighter urate control in the 2-monthly monitoring arm of the feasibility trial the total number of flares in the preceding 12 months was 3.2 (SD 4.71) for 2-monthly monitoring participants compared to 5.30 (SD 5.34) in the annual monitoring arm. The mean age of participants was 55.5 (SD 14.0) years; 61 (91%) of 67 identified as cisgender men, 5 (7.5%) of 67 as cisgender women and 1 (1.5%) of 67 as a transgender woman. 62 (92.5%) of 67 were White, 4 (6.0%) of 67 were Asian and 1 (1.5%) of 67 was Black.

Table 1. Baseline characteristics of participants

Characteristic	2-monthly monitoring (*n* = 40)	Annual monitoring (*n* = 27)
Age (yrs)	57.3 (11.3)	52.8 (17.2)
Gender	36 cisgender men (90%)	25 cisgender men (92.6%)
	3 cisgender women (7.5%)	2 cisgender women (7.4%)
	1 transgender woman (2.5%)	
Ethnicity	36/40 White (90%)	26/27 White (96.3%)
	3/40 Asian (7.5%)	1/27 Asian (3.7%)
	1/40 Black (2.5%)	
Flares (in 12 months)	3.2 (4.71)	5.3 (5.34)
Duration of gout (yrs)	11.45 (10.57)	9.21 (6.42)
Tophi	12/40 (30%)	8/27 (29.6%)
	Tophus number 4.8	Tophus number 4.8
	Max size 13.6 (14.7) mm	Max size 14.4 (14.8) mm
Urate level (mmol/L)	0.28 (0.075) (Study entry)	0.37 (0.12) (Study entry)
	0.26 (0.04) (Optimised)	0.29 (0.04) (Optimised)
Urate lowering therapy	Allopurinol 39/40	Allopurinol 27/27
	(mean dose 410 mg)	(mean dose 322 mg)
	Febuxostat 1/40 (120 mg)	
Co-existing conditions		
Obesity (BMI ≥ 30)	17/40 (42.50%)	15/27 (55.56%)
eGFR < 60 mL/min per 1.73 m^2	3/40 (7.50%)	1/27 (3.70%)
Type 2 diabetes	2/40 (5.00%)	3/27 (11.11%)
Hypertension	16/40 (40.00%)	9/27 (33.33%)
Hyperlipidaemia	8/40 (20.00%)	7/27 (25.93%)

Baseline characteristics of participants are reported as mean (standard deviation) for continuous variables or total number (percentage) for categorical variables. Note that all participants achieved urate target following dose optimisation at study entry before commencing randomised monitoring allocation

Primary outcome

The primary study outcome of maintaining urate target ≤ 0.36 mmol/L by the end of year 2 was achieved in 38 (95%) of 40 2-monthly monitoring participants compared to 17 (62.96%) of 27 annual monitoring participants (RR 1.51, [95% CI 1.12 to 2.03], Table 2). The planned intention-to-treat analysis assumes that participants failing to complete the trial did not attain the urate target. In the annual monitoring arm 4 (14.8%) of 27 participants discontinued participation in the trial, and 2 (7.41%) of 27 participants died. In the 2-monthly monitoring arm a high retention rate was seen with only 1 (2.5%) of 40 participants discontinuing intervention and no deaths. The total number of participants not completing the trial was significantly lower in the 2-monthly monitoring arm (RR 0.11, [95% CI 0.014 to 0.88]).

Secondary outcomes

Planned secondary outcomes are detailed in Tables 2, 3, and 4. No correction for multiple testing has been performed, and so the results of secondary outcomes of the trial should be considered exploratory. All participants with baseline urate > 0.3 mmol/L were offered dose titration involving remote 2-weekly urate

Table 2. Study outcomes

	12 months outcomes					24 months outcomes				
Categorical study outcomes										
	2-monthly urate	**Annual urate**	**RD**	**RR**	***p* value**	**2-monthly urate**	**Annual urate**	**RD**	**RR**	***p* value**
	(*n* = 40)	**(*n* = 27)**	**(95% CI)**	**(95% CI)**		**(*n* = 40)**	**(*n* = 27)**	**(95% CI)**	**(95% CI)**	
Urate ≤ 0.36 mmol/L	35/40 (87.50%)	22/27 (81.48%)	0.06	1.07	0.51	38/40 (95.00%)	17/27 (62.96%)	0.32	1.51	0.0021
			(–0.12 to 0.24)	(0.87 to 1.33)				(0.13 to 0.52)	(1.12 to 2.03)	
Tophaceous disease	8/38 (21.05%)	7/24 (29.16%)	–0.08	0.72	0.55	7/39 (17.95%)	4/21 (19.05%)	–0.01	0.94	> 0.99
	Tophus number 2.62 (2.67)	Tophus number 1.57 (1.13)	(–0.30 to 0.14)	(0.30 to 1.73)		Tophus number 1.71 (0.76)	Tophus number 2.00 (1.15)	(–0.22 to 0.20)	(0.31 to 2.85)	
	Max size 10.87 (9.09) mm	Max size 9.00 (6.40) mm				Max size 6.29 (7.27) mm	Max size 13.00 (9.09) mm			
Any flares in past 12 months	18/38 (47.37%)	14/24 (58.33%)	–0.11	0.81	0.44	3/39 (7.69%)	7/21 (33.33%)	–0.26	0.23	0.025
			(–0.36 to 0.14)	(0.50 to 1.30)				(–0.47 to –0.04)	(0.067 to 0.80)	
Remission	16/38 (42.11%)	7/24 (29.17%)	0.13	1.44	0.42	29/39 (74.36%)	13/21 (61.90%)	0.12	1.20	0.38
			(–0.11 to 0.37)	(0.70 to 2.99)				(–0.12 to 0.37)	(0.82 to 1.76)	
Continuous study outcomes										
	2-monthly urate	**Annual urate**	**Mean difference**		***p* value**	**2-monthly urate**	**Annual urate**	**Mean difference**		***p* value**
	(*n* = 38)	**(*n* = 24)**	**(95% CI)**			**(*n* = 39)**	**(*n* = 21)**	**(95% CI)**		
Urate (mmol/L)	0.29 (0.07)	0.28 (0.07)	0.010 (–0.026 to 0.046)		0.59	0.25 (0.07)	0.28 (0.08)	–0.03 (–0.070 to 0.010)		0.14
Allopurinol dose (mg/day)	429.73 (192.74)	466.67 (127.40)	–36.94 (–125.96 to 52.08)		0.41	405.41 (163.21)	419.05 (169.17)	–13.64 (–103.19 to 75.91)		0.76
Prescriptions issued (days/yr)	336.81 (62.47)*	299.70 (85.04)*	37.11 (–1.11 to 73.10)		0.044	348.97 (91.75)*	274.43 (101.63)*	74.54 (26.87 to 122.26)		0.0033
Discrete study outcomes										
	2-monthly urate	**Annual urate**	**Rate difference**		***p* value**	**2-monthly urate**	**Annual urate**	**Rate difference**		***p* value**
	(*n* = 38)	**(*n* = 24)**	**(95% CI)**			**(*n* = 39)**	**(*n* = 21)**	**(95% CI)**		
GP appointments	0.079 (0.36)	0.042 (0.20)	0.037 (–0.09 to 0.17)		0.57	0.026 (0.16)	0.048 (0.22)	–0.022 (–0.11 to 0.075)		0.66
Flares	0.79 (1.26)	1.63 (1.81)	–0.84 (–1.37 to –0.30)		0.0024	0.077 (0.27)	0.62 (1.02)	–0.54 (–0.82 to –0.27)		0.0001
Doses missed in last week	0.45 (1.25)	0.08 (0.28)	0.36 (0.08 to 0.65)		0.01	0.33 (0.93)	1.29 (2.51)	–0.95 (–1.39 to –0.52)		< 0.0001

Categorical study outcomes at the 12 month and 24 month study visits include the primary study outcome of proportion of participants achieving a urate target of ≤ 0.36 mmol/L at month 24. Results are reported as total number (percentage) then risk difference (RD) or relative risk (RR) with 95% confidence intervals (CI). An intention-to-treat analysis was performed with dropouts from the study assumed to have failed to meet urate target. Significance determined by Fishers exact test. Continuous outcomes for participants continuing in the study are given as the mean (standard deviation) with the mean difference (95% CI) and significance calculated using a two sample *T* test. Community prescribing data was available for all participants hence the number of participants for this analysis is *n* = 40 (2-monthly monitoring) and *n* = 27 (annual monitoring) with this difference indicated by (*). Discrete outcomes are given as mean (standard deviation) with the rate difference (95% CI) and significance calculated using a 2 sample Poisson rate test

monitoring until urate target had been achieved. Following this dose optimisation there was no difference in attainment of urate targets at the end of year 1 with the 0.36 mmol/L target achieved in 35 (87.5%) of 40 2-monthly participants and by 22 (81.5%) of 27 annual monitoring participants (RR 1.07, [95% CI 0.87 to 1.33], Table 2). Similarly, no difference in the mean urate levels were seen at the end of year 1 which averaged 0.29 (SD 0.07) mmol/L in 2-monthly monitoring participants and 0.28 (SD 0.07) mmol/L in annual monitoring participants (mean difference 0.010, [95% CI –0.026 to 0.046], Table 2). The proportion of participants suffering flares in year 1 was not significantly different in the 2-monthly arm with 18 (47.37%) of 38 sustaining flares in this time compared to 14 (58.33%) of 24 in the annual monitoring arm (risk difference –0.11, [95% CI –0.36 to 0.14], Table 2). However fewer total flares were reported in the 2-monthly arm over the first year with a flare rate of 0.79 (SD 1.26) compared to 1.63 (SD 1.81) in annual monitoring (rate difference –0.84, [95% CI –1.37 to –0.30], Table 2).

By the second year of the trial both the proportion of participants sustaining flares and the total number of flares reported were reduced in the 2-monthly monitoring arm; 3 (7.69%) of 39 participants in the 2-monthly arm sustained flares compared to 7 (33.33%) of 21 in the annual monitoring arm (risk difference –0.26, [95% CI –0.47 to 0.04], Table 2) with average number of flares in the 2-monthly arm 0.077 (SD 0.27) compared to 0.62 (1.02) in annual monitoring (rate difference –0.54, [95% CI –0.82 to –0.27], Table 2). All participants in the extension trial recorded urate levels of 0.36 mmol/L or less at the beginning of the trial (either at study entry, or shortly afterwards following dose optimisation), meaning that achieving remission was determined by additionally achieving both 12 months free of gout flares and resolution of tophi. No significant difference in remission was seen between treatment arms with remission criteria reached by 29 (74.36%) of 39 2-monthly monitoring participants, compared to 13 (61.90%) of 21 annual monitoring participants (risk difference 0.12, [95% CI –0.12 to 0.37], Table 2).

Table 3. Adverse events

Adverse event	2-monthly urate (*n* = 40)	Annual Urate (*n* = 27)	*p* value
Serious adverse events	Total 17 events in 11 (27.5%) individuals	Total 8 events in 5 (18.5%) individuals	0.40
Hospital admission/death		Including 2 deaths	
Adverse events	Total of 37 events in 23 (57.5%) individuals	Total of 25 events in 13 (48.1%) individuals	> 0.99

Information on adverse events was collected prospectively and sought specifically at week 24 and 52 visits. No significant difference in rate of adverse events was seen between 2-monthly and annual urate arms, with significance calculated using a 2 sample Poisson rate test

Table 4. Quality of life outcomes

Outcome	Baseline			1 year			2 year		
	2-monthly urate (*n* = 38)	Annual urate (*n* = 21)	*p* value	2-monthly urate (*n* = 37)	Annual urate (*n* = 18)	*p* value	2-monthly urate (*n* = 36)	Annual urate (*n* = 14)	*p* value
Mobility	1.34 (0.75)	1.29 (0.64)	0.77	1.24 (0.55)	1.39 (0.7)	0.40	1.22 (0.54)	1.29 (0.61)	0.72
Self-care	1.21 (0.62)	1.10 (0.44)	0.46	1.14 (0.42)	1.22 (0.55)	0.52	1.17 (0.45)	1.07 (0.27)	0.46
Activities	1.21 (0.62)	1.38 (0.67)	0.33	1.16 (0.44)	1.33 (0.59)	0.23	1.22 (0.54)	1.36 (0.63)	0.45
Pain	1.39 (0.82)	1.52 (0.68)	0.54	1.32 (0.71)	1.61 (0.78)	0.18	1.39 (0.64)	1.36 (0.5)	0.87
Anxiety	1.18 (0.51)	1.62 (0.92)	0.02	1.14 (0.48)	1.50 (0.71)	0.03	1.19 (0.52)	1.71 (1.44)	0.06
Health score	84.32 (16.06)	77.81 (10.03)	0.10	86.43 (12.83)	79.56 (15.31)	0.09	86.64 (11.96)	82.29 (16.08)	0.30

Quality of life scores were collected prospectively using the EQ-5D-5L questionnaire incorporated into the GoutSMART app. For functional domains score of 1 indicates no difficulty, 2 slight difficulty, 3 moderate difficulty, 4 severe difficulty, and 5 extreme difficulty. The global health score is rated out of a best possible 100. Participants were invited to complete the questionnaire at monthly intervals as well as opportunistically during any reported flares. Results are given as mean (SD) with significance estimated using 2-sided student *T* test

We saw no significant difference in the rate of adverse events or serious adverse events between the 2-monthly or annual monitoring arms of the trial (Table 3). Two deaths occurred in the annual monitoring arm of the trial, neither of which were attributed to study medication. Serious adverse events included myocardial infarction, stroke, arrhythmias, prostate, colon and hepatocellular cancer, melanoma, liver abscess, cholecystitis, pulmonary emboli, back pain, gastritis and haematuria. There were no admissions due to flares of gout over the course of the trial, though two emergency attendances with gout were noted (one from each arm).

No significant difference in allopurinol dose was seen between the two arms by the end of year 1 429.73 (SD 192.74) mg daily in 2-monthly monitoring compared to 466.67 (SD 127.40) mg daily in annual monitoring (mean difference –36.94, [95% CI –125.96 to 52.08]). This reflects the dose titration offered to all participants at study entry if they were found to have elevated urate, as well as dose reduction of allopurinol offered to participants in remission in the 2-monthly arm. Allopurinol dose reduction was attempted by 24 (82.8%) of 29 2-monthly monitoring participants who achieved remission with a mean reduction in allopurinol of 178.26 (SD 150.62) mg daily. The mean urate following dose reduction was 0.26 (SD 0.065) mmol/L which was not significantly different to 0.23 (SD 0.070) mmol/L in those not attempting dose reduction (mean difference 0.026, [95% CI –0.019 to 0.070]). We note that 1 (4.17%) of 24 individuals supported to dose reduce failed to maintain target at 2 years. Within the annual monitoring arm 5 (23.81%)

of 21 participants reduced their medication dose without supervision of whom 2 (40%) of 5 failed to maintain urate target at 2 years, both of whom had decided to stop allopurinol altogether due to good symptom control. We note that very few participants in the trial required an appointment in primary care to review gout with no significant difference seen between the treatment arms; mean of 0.079 (SD 0.36) appointments in 2-monthly monitoring compared to 0.042 (SD 0.20) appointments in annual monitoring (rate difference 0.037, [95% CI –0.09 to 0.17], Table 2), with similar results seen in year 2.

Compliance with medication was evaluated by self-report and by analysis of prescription records. At the end of the first year fewer patients in the annual monitoring arm self-reported missing doses of medication in the preceding week with average number of missed doses 0.45 (1.25) in the 2-monthly arm compared to 0.08 (0.28) in the annual monitoring arm (rate difference 0.36, [95% CI 0.08 to 0.65], Table 2), however, by the end of 2 years the reverse was seen with an average of 0.33 (0.93) missed doses reported by 2-monthly participants compared to 1.29 (2.51) missed doses in the annual monitoring arm (rate difference –0.95, [95% CI –1.39 to –0.52], Table 2). An objective measure of compliance was made possible through record linkage with community prescribing records available for all participants in the trial. We calculated the number of days of allopurinol prescribed by taking the total of all prescriptions issued in each year and dividing by the recorded daily dose of allopurinol. This indicated that an average of 336.81 (62.47) days of allopurinol was prescribed in the 2-monthly monitoring compared to 299.70 (85.04) days in annual monitoring over year 1 (mean difference 37.11, [95% CI –1.11 to 73.10], Table 2). In the second year of the trial this difference had widened with a mean of 348.97 (91.75) days prescribed to 2-monthly monitoring participants compared to 274.43 (101.63) days to annual monitoring participants (mean difference 74.54, [95% CI 26.87 to 122.26], Table 2). In an exploratory analysis we looked to see if a percentage change in prescriptions issued for the 14 most commonly co-prescribed medications was seen in the 2 years of the trial compared to the 2 years prior to enrolment, however we observed no significant difference between 2-monthly and annual monitoring arms, mean percentage change 0.21 (SD 0.79) in 28 2-monthly participants compared to 0.41 (SD 0.93) in 15 annual monitoring participants (mean difference 0.2, [95% CI –0.34 to 0.74], p = 0.46). With a similar analysis we observed an overall decrease in the number of analgesic prescriptions issued though no significant difference between the treatment arms was seen; mean percentage change –0.53 (0.50) in 39 2-monthly participants compared to –0.23 (0.89) in 26 annual monitoring participants (mean difference 0.30, [95% CI –0.05 to 0.65], p = 0.09).

The outcomes for quality-of-life scores are given in Table 4. We acknowledge that not all participants completed quality of life scores, with incomplete recording particularly seen within the annual monitoring arm. Overall, no significant difference was seen between 2-monthly monitoring and annual monitoring arms of the study, with scores across functional domains suggesting no difficulty or slight difficulty only, global health scores were typically between 80 or 90 out of a best possible 100. Overall participants reported good quality of life at entry into the trial with these levels maintained over the course of the extension associated with both annual monitoring and 2-monthly monitoring.

Finally, we performed a sensitivity analysis looking at outcomes restricted to only those participants who had taken part in the feasibility trial (Table S1). Similar trends were seen with significant improvements again in 24 month urate target attainment and number of flares at 24 months associated with 2-monthly monitoring. We note that in this analysis the mean dose of allopurinol taken by 2-monthly participants was significantly reduced at 24 months compared to annual monitoring participants (on average reduced by 95.45 mg/day), presumably reflecting that this cohort were more likely than new recruits to have been offered dose reduction which was discussed after achieving 12 months free of flares, tophus resolution and achieving urate target.

Discussion

Rheumatology specialty guidelines for gout recommend a treat-to-target urate approach followed by monitoring of urate levels, reflecting the fundamental importance of urate in determining disease prognosis and treatment effectiveness. Given a lack of clinical trial evidence upon which to base urate monitoring recommendations there is no consensus on how frequently this should be performed, with existing

guidance varying between a pragmatic suggestion for an annual urate check [2], to non-specific guidance for 'serial' or 'regular' urate measurements to ensure maintenance of urate targets [3, 4]. Conversely American primary care guidelines have advocated symptom based management alone without any urate monitoring [9]. To our knowledge this is the first trial comparing two different urate monitoring frequencies in gout. We have shown that 2-monthly urate monitoring is superior to annual monitoring in achieving urate target after 2 years of follow up and thereby provide support for the principle of urate monitoring, as well as evidence that more monitoring is better than less. We note also that 2-monthly monitoring of urate using a self-testing approach was well tolerated with a high participant retention rate.

All patients within the extension trial were offered dose titration of urate lowering therapy to achieve urate target and were offered at least annual monitoring of serum urate. Despite this being a secondary care cohort with severe disease at baseline, we observed complete cessation of gout flares in year 2 for most 2-monthly monitoring participants with only 3 (7.7%) of 39 reporting flares. Whilst a progressive reduction in flare frequency over time was seen within the annual monitoring arm there were still 7 (33.3%) of 21 participants sustaining flares in the second year of this approach suggesting that 2-monthly monitoring results in substantially fewer flares. A number of secondary outcomes showed no difference between cohorts. We acknowledge limitations in the collection of quality-of-life data but found that most participants appeared to be doing well by this measure, reporting either no difficulty or slight difficulty across functional domains on study entry, with these scores maintained over the course of the extension trial. Similarly, we observed very low rates of attendance in primary care for review of gout in both arms of the trial. The total number of participants with tophi decreased modestly over the course of the extension trial, with no difference in outcomes observed between the two study arms. Given the largest tophi averaged between 13 to 14 mm in diameter at study entry, then a failure to resolve tophi in this timeframe is in line with reported outcomes even with tight urate control [15].

A unique feature of the study was the opportunity to explore dose reduction of allopurinol in patients that had achieved disease remission. A recommendation or agreement that dose de-escalation can be performed is included in both BSR and EULAR guidelines [2, 3] though has not been previously evaluated. We found most participants were keen to explore dose reduction and with participant self-testing this was easily managed. The absolute reductions in urate lowering therapy dose were modest, typically between 100 and 200 mg allopurinol daily. In a single participant allopurinol was discontinued altogether for a short time, with a subsequent rise in urate and gout flare such that allopurinol required to be restarted. We are reassured that overall, we observed very good long term outcomes despite this intervention, which potentially risks undermining messaging on the importance of adherence to therapy. We note also that dose reduction was attempted without supervision by a number of participants in the annual monitoring arm and hope that our experience will encourage and inform shared decision-making decisions on dose reduction in the future.

Adherence to therapy in gout is recognised as being far lower than in many other chronic diseases, with a meta-analysis suggesting adherence rates of only 47% overall [7, 16]. High levels of adherence to therapy have however been achieved with an approach that includes patient education and involvement in treatment decisions [17]. The supported self-management approach we have developed achieves both these goals by reinforcing patients' understanding through direct biological feedback of the effect of urate lowering treatment, and placing patients at the centre of the decision making process. Consistent with these observations we observed significantly higher prescription rates for urate lowering therapy in participants allocated to 2-monthly monitoring compared to annual monitoring suggesting that closer support of self-management drives improved adherence to therapy. We note that there was no difference in the mean allopurinol dose prescribed between our cohorts, and observed significantly reduced allopurinol dosing in a sensitivity analysis confined to participants continuing from the feasibility trial, such that the improved outcomes seen are best explained by improved treatment compliance. However, since we did not observe a corresponding increase in the prescription rate of commonly co-prescribed medications, the effect on adherence appears to be disease specific rather than generalised.

We acknowledge limitations in our study. Whilst new participants into the extension trial were randomised, those feasibility trial participants who continued into the extension trial were not further randomised and as a result participants in the 2-monthly monitoring arm tended to be further along their treatment pathway than annual care participants. Given that the benefits of tight urate control are typically seen after 12 months of treatment [6], improved outcomes in the first year of the extension will be in part a legacy of the improved care received in the preceding feasibility trial. To mitigate this effect, we performed close urate monitoring and treatment escalation in all participants with elevated urate levels at entry into the extension trial such that there was no significant difference in urate outcomes, allopurinol dose or the proportion of participants sustaining flares between the two treatment arms after 12 months. Given the success of this dose optimisation at study entry we believe that the improved outcomes seen at the end of year two are best explained by the impact of ongoing close support offered to participants in the 2-monthly monitoring arm. We also acknowledge that our primary outcome is influenced by dropouts from the annual monitoring arm. An intention-to-treat analysis was chosen in order to avoid potential bias from non-adherent patients dropping out disproportionately from the more intrusive 2-monthly monitoring arm. In the event we observed a high retention of participants in the 2-monthly monitoring arm emphasising that this approach was very well tolerated. Conversely 4 (14.8%) of 27 participants dropped out of the annual monitoring arm suggesting that the greater problem is disengagement with care associated with more distant, annual review. Our patients were predominantly recruited from secondary care, rather than primary care where most patients with gout are managed limiting the generalisability of our conclusions, and the GoutSMART app that we have used to communicate with patients remains an in-house development of a single health board that is not available outwith NHS Lothian. The requirement to use a smartphone for communication of results will exclude some patients though only 6 (6.5%) of 92 screened patients in the feasibility trial were excluded on this basis, with this number expected to decline over time.

Our study highlights the potential benefits of involving patients in their own care, with a supported self-management approach transforming outcomes and adherence to therapy in gout, which is often an outlier condition for poor outcomes and low adherence to therapy [7]. This has been made possible by urate point-of-care tests which are widely available, cheap and in our experience well tolerated, however they are not widely used, and we have not shown that their provision in isolation would yield improved results. Despite the unique role of urate in measuring treatment effectiveness and compliance, interpretation of results is often challenging particularly when flares occur with normal urate levels. We note also the experience from home blood pressure monitoring in patients with hypertension associated morbidity, where the benefit from home monitoring was only seen in trials that provided active feedback or tailored support to submitted readings, whilst low intensity interventions with automatic or no ongoing feedback resulted in no benefit [18]. Accordingly our supported self-management approach offered direct result interpretation and treatment advice in response to submitted urate or flare diary updates, and we encourage anyone looking to use point-of-care urate testing to ensure that readings are incorporated directly into the clinical care pathway.

In conclusion 2-monthly urate monitoring is associated with improved maintenance of urate target over 2 years when compared to annual monitoring in patients on urate lowering therapy that have achieved urate target. We observed good clinical outcomes for most participants over 2 years of follow up, but a smaller number of flares, and proportion of participants with flares, was seen with 2-monthly monitoring compared to annual monitoring suggesting that this ongoing close engagement improves long term clinical outcomes. We acknowledge that further trials exploring the cost-effectiveness of this intervention, as well as trials exploring differing monitoring frequencies are now needed to confirm this finding and establish best practise in continuing care for patients with gout.

Supplementary materials

The supplementary table for this article is available at: https://www.explorationpub.com/uploads/Article/file/100775_sup_1.pdf.

Declarations

Acknowledgments

Study results were presented as an oral communication at the 15th European Crystal Network workshop in 2024.

Author contributions

PLR: Investigation (principal investigator of the study), Supervision, Validation, Writing—original draft. DA: Methodology, Investigation (development of study documents and review of participants). CB: Investigation (obtained community prescribing data), Formal analysis, Validation. HA: Investigation (reviewed the hospital records for all participants). RH: Formal analysis, Writing—review & editing. AK: Software (developed the GoutSMART app and webportal), Data curation (provided IT support throughout the study). The corresponding author affirms that the manuscript is an accurate and transparent account of the study. All authors have had direct access to all study data and PLR has verified the findings presented. All authors have contributed to and approved the final manuscript.

Conflicts of interest

None of the authors have any conflicts of interest to declare.

Ethical approval

Ethical approval was obtained from South East Scotland Research Ethics Committee (Reference 18/SS/0031) and NHS Lothian Caldicott Guardian. The extension trial protocol has been uploaded with the results of the feasibility trial on ClinicalTrials.gov, NCT03274063.

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Not applicable.

Availability of data and materials

Data will be shared on reasonable request to the corresponding author. Study protocol is submitted as a supplementary file.

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