Patient-led urate self-monitoring to improve clinical outcomes in people with gout: a feasibility study

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Abstract

Objective. Self-monitored, point-of-care urate measuring devices are an underexplored strategy to improve adherence to urate-lowering therapy and clinical outcomes in gout. This study observed patient-led urate self-monitoring practice, and assessed its influence on; allopurinol adherence, urate control, and health-related quality-of-life.

Methods. People with gout (n=31) and prescribed allopurinol self-monitored their urate concentrations (HumaSens2.0^{plus}) at baseline and thereafter monthly for 12 months (3 months per quarter). Adherence to allopurinol was measured using medication event monitoring technology (MEMS® cap). Time spent below target urate concentration (<0.36 mmol/L) was determined. Health-related quality-of-life was measured using a survey (EQ-5D-5L). Gout flares were recorded. Two-tailed Spearman correlation and Wilcoxon matched-pairs signed-rank test (p<0.05) were used for statistical comparisons.

Results. Most participants were male (94%) with urate concentrations below target (74%) at baseline. Overall, seven participants demonstrated repeated periods of "missed doses" (≤2 allopurinol doses missed consecutively) and "drug holidays" (≥3 missed). Most (94%) participants persisted with allopurinol. Time spent within target urate concentrations increased 1.3-fold (79% to 100%, p=0.346) and the incidence of gout flares decreased 1.6-fold (8 to 5, p=0.25) in the final compared to the first quarter of the study. Health-related quality-of-life was reduced for participants reporting at least one gout flare (median utility values 0.9309 versus 0.9563, p=0.04).

Conclusion. Patient-led urate self-monitoring may support the maintenance of allopurinol adherence, improve urate control, thus reducing the incidence of gout flares. Further research on patient-led urate self-monitoring in a randomised controlled study is warranted.

Significance and Innovations

- Point-of-care urate testing may improve gout management by supporting medication adherence and attaining clinical targets.
- Time within target urate concentration may be increased the longer people with gout self-monitor urate.
- The incidence of gout flares may be decreased the longer people with gout self-monitor urate.

Gout is a chronic inflammatory arthritis characterised by acute episodes of painful joints, known as 'gout flares'. The acute inflammation is triggered by monosodium urate crystals in joint synovial fluid, often associated with chronically elevated urate concentrations (1). Despite effective urate-lowering therapy (ULT; *e.g.,* allopurinol) for long-term management, up to 50% of people with gout discontinue therapy within the first six months (2). Patient-reported factors that influence ULT adherence behaviour include; understanding of ULT and its importance for preventing gout flares, and experiences of healthcare professionals providing gout management advice (3). An intervention which addresses these factors should improve ULT adherence and support attainment of target urate concentration (<0.36 mmol/L (4)), thereby decreasing the incidence of gout flares. As gout flares are associated with poor quality-of-life (*e.g.*, decreased work productivity and self-care (5)), such an intervention may also improve social outcomes.

Previous interventions to improve gout management that account for ULT adherence have been pharmacist-led, nurse-led, shared-care (reviewed in (6)), and patient-centred (7). While the impact of these interventions on ULT adherence appear positive, the reporting of adherence measures is poor and must be interpreted carefully (6). Further, only a nurse-led intervention improved ULT adherence while also accounting for persistence (8,9,10). The high rate of discontinuation and re-initiation of ULT (11), and the lack of appropriate measurement of adherence in gout, particularly for persistence, may, in part, explain the limited effect of these interventions on urate control.

Researchers designing interventions to improve gout patient adherence may benefit from reflecting on other chronic conditions, where patient-led self-monitoring services improve medication adherence (12) and clinical outcomes, such as blood pressure control (13) in hypertension. The benefits of self-monitoring using a biomarker is recognised globally (14),

with The World Health Organization stating the approach fosters active patient participation in their healthcare (15). Consequently, point-of-care (POC) devices for blood glucose are subsidised in many countries (*e.g.,* the National Diabetes Services Scheme in Australia (16)). However, despite having; effective medications, a measurable biomarker, and POC devices available, self-monitoring remains underexplored in gout (7). Given that people with gout's understanding of ULT and gout flares impacts their persistence (3), urate self-monitoring may support and develop patient understanding of how ULT impacts gout, thereby facilitating adherence. This observational proof-of-concept feasibility study aimed to examine patient-led urate self-monitoring by assessing the impact of this practice on their; adherence to allopurinol, urate control, incidences of gout flares, health-related quality-of-life and medical resource use.

Participants and Methods

Study design and participants

This observational proof-of-concept feasibility study (Australian and New Zealand Clinical Trial Registry: ACTRN12621001730897) was conducted from June 2021 to April 2023 (see Supplementary Data S1 for additional details). Ethical approval was obtained from the University of Sydney Human Research Ethics Committee (HREC 2021/216). Participants across Australia were recruited from a database of people with gout interested in participating in research (created by the Gout Self-Management App study (17), which included some gout education) and through advertisements in social media. Recruitment was stratified (1:1 rural to urban) with rurality assessed using the postcode Remoteness Area rating (18).

Eligible participants were people with gout who were prescribed allopurinol at study enrolment (but may not have initiated therapy), at least 18 years old, and proficient in the English

language. People who were assisted in their medication taking were ineligible to participate. Written informed consent for participation was obtained from eligible individuals.

Study procedures

Demographic data was collected at study enrolment (Supplementary Data S1). All study procedures were conducted via telehealth and equipment was posted to participants. Participants received a POC device with associated consumables (HumaSens2.0^{plus} Multiparameter System) which determines urate concentration using a capillary blood sample (*i.e.,* finger prick), and were trained on device use by JC using video conferencing. Accuracy of the device is comparable to pathology testing (19,20). Participants also received their allopurinol every 3 months, as prescribed by their healthcare professional. A Medication Event Monitoring System cap (MEMS®, Aardex) recorded the date and time of bottle opening as a proxy for medication taking.

Participants manually recorded (*e.g.*, a written record, or text sent to a study investigator) urate concentrations using the POC device at least once a month for 12 months. Consumables (25 testing strips every 3 months) were provided to test more frequently as dictated by the participant. Urate concentration data were collected during monthly telehealth visits (approximately 5 minutes) with a study investigator (TM or JC). Data from the MEMS® cap was uploaded by participants through a mobile phone application during each telehealth visit. In addition, urate data and information on any gout flares and/or adverse events experienced were reported. Participants were informed that staying below target urate concentration (0.36 mmol/L) reduces their risk of gout flares. After each visit, participants were provided a graphical representation of their urate concentrations, including the urate target. Participants

were aware their medication-taking behaviour was monitored but were not provided this data. At study conclusion, the POC device and MEMS® cap were returned to study investigators.

Based on MEMS®, gout flares and urate data, the study clinician RD (rheumatologist) could recommend a change in allopurinol dose to the participants' prescriber. Dose adjustments remained at the discretion of the prescriber and were communicated to study investigators by participants. Gout flares were defined (21) and reported to study investigators immediately or during telehealth visits.

Operational definitions of adherence

We used the proposed timelines-events-objectives-sources (TEOS) framework (22,23) and the International Society for Medication Adherence (ESPACOMP) Medication Adherence Reporting Guideline (EMERGE) (24) to ensure suitable operationalisation, quantification and consistent adherence reporting (Supplementary Data S1). Adherence phases were defined as;

1. Initiation: a delay of >7 days between the prescription of allopurinol and the first dose recorded by the MEMS® cap was considered non-initiation of study drug. Participants already taking allopurinol were dispensed a new supply.
2. Implementation: variability in the implementation of allopurinol was defined using an adaption of Urquhart's 'Rule of Sixes' (25). Observed patterns of suboptimal implementation were defined as 'missed doses' and 'drug holidays', categorised by the number of adherent days after the period of missed doses (Figure 1). Each participant was assigned an 'implementation type' based on their most common pattern observed.
3. Persistence: participants who did not open the pill bottle for ≥30 consecutive days were assumed to have stopped allopurinol.

154 ***Health-related quality-of-life, healthcare utilisation and costs***

155 Participants completed the EuroQoL EQ-5D-5L questionnaire (26) at baseline and at 3-, 6-, 9-
156 , and 12-month follow-ups, and when experiencing a gout flare to determine their health-related
157 quality-of-life. A health utility score (ranging from -0.301 to 1) was generated at each timepoint
158 using an Australian value set (27).

159

160 Medical resource usage was collected at baseline and at 1-, 2-, 4-, 6-, 9-, and 12-month follow-
161 ups using a questionnaire (28) adapted for gout (Supplementary Data S1). Data are reported as
162 counts of items of resource use. A comparison of the expected direct costs of a self-monitoring
163 service to the medical costs of a gout flare was undertaken.

164

165 ***Statistical analysis***

166 Demographics were analysed using descriptive statistics. The period urate concentrations were
167 <0.36 mmol/L was determined using linear interpolation method (29). When applicable, data
168 was described in monthly increments or as study quarters (3 months per quarter). The
169 relationship between self-monitoring events and measured outcomes were assessed using two-
170 tailed non-parametric Spearman correlation or Wilcoxon matched-pairs sign ranked test
171 (p<0.05) using GraphPad PRISM (v9.5.0) and R Studio (v2022.12.0+353). For participants
172 lost to follow up, MEMS® and urate data were analysed up to the last datapoint collected. For
173 adherence analysis, data prior to dose escalation was excluded when applicable.

174

175 Summary utilities were determined for each participant by calculating the area-under-the-curve
176 for the utility scores using a trapezoidal method. Trends in the utility scores over time were
177 assessed using linear mixed modelling. Utility and EQ-VAS scores were compared at baseline
178 and month 12, and in the presence and absence of gout flares using Stata (v17.0)

(Supplementary Data S1). The EQ-VAS score (from 0 to 100) represents the participant's self-assessment of their health (0 being the worst health imaginable, 100 being the best).

Results

Participant characteristics

In total, 32 people with gout were enrolled, with one participant withdrawing (Figure 2). Participants were predominantly male (94%) and over 50-years old (74%, range 34-86 years old) (Table 1). Most participants were diagnosed with gout over 10 years ago (89%, range 5-45 years) and had been prescribed allopurinol for at least 5 years (71%, range 0-40 years). At baseline, the most common dosing regimen of allopurinol was 300 mg once daily (55%, range 100-600 mg; one participant took 300 mg every second day). The average urate concentration at baseline was 0.33 mmol/L (range 0.20-0.57 mmol/L). Most (63%) participants had not received specialist care for their gout. Information on participant care at baseline is provided (Table 1).

Self-management and urate control

Participants self-monitored reliably, with lancing technique and device battery changes being the only issues reported. Collectively, participants recorded their urate concentration 831 times (Figure 3). One participant did not report a 12-month urate concentration (loss of contact). Each participant recorded their urate on average 18 times (median; 1.5 times per month, range 1.1-6.5 times per month), and measured consistently throughout the 12 months (quarter 1, 5 readings per participant (median, range 3-22); quarter 4, 4 readings per participant (median, range 3-26); p=0.17).

Nine participants were within target urate and one participant was above target urate for the entire study. For each participant, urate concentrations fluctuated on average by 0.19 mmol/L (range 0.08–0.40 mmol/L) throughout the study. The proportion of time a participant's urate concentration was within target range increased by 1.3-fold (study quarter 1, 79%, study quarter 4, 100%, p=0.35) (Figure 4A).

Six participants up-titrated their dose of allopurinol (*e.g.*, Figure 5A), and one participant switched to febuxostat (Figure 5B) after recording urate concentrations above the target. While allopurinol dosing recommendation letters were provided to the participants' general practitioner, participants told study investigators that they were the ones who instigated the conversation with their general practitioners about their dose during their standard consult.

Almost half (48%) of the participants reported a gout flare. Of these, seven reported experiencing more than one gout flare. The incidence of gout flares decreased 1.6-fold (quarter 1, 8 gout flares; quarter 4, 5 gout flares; p=0.25) (Figure 4B).

Self-management and adherence

The impact of self-monitoring urate concentrations on attainment of target urate concentration, adherence to allopurinol, and optimisation of allopurinol dose is illustrated with representative case examples (Figure 5). For four participants, there was a notable decrease in urate concentrations (p<0.02). For some participants, self-monitoring did not impact their adherence behaviour or their urate concentration (*e.g.*, Figure 5C).

Twenty-nine participants had complete adherence data, over a median period of 364 days. Two participants had incomplete adherence data, recording up to Day 305 (last two months missing)

and Day 368 (last nine days missing). There were 1315 missed doses of ULT during the study, with a median of 32 per participant (range 1-180). Further, 91.2% (median, range 37.3-99.7%) of doses were taken as prescribed.

Initiation

One participant commenced allopurinol during the study, as they had received a script for allopurinol just prior to enrolment. The remaining participants had already initiated ULT.

Implementation

Overall, 773 events indicative of suboptimal implementation were identified, including; 58 occasional missed doses, 619 repeated missed doses, 92 repeated drug holidays, 4 occasional drug holidays. One participant recorded "perfect" implementation with consistent alignment between the prescribed and actual dose taking for the entire study period. For the remaining participants, five different 'implementation types' were identified (Supplementary Table S1): 1) no missed doses (n=2), 2) predominantly occasional missed doses (n=4); 2) predominantly repeated missed doses (n=8); 3) both repeated missed doses and repeated drug holidays (n=7), and 4) a mix of occasional missed doses and repeated missed doses (n=10). No obvious trends in implementation types over time were observed (Supplementary Table S2).

Persistence

Overall, 29 participants persisted with allopurinol (most consecutive missed doses, median 4 days, range 2-35 days). For the two participants who discontinued therapy, one had recorded urate concentrations above 0.36 mmol/L and ceased allopurinol for 35 days. The participant then switched to febuxostat (treatment duration two months), but consequently ceased febuxostat and re-initiated allopurinol 26 days later (Figure 5B). The other participant had self-

recorded urate concentrations below 0.36 mmol/L. At study completion, 30 days after discontinuing allopurinol, their urate concentration was 0.52 mmol/L (Figure 5D).

Health-related quality-of-life, health-care utilisation and costs

Individual utility and EQ-VAS scores are presented in the Supplementary material (see Supplementary Figures S1 and S2, Tables S3 and S4). There was no trend in the utilities and EQ-VAS scores over time, so linear mixed modelling was not conducted. The median utility score was 0.96. Utilities were >0.9 throughout the study for 16 participants, regardless of gout flare occurrence. The median EQ-VAS score was 80.00.

The median utility score (0.96 and 0.96, p=0.59) and EQ-VAS score (80 and 80, p=0.63) at baseline and month 12 values did not change. The median utility and EQ-VAS scores during a gout flare were lower than at other times (0.92 versus 0.96, p=0.0056 and 70 versus 80, p=0.0042, respectively). For participants who experienced at least one gout flare, the median utility and EQ-VAS scores were lower compared to those who did not experience a gout flare (0.93 versus 0.96, p=0.039, 80 versus 84, p=0.0027, respectively).

Self-reported medical resource use is summarised in the Supplementary material (Supplementary Table S5). The comparison of the expected costs of a self-monitoring service and the reported medical costs of a gout flare (*e.g.*, medications, clinician time) is presented in Supplementary material (Supplementary Table S6). The self-monitoring service is expected to cost about AU$285 per annum per person, while the reported cost of gout flares (adjusted for inflation) ranges from about AU$390 to >AU$4000 per flare.

Discussion

Self-monitoring urate concentration may support people with gout to adhere to their ULT, attain and maintain target urate concentration, thus reducing the incidences of gout flares. Incidentally, this may provide a rationale for dosage up-titration. Our study is the first to determine the impact of urate self-monitoring on urate control and ULT adherence behaviour while considering important clinical variables, such as urate concentration, gout flare frequency, health-related quality-of-life and medical resource use. As a proof-of-concept feasibility study, our findings support large-scale evaluation of gout patient-led self-monitoring of urate.

Time spent within target urate concentration increased with urate self-monitoring.

The increased time spent within target urate concentration range suggests that urate self-monitoring fosters practices that improve urate control, such as adherence to ULT. Our findings are consistent with a patient-centred study where urate self-monitoring facilitated the attainment of target urate concentration in 80% of people with gout (7). Many variables impact urate concentration beyond adherence to ULT such as hydration, weight, diet, time of the day, and taking other medications (30). Regular self-monitoring of urate enables people with gout to self-assess how their behaviour influences their urate control, which can motivate people to modify their behaviour to achieve optimal urate control. This goal setting requires the patient to know the target urate concentration. The behavioural impact of urate self-monitoring aligns with the COM-B Framework (31) where the ability to use a urate device (Capacity), having access to a urate device (Opportunity), and an understanding of the target urate concentration (Motivation) encourages 'behavioural change' such as improved ULT adherence. This is analogous to people with diabetes, self-monitoring glucose (32) and modifying their behaviour to achieve optimal glucose control (33).

Urate concentrations within an individual varied (even with the same allopurinol dose), irrespective of their adherence and time spent within the target urate. This biological variation should be considered when interpreting a urate concentration in isolation. Additionally, while the trigger of a gout flare remains unclear, there is evidence that fluctuations in urate concentrations may increase the risk of a gout flare (34). Trends in urate concentration over time may better reflect an individual's urate control to inform clinical decision making, especially periods of urate fluctuation.

The incidences of gout flares decreased with urate self-monitoring.

The frequency of gout flares decreased in the last six-months of self-monitoring, which might reflect improvements in urate control. Whilst this could reflect regression towards the mean (35) people also may have identified dietary triggers for gout, allowing them to subsequently avoid certain foods. Additionally, access to a POC urate device enabled participants to identify elevations in urate concentration, thereby identifying a greater risk of painful gout flares, consequently adjusting behaviour to lower their urate. This behaviour is consistent with the fear of hypoglycaemia in people with diabetes, encouraging glucose self-monitoring to ensure adequate glucose control (36).

Allopurinol implementation is variable, even in persistent people.

Our participants were persistent in taking allopurinol, with only two participants discontinuing therapy over 12 months. This may reflect the real-time feedback on their urate control provided by self-monitoring urate, as participants could contextualise their behaviour (including medication taking), while informing medication decisions and gout understanding. This is consistent with the effect of self-monitoring glucose in people with diabetes on adherence to antiglycaemic medication (33). This ability to reflect on real-time feedback on urate control

may also allow for people who struggle to initiate ULT to engage more with their new medication. Our participants were also motivated; most had been prescribed allopurinol for over 5 years (so they had overcome initiation barriers (3)). Given that most people with gout discontinue ULT within six-months of their first prescription (2), the evaluation of urate self-monitoring in people with gout who are initiating or re-initiating ULT would be of interest, as real-time feedback on urate control may assist in encouraging people with gout to persist with ULT, particularly when the risk of gout flares is high.

Importantly, awareness of adherence monitoring does not impact participant adherence behaviour (37). Despite being persistent, participants demonstrated variation in their allopurinol adherence behaviour, with repeated and patterned missed doses. Forgetfulness, continuing to experience gout flares whilst on therapy (*i.e.,* belief medication is not working), or experiencing less gout flares whilst on therapy (*i.e.,* belief medication is no longer necessary) are possible reasons for irregular allopurinol dosing (3). However, allopurinol appears to be a forgiving medication (38), with participants urate control being adequate despite these missed doses.

People with gout change their behaviour in response to urate concentration.

For our two discontinuers, urate self-monitoring influenced their decisions to cease therapy. One discontinued ULT in response to poorly controlled gout (*i.e.,* elevated urate concentrations, experiencing gout flares regularly), while the other had well controlled gout (*i.e.,* achieved target urate concentrations, absence of gout flares). A perception that ULT is ineffective or unnecessary are common reasons for discontinuing ULT (39), particularly in the absence of feedback on urate control. Interestingly, both discontinuers re-initiated allopurinol after reassurance that ULT was effective/necessary from self-monitoring their urate during

their period of non-persistence. This highlights the ability of self-monitoring interventions to provide opportunities for shared decision making with relevant healthcare professionals informed by patient-recorded evidence.

Urate self-monitoring provides real-time data to inform patient-led shared decision-making with clinicians (*e.g.,* aid with ULT prescribing, as experienced by some of our participants) and/or pharmacists (*e.g.,* supporting people when dispensing ULT). Further, many people with gout express the desire to suspend their ULT (39). Urate self-monitoring may help to inform the optimal duration of these drug holidays (40) in consultation with their healthcare professional. By empowering people with gout to contribute to, and to take charge of, their gout management, this approach may evolve from self-management towards self-efficacy (41).

Patient-led urate self-monitoring is feasible.

This study provides preliminary evidence to support further research on patient-led urate self-monitoring through a randomised controlled trial. Our data suggests that a urate self-monitoring service has the potential of being cost neutral if one gout flare per annum is avoided. Further, delivery of the service was equitable, as all study procedures were delivered by telehealth, enabling people with gout in rural regions who face barriers to accessing healthcare (42) to participate. Additionally, our participants valued the opportunity to self-monitor urate, as evident by our low withdrawal rate and minimal missing data. Further, the brief interactions with study investigators allowed participants to integrate urate self-monitoring into their routine. Engaging stakeholders to identify the barriers and facilitators to implementation of urate self-monitoring are essential. Future research should consider including people with gout at different stages of adherence, particularly those initiating ULT in whom persistence is often poor. Engaging people with gout whose urate concentration is consistently above target, or

persist with gout flares despite taking allopurinol beyond initiation is also required. Further examination of the cost-effectiveness of long-term self-monitoring of urate on a larger scale is also required to understand the healthcare benefits of this intervention.

Study Design Limitations

A limitation of our study was restricting recruitment to people with gout who were already prescribed ULT, thus we are unable to assess the impact of urate self-monitoring on the desire to initiate ULT. Additionally, participants with target urate at baseline were recruited. Therefore, the findings from this study are potentially conservative. Despite this, they still experienced gout flares and were able to derive benefit from self-monitoring urate. We also recruited from a database of people with gout interested in research, some of whom had participated in previous gout management studies, and as such are likely motivated to manage their gout. Supplying allopurinol to participants may have improved adherence to ULT as this removed the inconvenience of collecting a new script, a known barrier to medication adherence (43).

Conclusions

Patient-led urate self-monitoring by people with gout using a POC device may support their adherence to ULT. When people with gout could self-monitor urate, they maintained target urate concentration, and experienced a reduced incidence of gout flares. This approach to gout management has the potential to shift clinical practice towards empowering people to be invested in their gout management. Through research on intervention implementation, there is potential to establish a subsidy program analogous to those in place for other conditions that encourage self-monitoring. Further, a patient-led approach considers accessibility of individuals for whom specialist care is unaffordable and/or inaccessible. By allowing people

403 to generate their own record of urate concentrations, people with gout will play a fundamental
404 role in conversations with their healthcare professional and foster condition self-ownership.
405
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Tables

Table 1. Baseline characteristics of people with gout self-monitoring their urate concentrations.

Baseline Characteristic	Participants (N=31)
Age, years	60 (34-86)
Male gender, n (%)	29 (94%)
Living in an urban* area, n (%)	17 (55%)
Allopurinol dose (mg/daily), mode (range)	300 (100-600)
Urate concentration (mmol/L)	0.33 (0.20-0.57)
Years since gout diagnosis	21 (5-45)[a]
Years since first allopurinol prescription	11 (0-40)[a]
Years between gout diagnosis and first allopurinol prescription	9 (0-37)[a]
Seen a rheumatologist and/or a specialist for their gout, n (%)	11 (37%)[b]
Have urate concentration pathology tests every 12- months, n (%)	10 (33%)[b]
Received an explanation of how allopurinol works by their healthcare professional, n (%)	16 (53%)[b]

Data reported as mean (range), unless stated otherwise.

*Australian Statistical Geography Standard Remoteness Area (RA) Category 0.

[a] Out of 28 participants.

[b] Out of 30 participants.

Figure Legends

Figure 1. Flow chart of ULT implementation terminology.

Figure 2. CONSORT diagram. Urban location was based on a Remoteness Area category of 0 from the Australian Statistical Geography Standard (inner regional = 1, outer regional = 2).

Figure 3. Urate concentrations self-measured by participants (N=31) using a point of care device (HumaSens2.0^{plus} Multiparameter System). Dashed line represented the recommended target urate concentration range (< 0.36 mmol/L). The final study visit for eleven participants exceeded 365 days (range 305-396 days), reflecting the availability of participants.

Figure 4. Change in clinical outcomes with urate-self-monitoring. The proportion of time (median time % ± 95% CI) spent within the urate concentration target range (**4A**) and the number of gout flares (**4B**) per quarter for 31 people with gout self-monitoring urate concentrations over 12 months. Q#: study quarter (each lasting 3-months).

Figure 5. Examples of participant experiences urate self-monitoring and their corresponding adherence behaviour. Urate concentration: black line, left axis. ULT adherence: grey line, right axis, measured using MEMS®. Asterisks denotes a gout flare. Arrow represents change in ULT therapy (e.g., dose alteration). Dashed line: target urate concentration (<0.36 mmol/L). **5A**: participant up-titrated allopurinol dose after recording elevated urate concentration, subsequent concentrations were within target. **5B**: participant discontinued allopurinol. Continued to record elevated urate and returned to therapy. Subsequent concentrations were close to or within target. **5C**: participant was persistent, urate concentrations were within target. **5D**: participant was persistent, recorded urate concentrations within target. Ceased allopurinol, recorded a concentration above target.

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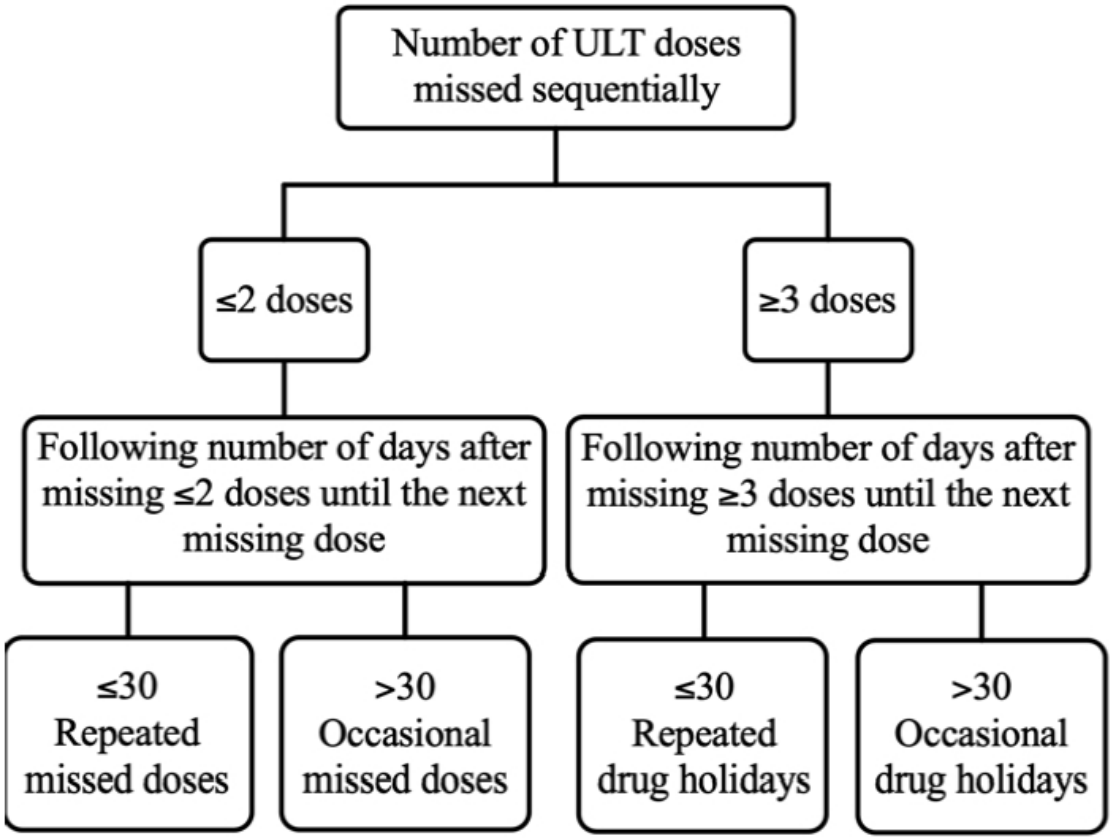
569 Figure 1



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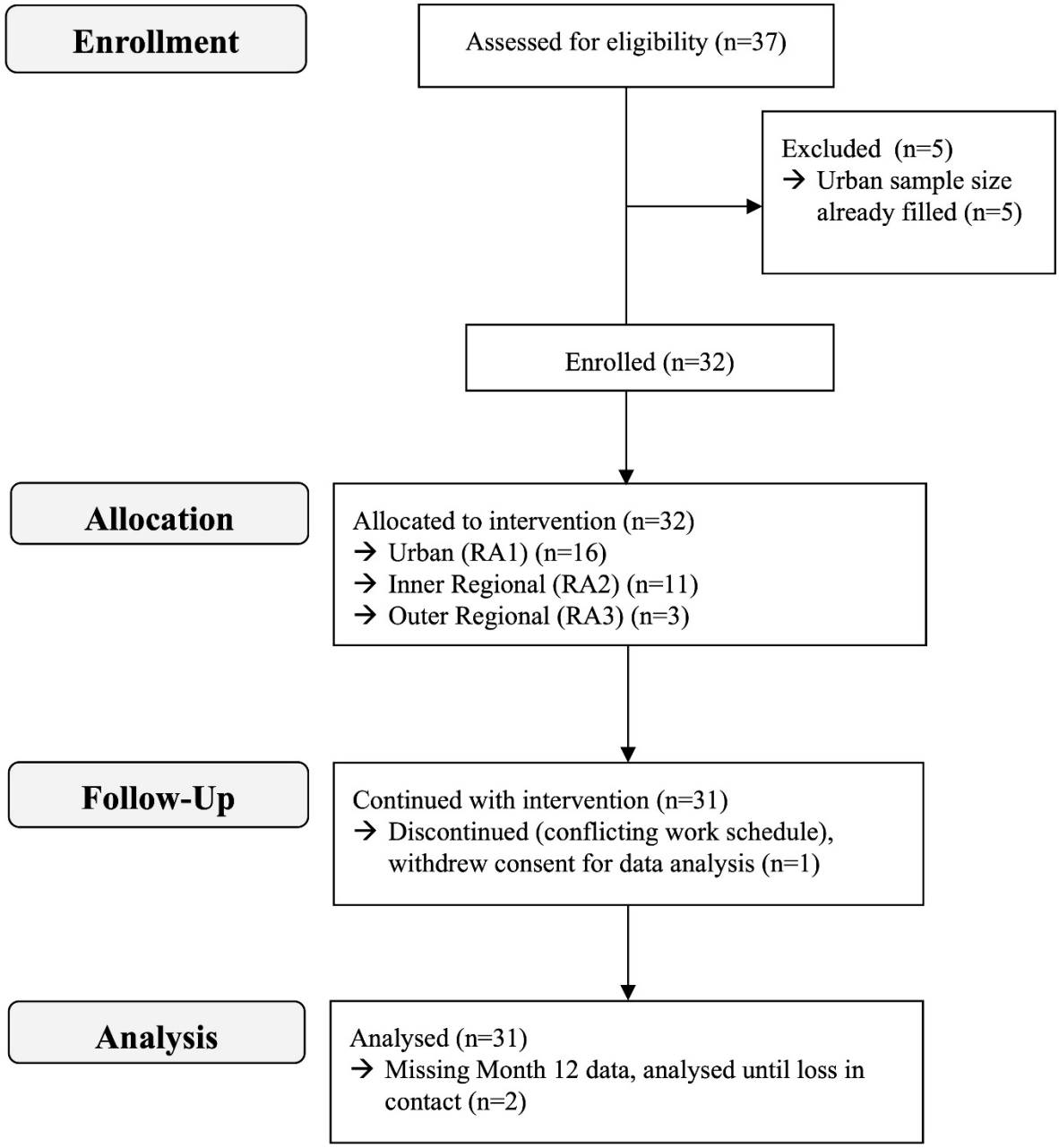
572 Figure 2



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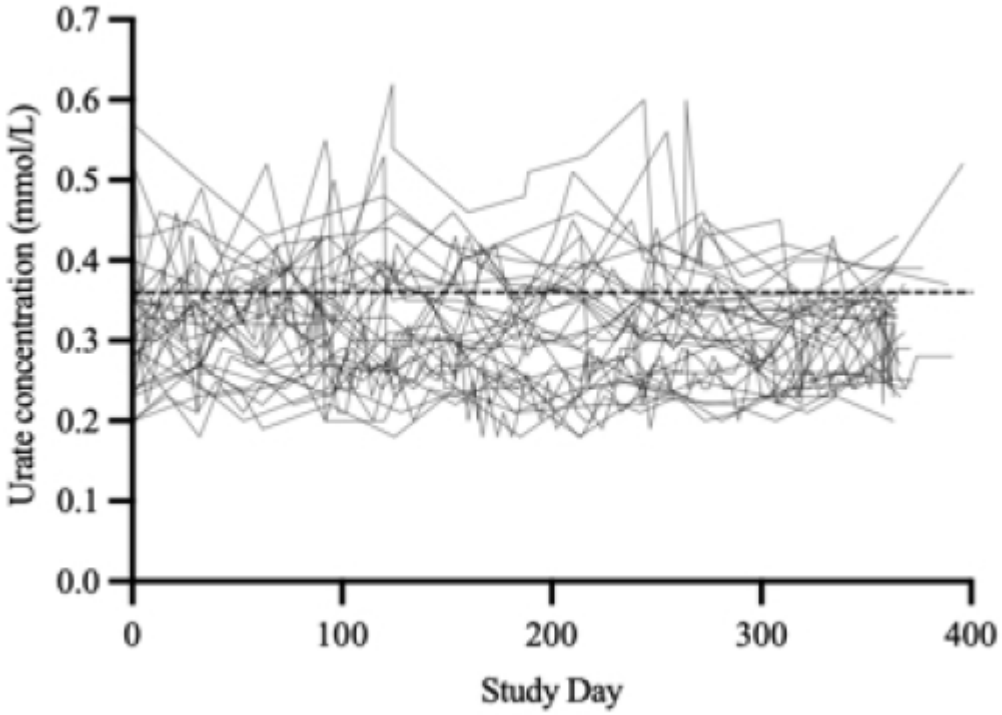
575 Figure 3



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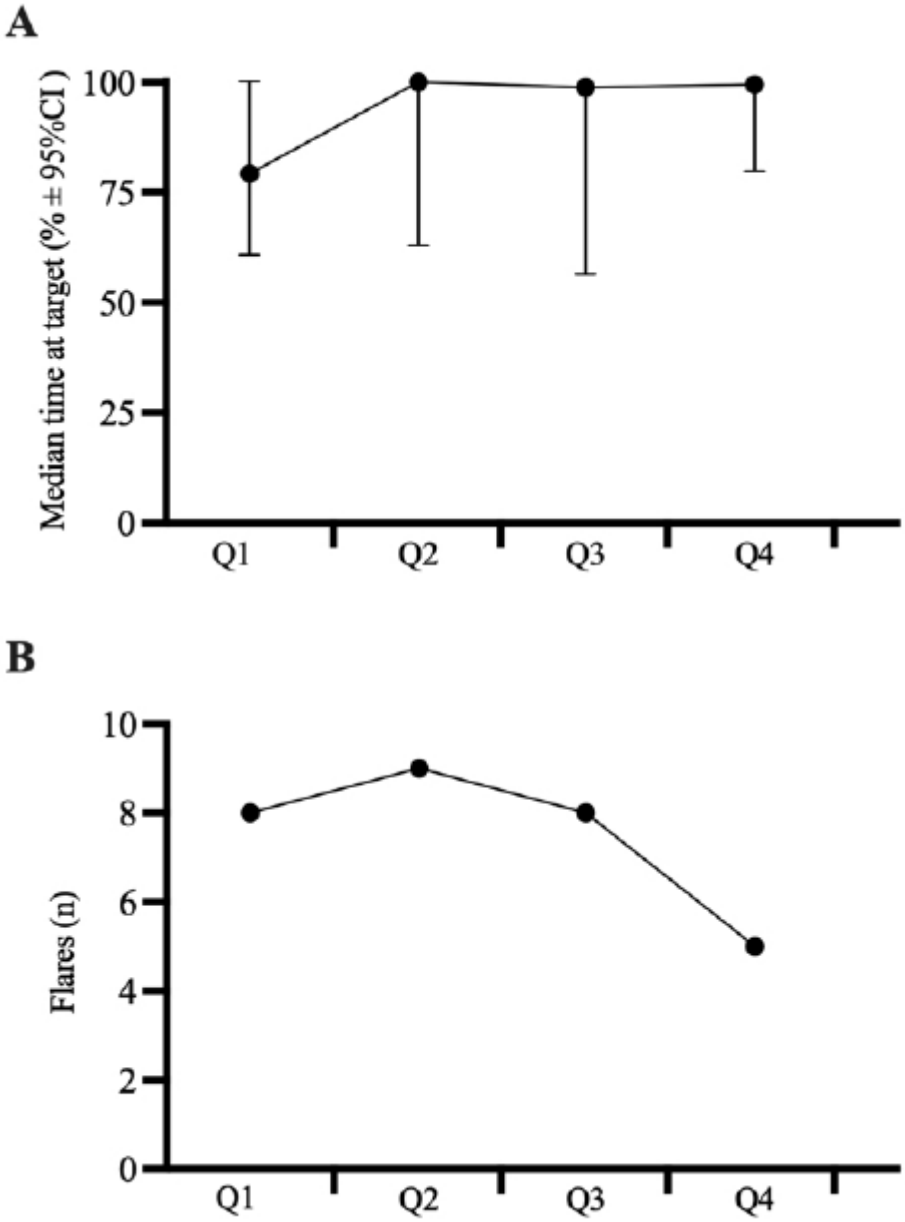
578 Figure 4



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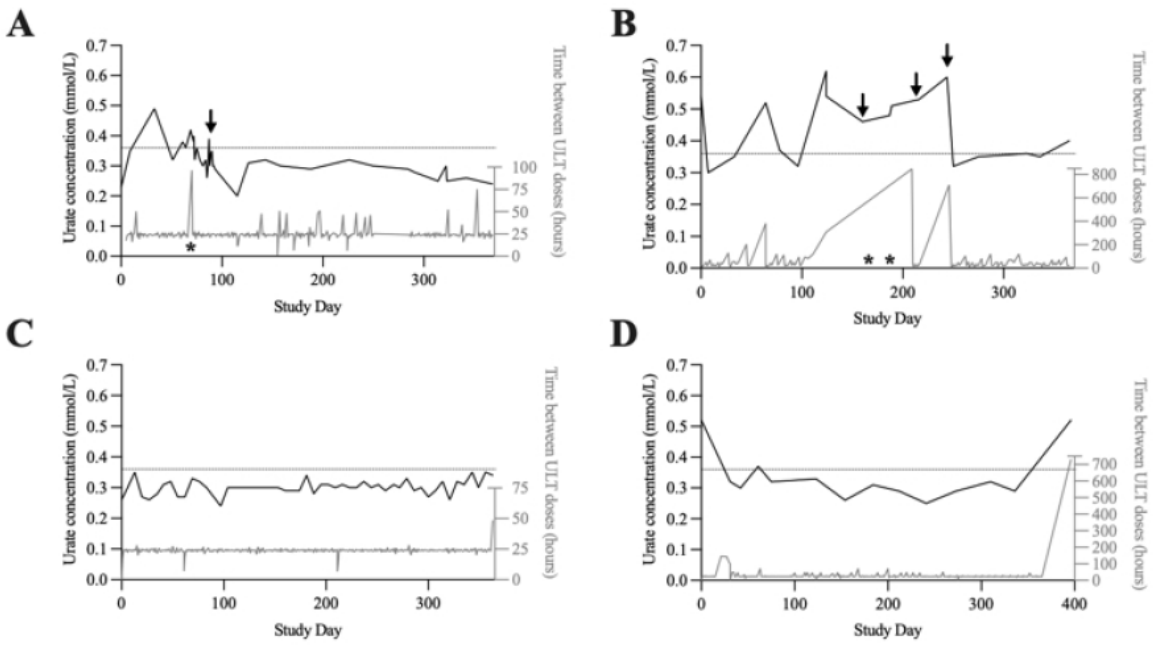
581 Figure 5



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