PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Patient reported gout attack frequency and allopurinol use in general practice in the Netherlands: a prospective observational cohort study protocol
AUTHORS	van Leeuwen, Kevin; Bohnen, Arthur; Jacobs, Marloes; van Der Lei, Johan; Janssens, Hein J.E.M.; Koffeman, Aafke R.; Bindels, Patrick; Bierma-Zeinstra, SM

VERSION 1 – REVIEW

REVIEWER	Dr James A Prior Keele University, UK
REVIEW RETURNED	30-May-2018

GENERAL COMMENTS	The authors present an interesting study protocol outlining their intention to examine the association between the frequency of attacks experienced by gout patients and the use of allopurinol as a urate-lowering therapy. This is an important area of research which requires clarification. As the authors rightly point out, though we know allopurinol reduces serum urate and that the evidence points to a reduction in gout attacks as a result, the evidence to directly support this remain allusive. Below I have provided some comments which may help with the clarity of the manuscript. Title I'd make reference to allopurinol in the title, this will more accurately depict the purpose of the paper and make it more distinct from other work examining gout attacks Abstract – Methods & analysis • Line 21 – At present this reads like gout attack is the exposure, not the outcome. You've actually defined your cohort as those with gout (using a consultation code), so please amend to reflect this. • Line 26 - At present, the third sentence makes it sound like you'll be collecting all data every 3-months, rather than just the attack data. Make it clear that all data is collected at baseline, 12 and 24-months, but attack data will be collected every 3-months (as per your table). • Line 28 – Your primary outcome is frequency of gout attack, but what do you mean by frequency, is this mean at 24-months? I think this might be best because initiation of allopurinol can induce attacks, so you may get an artificially high number of attacks early on. It can also take between 6-9 months for number of flares to begin to drop • Line 34 – Your analysis statement could be clearer. Perhaps something to the effect of "Multilevel Poisson regression analysis will be used to examine the association between the number of gout attacks at 24-months(?) experienced by gout patients using

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	allopurinol compared to those gout patients not using this treatment." Strengths & limitations • I think you need to highlight an additional limitation around your allopurinol treatment cohort. You plan to use a prevalent gout sample and therefore there will be variation in treatment duration. Some of your treatment cohort could have been receiving allopurinol for years, others potentially just days. If allopurinol is associated with attacks then treatment duration may affect your findings. It would have been useful if you could have measured serum urate at 24-months to determine if urate had reached guideline target levels to help you understand the role of allopurinol. Background and rationale • Page 5, line 21 – I disagree that gout is often managed with ULT. Despite clear guidelines and benefits, (in the UK) only 30% of patients are prescribed allopurinol and, of those, only 40% have treatment escalated to achieve the target serum urate level<360µmol/L, suggesting that many patients with gout could receive better treatment (Cottrell E, Crabtree V, Edwards JJ, et al. Improvement in the management of gout is vital and overdue: an audit from a UK primary care medical practice. BMC Fam Pract 2013). Please amend this sentence to reflect this. Also I wouldn't say this treatment in "controversial", it is recommended by BSR, EULAR & ACR guidelines. However, I do agree there is limited data regarding patient outcomes. Again, please make this sentence clearer Methods • As you are recording serum urate at baseline, please indicate in the methods if you will be stratifying those patients in the treatment cohort who are below or above 360µmol/L (target level). It would be important to know if some of the sample have actually reached target serum urate levels at baseline • Page 6, line 51 – Please state what "ICPC" is in full as first usage Sample-size calculation • Page 7, line 21 – I'm unclear how you arrived at n=681 and then state that you'll have a treatment cohort of n=227? Do you expect a response rate of 33%? Also you've not indicated an expected % loss to follow-up, this will be important to when your primary outcome is (i.e. attacks at 12-months or 24-months). Please clarify Data collection and research measures Page 8, line 6 – BMI is calculated using height, not length. This also need correcting in Figure 1 Data analysis Page 9, line 43 – I think "treatment allopurinol" needs to be "allopurinol reatment"

REVIEWER	A/Prof Philip Robinson University of Queensland Faculty of Medicine Brisbane, Australia
REVIEW RETURNED	09-Jul-2018

GENERAL COMMENTS	The comment in the introduction "Such treatment is controversial, as there is hardly any evidence that it actually reduces the gout attack frequency and/or resolves tophi if present, or prevents long term joint damage" is not accurate. While I acknowledge that RCT evidence is lacking, the body of total evidence supports its use and,

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	as a result, allopurinol treatment is recommended by the ACR/EULAR gout guidelines and the BSR gout guidelines. The lack of evidence does not mean lack of efficacy and therefore, as all clinicians do in clinical practice, have to make decisions based on the best available evidence. How will the 3 monthly questionnaires be given to patients, posted to them, or during a consultation with the GP, or online, further detail is needed about this and what steps will be taken (in detail) if questionnaires are not filled out by participants. The use of patient self evaluation for tophi seems very unusual, why not ask GPs to assess for tophi at the baseline visit? This seems to make this assessment highly unreliable. I cannot comment on the appropriateness or not of the propensity matching statistical methods.

VERSION 1 – AUTHOR RESPONSE

Comments Reviewer 1: Dr James A Prior

1. The authors present an interesting study protocol outlining their intention to examine the association between the frequency of attacks experienced by gout patients and the use of allopurinol as a urate-lowering therapy. This is an important area of research which requires clarification. As the authors rightly point out, though we know allopurinol reduces serum urate and that the evidence points to a reduction in gout attacks as a result, the evidence to directly support this remain allusive. Below I have provided some comments which may help with the clarity of the manuscript.

Answer: Thank you for the compliments.

2. Title
   I'd make reference to allopurinol in the title, this will more accurately depict the purpose of the paper and make it more distinct from other work examining gout attacks

Answer: We have changed the title to: Patient reported gout attack frequency and allopurinol use in general practice in the Netherlands: a prospective observational cohort study protocol

3. Abstract – Methods & analysis
   Line 21 – At present this reads like gout attack is the exposure, not the outcome. You've actually defined your cohort as those with gout (using a consultation code), so please amend to reflect this.

Answer: We have made amendments to the text to make the definition and selection process of the prospective cohort more clear.

4. Abstract – Methods & analysis
   Line 26 - At present, the third sentence makes it sound like you'll be collecting all data every 3-months, rather than just the attack data. Make it clear that all data is collected at baseline, 12 and 24-months, but attack data will be collected every 3-months (as per your table).

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Answer: we have amended the text.

5. Abstract – Methods & analysis
   Line 28 – Your primary outcome is frequency of gout attack, but what do you mean by frequency, is this mean at 24-months? I think this might be best because initiation of allopurinol can induce attacks, so you may get an artificially high number of attacks early on. It can also take between 6-9 months for number of flares to begin to drop

Answer: The frequency of gout attacks is the mean frequency during the follow up of two years. We have amended the text.

6. Abstract– Methods & analysis
   Line 34 – Your analysis statement could be clearer. Perhaps something to the effect of "Multilevel Poisson regression analysis will be used to examine the association between the number of gout attacks at 24-months(?) experienced by gout patients using allopurinol compared to those gout patients not using this treatment."

Answer: we have amended the text.

7. Strengths & limitations
   I think you need to highlight an additional limitation around your allopurinol treatment cohort. You plan to use a prevalent gout sample and therefore there will be variation in treatment duration. Some of your treatment cohort could have been receiving allopurinol for years, others potentially just days. If allopurinol is associated with attacks then treatment duration may affect your findings. It would have been useful if you could have measured serum urate at 24-months to determine if urate had reached guideline target levels to help you understand the role of allopurinol.

Answer: That is correct, we have added this additional limitation. We expect that most people already use allopurinol before the start of the study. If we see that the length of treatment with allopurinol is a confounder factor, we will adjust for it in the regression and/or stratify for the length of use.

8. Background and rationale
   Page 5, line 21 – I disagree that gout is often managed with ULT. Despite clear guidelines and benefits, (in the UK) only 30% of patients are prescribed allopurinol and, of those, only 40% have treatment escalated to achieve the target serum urate level<360µmol/L, suggesting that many patients withgout could receive better treatment (Cottrell E, Crabtree V, Edwards JJ, et al. Improvement in the management of gout is vital and overdue: an audit from a UK primary care medical practice. BMC Fam Pract 2013). Please amend this sentence to reflect this. Also I wouldn't say this treatment in "controversial", it is recommended by BSR, EULAR & ACR guidelines. However, I do agree there is limited data regarding patient outcomes. Again, please make this sentence clearer

Answer: We agree that these statements are too bold en are not completely supported by evidence. We have made amendments to the text.

9. Methods
   As you are recording serum urate at baseline, please indicate in the methods if you will be stratifying those patients in the treatment cohort who are below or above 360µmol/L (target level). It would be important to know if some of the sample have actually reached target serum urate levels at baseline

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Answer: we will include the baseline serum uric level as a confounder in the Poisson regression model. We will do this as a continuous level or dichotome level depending on linearity. We added a comment in the text (Data analysis).

10. Methods
    Page 6, line 51 – Please state what "ICPC" is in full as first usage

Answer: we have amended the text.

11. Methods - Sample-size calculation
    Page 7, line 21 – I'm unclear how you arrived at n=681 and then state that you'll have a treatment cohort of n=227? Do you expect a response rate of 33%? Also you've not indicated an expected % loss to follow-up, this will be important to when your primary outcome is (i.e. attacks at 12-months or 24-months). Please clarify

Answer: We have rewritten the paragraph to make it more clear how we calculated the sample size and the resulting power.

12. Methods - Data collection and research measures
    Page 8, line 6 – BMI is calculated using height, not length. This also need correcting in Figure 1

Answer: We have amended the text and the figure.

13. Methods - Data analysis
    Page 9, line 43 – I think "treatment allopurinol" needs to be "allopurinol reatment"

Answer: correct, amended the text.

Comments Reviewer 2: A/Prof Philip Robinson

1. The comment in the introduction "Such treatment is controversial, as there is hardly any evidence that it actually reduces the gout attack frequency and/or resolves tophi if present, or prevents long term joint damage" is not accurate. While I acknowledge that RCT evidence is lacking, the body of total evidence supports its use and, as a result, allopurinol treatment is recommended by the ACR/EULAR gout guidelines and the BSR gout guidelines. The lack of evidence does not mean lack of efficacy and therefore, as all clinicians do in clinical practice, have to make decisions based on the best available evidence.

Answer: You are correct, we formulated this too strongly and have amended the sentence.

2. How will the 3 monthly questionnaires be given to patients, posted to them, or during a consultation with the GP, or online, further detail is neededabout this and what steps will be taken (in detail) if questionnaires are not filled out by participants.

Answer: All questionnaires will be electronically mailed to the patients using GemsTracker (GEneric Medical Survey Tracker). This is a software package for (complex) distribution of questionnaires and forms during clinical research and quality registrations in healthcare. Patients not able to work with a computer receive the questionnaire on paper. The deadline of each questionnaire is 4 weeks. Patients are reminded after 1 week (email), 2 weeks (telephone call), 3 weeks (email). If a questionnaire is not filled out, we record that questionnaire as missing.

3. The use of patient self evaluation for tophi seems very unusual, why not ask GPs to assess for tophi at the baseline visit? This seems to make this assessment highly unreliable.

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Answer: GPs in the Netherlands have a high administrative burden. Because there was no budget to compensate GPs for invested time, we tried to minimize the efforts of the GP. We added photographs of tophi in the questionnaire. The Tophus Impact Questionnaire is a validated questionnaire (Aati O, Taylor WJ, Siegert RJ, Horne A, House ME, Tan P, et al. Development of a patient-reported outcome measure of tophus burden: the Tophus Impact Questionnaire (TIQ-20). Ann Rheum Dis. 2015;74(12):2144 PubMed -50).

4. I cannot comment on the appropriateness or not of the propensity matching statistical methods.

VERSION 2 – REVIEW

REVIEWER	James Prior Keele University
REVIEW RETURNED	11-Sep-2018

GENERAL COMMENTS	I am happy that the necessary comments have been addressed by the authors .

REVIEWER	A/Prof Philip Robinson University of Queensland
REVIEW RETURNED	01-Sep-2018

GENERAL COMMENTS	I am happy that the authors have addressed my comments adequately .

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