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Designing a Strategy Trial for the Management of Gout: The Use of a Modified Delphi Panel

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Objective. Disagreement exists between rheumatology and primary care societies regarding gout management. This paper describes a formal process for gathering input from stakeholders in the planning of a trial to compare gout management strategies.

Methods. We recruited patients, nurses, physician assistants, primary care clinicians, and rheumatologists to participate in a modified Delphi panel (mDP) to provide input on design of a trial focused on optimal management for primary care patients with gout. The 16 panelists received a plain-language briefing document that discussed the rationale for the trial, key clinical issues in gout, and aspects of trial design. The panelists also received information and considerations on nine voting questions (VQs), judged to be the key design questions. Cognitive interviews with panelists ensured that the VQs were understood by the range of panelists involved in the mDP. Panelists were asked to score all VQs from 1 (definitely no) to 9 (definitely yes). Two voting rounds were conducted—round 1 by email and round 2 by video conference.

Results. The VQs were modified through the cognitive interviews. The round 1 voting resulted in consensus on eight items, with consensus defined as median voting score in the same tercile (1-3, 4-6 or 7-9). Re-voting at the meeting (round 2) reached consensus on the remaining item.

Conclusion. An mDP with various stakeholders facilitated consensus on the design of a trial of different management strategies for chronic gout. This method may be useful for designing trials of clinical questions with substantial disagreement across stakeholders.

INTRODUCTION

Gout is the most common inflammatory arthritis, affecting 4% of US adults (1). Although gout is primarily considered an acute arthritic ailment, its causes are metabolic, with overproduction or underexcretion of serum urate. Moreover, it becomes a chronic condition in a minority of patients with recurrent gout flares, kidney stones, and tophi (2). Gout was described in the Ebers papyrus dated from 1500 BC, and a variety of treatments have been used for gout for thousands of years. However, persistent gaps in the evidence base make it difficult to define the optimal longitudinal medical management of gout.

The lack of agreed upon evidence has led to controversies in some aspects of gout management. Guidelines from rheumatology organizations recommend treating patients who have hyperuricemia and more than an occasional gout flare with urate-lowering

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treatment (ULT) to attain a lower target serum urate (SU) level, such as 6 mg/dl (3,4). This "treat to target serum urate" (TTT-SU) approach is based on the understanding that higher serum urate levels are associated with an increased risk of gout flare. In addition, there are some observational data and some treatment trials that suggest that the frequency of gout flares is reduced when SU levels are lowered (5–8). However, internal medicine organizations, such as the American College of Physicians (ACP), have pointed out the lack of strong evidence supporting the TTT-SU approach (9), and others have critiqued the design of recent randomized controlled trials designed to test TTT-SU as unbalanced. More specifically, the ACP noted that the evidence at the time of their review was insufficient to conclude whether the benefits of escalating urate-lowering therapy to reach a target SU outweigh the potential harms. They raised the possibility of an alternative "treat to avoid symptoms" (TTASx) approach, which has not been carefully defined but focuses on escalating therapy based on the frequency of gout flares.

This controversy—whether to use a TTT-SU approach versus a TTASx approach—requires better evidence to resolve. Given the prevalence of the condition, a large proportion of patients with gout are currently managed by primary care clinicians (10). Thus, we are designing a trial that would be feasible to conduct in primary care practices, with an intervention that could be managed by nonphysicians, primarily nurses and physician assistants. Although TTT-SU is defined in prior guideline documents (3,4), we propose starting low-dose ULT, titrate up to SU (<6 mg/dl) treatment target goal, and maintain indefinitely. This strategy would be pragmatic and generalizable to primary care practice outside of the setting of the randomized controlled trial. A major challenge of such a trial is defining a TTASx comparator arm: should it allow ULT? Should it provide standardized diet and lifestyle education?

We convened a modified Delphi panel (mDP) of the relevant stakeholders—patients, primary care physicians, nurses, and rheumatologists—using a formal process of voting and discussion (11,12). The Delphi panel is a commonly used approach in health care for areas in which there is less than perfect data to make decisions. It also has been used in the social sciences as a method for formalizing input from multiple parties, using voting and discussion (13–15). Herein, we describe the process for organizing and deliberating over key issues in the gout trial design using a modification of a typical Delphi panel.

METHODS

Design of the mDP. Although designing a trial involves countless decisions, we focused on several key areas with the mDP. These areas were determined based on a prior conference we held during 2018 (NIH R13-AR-073334) that invited rheumatologists, primary care clinicians, and other gout researchers to discuss key issues in gout management. Based on this conference, we determined the key controversies and described them in a briefing document, covering the basics of gout and trial design. It included a section regarding gout, gout risk factors, gout treatment, gout management strategies, basic issues of trial design, and the design areas of particular focus for this trial. Special attention was paid to making the text understandable to all panelists. The briefing document was 15 pages in length and was sent to all panelists a month before the mDP meeting. The goal of the briefing document was to prepare panelists for the mDP and for two rounds of voting (described below).

The mDP considered three areas of study design based on the proceedings of the prior conference and the collaborative brainstorming of the participants of the prior conference. First, we asked the panelists about key study outcomes, including the number of gout flares, the severity of gout flares, and gout-specific and overall quality of life. These three outcomes were not considered mutually exclusive, meaning a panelist could vote for each of the three. Panelists were asked to rate the importance of these potential study outcomes on a scale of 1 to 9 scale, where 1 = definitely no, 5 = neutral, and 9 = definitely yes (see voting document in Supplemental Methods). We gave examples of how the outcomes could be measured in the briefing document.

Second, we asked the panelists about three separate aspects of defining the study's eligibility criteria. Specifically, whether the trial population should be defined based on a SU level above a certain cutoff, whether the number and recency of gout flares should be included, and whether patients who were already on a low dosage of a urate-lowering drug should be included in the trial. Just as with the outcomes questions, we used a 1 to 9 scale for voting, as noted above.

Third, we assessed panelists' views on the treatment in the TTASx comparator arm and compared them with those of TTT-SU. We focused on three aspects of the comparator arm strategy: whether urate-lowering drugs should be allowed in the event of frequent and bothersome gout flares; if urate-lowering drugs were allowed, whether dose titration should be allowed, again in response to ongoing gout flares; and whether the treatment strategy should follow a set protocol versus allowing usual clinical care without a set protocol. The two questions regarding urate-lowering drugs used the same 1 to 9 scale that was used above. The final question regarding using a protocol or not put these two options on opposite ends of a nine-point scale.

Selecting and educating panelists. We selected a broadly representative group of panelists from five categories of constituents who could inform the trial design: patients with gout, nurses, physician assistants, primary care physicians, and rheumatologists (see Table 1 for list of panelists). The panelists were all given the same stipend for their time and effort.

Table 1. De-identified modified Delphi panelists

Participant	Constituency	Relevant Prior Experience
A	Primary care physician	General medicine practice, directs the MGH primary care practice–based research network
B	Patient	Patient with gout
C	Primary care physician	General medicine practice, studies the influence of ethnic, cultural, and environmental factors on health
D	Primary care physician	General medicine practice, studies medication nonadherence
E	Rheumatologist	Rheumatologist, authored the ACR gout guidelines
F	Physician assistant	PA in primary care, specializes in chronic disease care
G	Registered nurse	Specializes in gout care
H	Patient	Patient with gout
I	Primary care physician	General medicine and rheumatology practices and involved in the ACP gout guideline development
J	Patient	Patient with gout
K	Rheumatologist	Rheumatologist, authored the ACR gout guidelines
L	Nurse practitioner	Nursing practice specialist, focusing on anticoagulation
M	Rheumatologist	Rheumatologist, authored the ACR gout guidelines
N	Primary care physician	General medicine practice, studies chronic disease management
O	Rheumatologist	Rheumatologist with gout expertise, conducted gout trials
P	Patient	Patient with gout

Abbreviations: ACP, American College of Physicians; ACR, American College of Rheumatology; MGH, Massachusetts General Hospital; PA, physician assistant.

Cognitive interviews. We interviewed five panelists prior to sending out the voting questions (VQs) to the full group but after they had received the briefing document. The goal of these interviews was to determine if the voting instructions were clear and whether the questions were understood (16). We included two patients, one nurse, one primary care physician, and one rheumatologist in the cognitive interviews. The interviews were conducted by one of the study investigators (DHS) with one research staff (DS) taking notes. The questions were consistent across the cognitive interviews and included explaining the instructions, explaining the voting scale, describing the meaning of each of the VQs, and asking the panelists how we could make the voting easier.

Voting procedures. All panelists in the mDP were sent the final VQs 14 days prior to the mDP meeting in a worksheet format. This document also included important issues to consider when voting. The actual voting was conducted using a computer-based tool for collecting voting responses (SurveyMonkey) and was sent to panelists 12 days prior to the Delphi panel. The round 1 premeeting votes were tallied, and anonymous results were presented to panelists during the meeting prior to the discussion of each question. Almost all Delphi panels used in health care are considered mDPs because they encourage discussion by panelists. Repeat voting occurred during round 2 on all VQs for which consensus had not initially been reached (see below).

Round 2 face-to-face meeting. The mDP meeting was held virtually, given the coronavirus pandemic and the national distribution of panelists. The meeting was scheduled to last for 4 hours. At the beginning of the meeting, panelists introduced themselves, and they were given a brief background on the trial, the reason for, and importance of their participation. They also received a brief technical summary of how the meeting would be conducted. The investigators explained that although the premeeting voting had met our definition of consensus (see below) for eight of the nine questions, we would at least briefly discuss each question to ensure there were no changes in panelists' opinions. For each question, we gave a brief summary of the clinical and methodologic issues (which had been covered in the briefing document) and presented the distribution of votes without identifying individuals. Panelists commonly volunteered the rationale for their votes. More time was spent on the ninth item where consensus had not been reached. The panel moderators (JSW and MJB) attempted to ensure all panelists participated in the discussion, particularly the patient members.

The number of rounds of voting was not predetermined, but only two rounds were needed because of the consensus that was achieved by the second round.

Statistical analyses. In any Delphi process, decision rules are determined in advance to both define and determine consensus. Consensus on a topic is usually determined if a certain number or percentage of votes falls within a prescribed range, without a similarly determined number in the extreme ranges. Our criteria for consensus were determined a priori to avoid bias. Consensus was defined as a median voting score in the top or bottom tercile (7 to 9 or 1 to 3) without disagreement, as defined by the RAND method (11). Because there were 16 responses, the seventh and eighth responses were averaged to calculate the median.

RESULTS

The cognitive interviews informed the voting instructions and questions, and several minor edits were undertaken (see Figure 1 and Supplementary Materials for Voting Questions and Considerations). The changes based on the cognitive interviews were primarily made to enhance the consistency in understanding of

Table 2. Final results for voting questions (see Figure 1 for voting questions)

Voting Question[a]	Modified Delph Panelists																Final Voting Results				
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Group Median, (Range)	Number of Votes by Tercile			Consensus
																		1-3	4-6	7-9	
1a	7	5	9	9	9	8	9	7	9	9	8	8	9	7	9	9	9 (5-9)	0	1	15	Yes
1b	8	5	9	6	9	5	7	9	5	9	8	6	7	8	5	9	7 (5-9)	0	7	9	Yes
1c	9	9	9	8	9	7	7	5	6	9	6	9	7	9	7	9	7.5 (5-9)	0	3	13	Yes
2a	9	8	9	8	8	9	9	8	9	1	7	5	9	9	7	9	8.5 (1-9)	1	1	14	Yes
2b	8	3	9	4	8	8	8	8	9	9	7	7	9	8	6	9	8 (3-9)	1	2	13	Yes
2c	7	8	9	7	1	6	8	9	9	9	7	7	8	7	5	9	7.5 (1-9)	1	2	13	Yes
3a	9	9	9	8	9	7	8	8	9	8	9	8	5	9	3	9	8 (3-9)	1	1	14	Yes
3b	9	8	9	9	5	6	6	4	7	9	7	7	8	8	8	9	8 (4-9)[b]	0	4	12	Yes[a]
3c	2	8	9	7	2	6	7	8	1	9	7	9	2	2	7	5	7 (1-9)	5	2	9	Yes

[a] See figure and supplement for description of the voting questions.
[b] There was not consensus during the premeeting vote on this voting question, with a median of 6 and thus not in the top tercile. After discussion at the modified Delphi panel, consensus was reached.

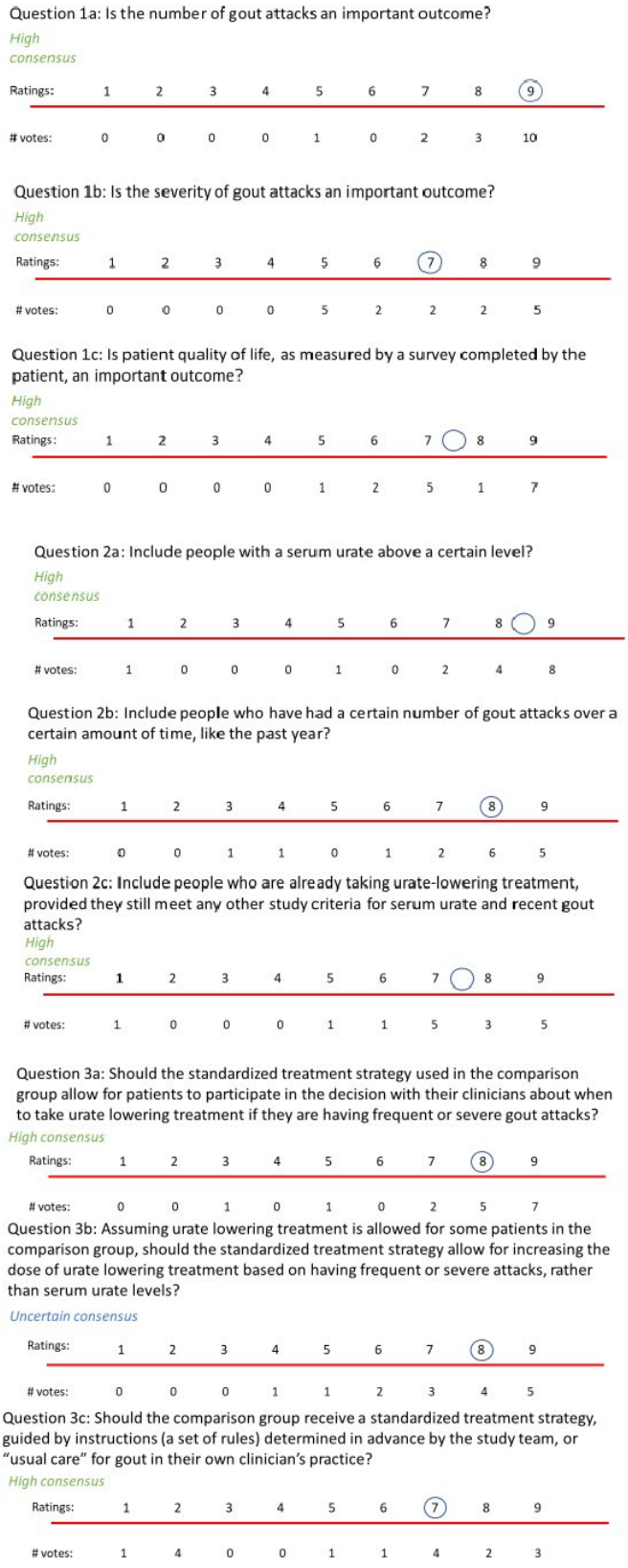

Figure 1. Voting questions and final voting results. These figures were used during the meeting to illustrate the voting questions and responses from the group during the premeeting round 1 voting. The circled number describes the group median for the voting score.

the VQs. The cognitive interviews gave specific feedback that led to us changing the wording and order of questions.

The premeeting voting results were presented during the first part of the mDP meeting. Results and comments from panelists were discussed during the meeting. Clarifications were made on some VQ considerations through presentations to the panelists. All VQs were discussed, but only Question 3b was re-voted on.

The premeeting voting results found consensus on 8 of 9 VQs, all in the "yes" tercile (see Table 2). There was a broader spread of voting responses for the third question regarding the comparator treatment strategy. We did not reach consensus before the meeting on one VQ pertaining to the use of SU levels to determine whether to adjust ULT in the comparator arm (TTASx). At the mDP meeting, results for this VQ were presented in detail and panelists were asked to explain their initial votes. This prompted a discussion that allowed panelists to reach consensus (see Figure 1 and Table 2), with everyone voting in the "yes" tercile.

DISCUSSION

There is substantial conflict between gout guidelines from rheumatology and general internal medicine physician groups on the optimal chronic treatment of gout; primary care and specialty guidelines generally agree on the management of gout flares. Much of this controversy stems from the question of whether treating to a target SU level leads to better outcomes than simply treating to avoid symptoms in terms of gout flares (17,18). Although there are some data on this topic, the question has not been directly tested in an appropriately randomized controlled clinical trial focused on the clinical endpoints that are most important to patients. Designing such a clinical trial raises several difficult questions, among them: what are the correct outcomes to study? Which patients are most relevant to enroll, and what should the management protocol in the comparator arm (TTASx) include?

We engaged a mDP that included patients, nurses, and physician assistants, primary care clinicians, and rheumatologists to help us design such a trial. After giving them a briefing document, we found that there was consensus in a premeeting vote on many aspects of the trial, such as outcomes to measure and patient populations to include. We did not observe important differences in opinions between rheumatologists and nonrheumatologists (see Tables 1 and 2). However, premeeting voting did not achieve consensus on the routine use of SU measurement in the comparator arm: some voted that SU measurements should be routine in both arms. A half-day mDP meeting reviewed the premeeting results and discussed all the VQs, even where premeeting consensus had been reached. The meeting discussion produced consensus across all VQs. The consensus was all in the upper tercile, corresponding to agreement with the proposed design issue raised by the study team.

With consensus reached on all the major questions posed, we plan to move forward with planning such a trial following the

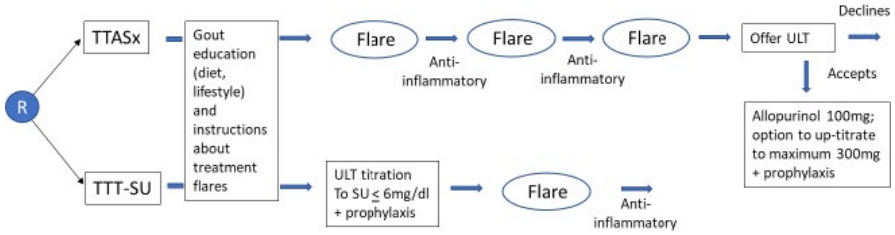

Figure 2. Preliminary algorithms for the two TTASx control strategy. Patients will be equally randomized to the two arms of the trial TTT-SU and TTASx. Thus, patients in both arms will be allowed to be on baseline ULT of no more than 200 mg/d. All patients will receive education on diet and lifestyle at baseline and subsequent visits. In addition, each patient will be provided anti-inflammatory medications according to their prior experience and comorbidities; these could include colchicine, an nonsteroidal anti-inflammatory drug, and/or oral corticosteroids. Patients in the TTASx arm will not be allowed allopurinol dosages greater than 300 mg. Patients in both arms will be recommended colchicine prophylaxis for 3 months after starting ULT or a higher dosage of ULT. ULT, urate-lowering therapy; TTASx, treat to avoid symptoms; TTT-SU, treat to target serum urate.

recommendations of the Delphi panel (see Table 2 for final voting). The primary outcome will be gout flare rate over at least 24 months with the severity of flares and gout-related quality of life as secondary outcomes. Because many gout flares are self-medicated, it would be impossible to have patients be seen by clinicians during every flare. Patient panelists during the mDP stressed the importance of knowing how to manage gout flares without a physician. There are several possible ways to collect information from patients on gout flares—paper diaries, electronic diaries, text-based reporting—that we are currently exploring. We do recognize the challenges of preemptive treatment of gout flares and will stress the importance of keeping a diary with the enrolled patients. Although additional secondary outcomes were not the focus of the mDP, we also plan to study cardiometabolic, renal, and glycemic measures in subgroups enrolled in the trial. There are observational data suggesting that elevations in SU levels are associated with cardiovascular, renal, and glycemic outcomes, but there are no strong data that support the theory that altering SU causes improvements in any of these parameters (19–23). Details of which measures will be collected are being formulated. We aim to measure secondary intermediate outcomes (eg, estimated glomerular filtration rate, coronary computed tomography angiography, blood pressure, glycated hemoglobin) that have strong correlation with actual clinical outcomes and can be measured at multiple sites in a reliable manner.

The patient selection criteria for the trial will include SU levels and recency of gout flares. Although details are still being finalized, we anticipate inviting patients with SU greater than 7.0 mg/dl measured in the past year. Patients must also have experienced a self-reported gout flare in the past year. Although severe chronic kidney disease will be an exclusion, mild and moderate chronic kidney disease will be allowed, but alternative dosing recommendations will be in place for safe prescribing.

As noted, the design of the comparator arm of TTASx required more debate to get to consensus. The primary issues raised were regarding the degree of standardization for the comparator arm, whether adjusting ULT would be permitted, and if so, what role SU measurements would play in adjusting doses. With discussion, we were able to reach consensus, and details of the comparator arm are currently being determined. A preliminary algorithm for the TTASx treatment strategy is described in Figure 2. ULT is allowed with a maximum dosage in place and no routine SU measurements. Other issues that came up during the mDP discussion but were not voted on included the level of randomization (cluster vs individual), whether to admit patients with tophaceous gout, and the use of prophylactic anti-inflammatory treatments when starting and adjusting ULT.

We are not aware of prior examples of an mDP being used to design a multidisciplinary trial. We believe that this is an ideal use of an mDP with many different stakeholders with interests in the results of the trial. Because we anticipate recruitment in primary care, participation by these different clinician stakeholders was critical. Moreover, if one of the strategies proves to be superior, we believe that nurses, physician assistants, or pharmacists would be able to administer such interventions. This would not be practical for all clinicians, but we decided to integrate them into this trial and the mDP. Patients are at the heart of longitudinal care of gout, so a trial must compare potential intervention strategies that are acceptable to patients, and any differences in outcomes between the strategies should be seen as clinically, not just statistically, significant. Furthermore, the mDP allowed each of these groups to "have a voice" and to contribute equally during the process.

There were several limitations of this mDP. First, it was limited in breadth to panelists from four academic medical centers and thus may not reflect all opinions. Second, although it did involve 16 people, this is a relatively small sample. Third, the mDP did not consider all study design issues as VQs. This was intentional, as we determined that some issues would be difficult to discuss without specialized knowledge of clinical trial design.

In conclusion, we convened a consensus process using an mDP to help design a gout strategy trial. The mDP's inclusion of a broad range of constituents facilitated decision-making aimed at designing a trial acceptable to all parties—patients, nurses, physician assistants, primary care physicians, and rheumatologists.

Because gout is primarily managed in primary care and this trial plans to recruit patients in this setting, substantial input from patients and primary care physicians should improve the chances of success. Furthermore, nurses will serve to deliver the intervention, following an algorithm designed by primary care physicians and rheumatologists. We believe that this multiparty, formalized process is innovative and can be considered more broadly for other similar questions where there is divergence in opinion across different provider types.

AUTHOR CONTRIBUTIONS

All authors were involved in acquiring data, analyzing the data, and drafting the article or revising it critically for important intellectual content. All authors approved the final version to be published. Dr. Solomon had full access to the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Solomon, Weissman, Choi, and Barry.
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