Patient-Centered Outcomes and Key Study Procedure Finalization in the Pilot Feasibility Gout Randomized Trial

Comparative Feasibility Study in GOUt, CHerry Extract Versus Diet Modification (Mini-GOUCH)

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Objective: The aim of this study was to report patient-centered outcomes and finalization of key study procedures from a 9-month pilot internet randomized controlled trial of cherry extract versus diet modification.

Methods: We randomized 84 people with physician-confirmed gout in an internet study to cherry extract (n = 41) or dietitian-assisted diet modification for gout (n = 43). All study outcomes were collected via internet and phone calls. We finalized key study procedures. We assessed acceptability and feasibility of the intervention and satisfaction with study website.

Results: Study participant satisfaction with the intervention was high. The intervention was perceived as easy, enjoyable, understandable, and helpful (scores 65–88 for all; higher = better). The amount of time spent for the study was acceptable. Participant satisfaction with website interaction and content was very high; 85% or more were moderately to extremely satisfied. Significantly lower total calories, total carbohydrate, and saturated fat intake were noted at 6 months in the diet modification versus cherry extract group; differences were insignificant at 9 months. Six of the 8 Health Assessment Questionnaire sections/domains improved significantly from baseline to 9 months in cherry extract versus 2 Health Assessment Questionnaire sections/domains in the diet modification group. Key study procedures were finalized for a future trial, including an internet diet assessment tool, gout flare assessment, provider confirmation of gout diagnosis, patient reporting of classification criteria, and centralized laboratory-assisted serum urate testing.

Conclusions: High patient acceptability and feasibility of study/intervention and finalization of key study procedures indicate that hypothesis-testing internet gout trials of cherry extract and/or diet modification can be conducted in the future.

Key Words: cherry extract, gout, internet study, patient acceptability

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Gout, the most common inflammatory arthritis affecting Americans with an increasing prevalence,[1] is challenging to manage despite the availability of effective urate-lowering therapy (ULT) and anti-inflammatory drugs.[2] Management is challenging because of several factors, including concomitant comorbidities, patient and physician knowledge gaps, low adherence to ULT, and differences between patient preferences and physician recommendations.[1–5] Many patients believe that gout is primarily caused by diet and prefer diet modification and dietary supplements (e.g., cherry extract) as alternatives to pharmacological treatment.[5–8] Patients with gout consider studies of nonpharmacological therapies to be the highest priority for research,[9] yet there is a lack of trials assessing the efficacy of diet modification and dietary supplements.[10] Assessment of complementary and alternative therapies is one of the national priorities in comparative effectiveness research.[11] Evaluation of nonpharmacological

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Ethics approval and consent to participate: The University of Alabama at Birmingham's (UAB's) Institutional Review Board (IRB) approved this study. Each patient participating in the study provided informed consent. All investigations were conducted in conformity with ethical principles of research.

The authors will make data available to colleagues, after appropriate approvals and permissions from the respective IRBs including the UAB IRB have been obtained, and UAB data security and data transfer requirements are met.

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gout treatments using a rigorously designed trial can address this priority.

Therefore, we designed a 9-month internet pilot feasibility study, coMparative feasibility study IN GOUt: CHerry extract versus diet modification (mini-GOUCH).[12] We reported study procedure completion rates (primary outcome), effect estimates for proposed outcomes for future randomized controlled trial (RCT) (gout flares and function), and key secondary outcomes (serum urate [SU], pain, adverse events [AEs]) recently.[12] The objective of this report was to describe (1) patient-reported outcomes including acceptability and feasibility of intervention and study, diet component modification, exploratory outcomes (Health Assessment Questionnaire [HAQ] sections, dietary changes, current pain, well-being, satisfaction with ULT medication) and (2) finalization of key study procedures/tools including modification of an internet diet tool modified for gout, every 2 weeks gout flare surveys, confirmation of gout diagnosis by health care provider, patient reporting of the gout classification criteria, and the use of a centralized laboratory to obtain SU.

METHODS

Study Overview, Study Sample, Patient Enrollment, and Screening Using an Internet Website

We built an internet website (www.cherries4gout.com) and modified VioScreen, a reliable and user-friendly graphical National Institutes of Health–funded Food Frequency Questionnaire (FFQ),[13–15] into an internet tool, *GoutWell*, that sent gout education and adherence messages (details in the Results section). Patients completed study follow-up assessments every 3 months and the gout flare assessments every 2 weeks, both via the internet surveys. Nonresponders received automatic reminder emails every 24 hours for 5 days, followed by a phone follow-up to complete the surveys. Details of study screening, enrollment, and follow-up were described previously.[12] All participants were recruited online. Screening, baseline, and follow-up "virtual visits" were completed via using the internet and the phone in this internet gout study. This pilot, parallel-arm, 1:1 allocation ratio, randomized trial was open-label because of the nature of the interventions.

Briefly, potential participants were invited for study enrollment from February 2016 to October 2016 by providing an internet link to the study website (www.cherries4gout.com) that provided description of the study and study procedures.[12] The study was approved by University of Alabama at Birmingham's Institutional Review Board.

Study inclusion criteria were as follows: (1) adults 18 years or older; (2) a valid current US mailing address and email address; and (3) patient self-reported physician diagnosis of gout, confirmed by contacting participant's health care provider who also provided American College of Rheumatology (ACR) gout classification criteria,[16] as did patients. Study exclusion criteria were as follows: patient self-reported rheumatoid arthritis or spondyloarthritis (other inflammatory arthritides often confused with gout); physician confirmation that diagnosis was not gout; and the current use of cherry extract, juice, or concentrate.

Randomization and Study Intervention

We randomized participants using an online computerized permuted variable block design with simple randomization in a 1:1 ratio to either group: 3,600 mg of cherry extract daily (3 capsules of 1200 mg each daily) or individualized diet modification. Each study participant received either the 3-month supply of cherry capsules or individualized diet recommendation (based on the most recent baseline FFQ data) via certified mail at 3, 6, and 9 months, and receipt was confirmed with email or a phone call. Each participant also received either study coordinator calls to encourage cherry extract adherence or dietitian calls to discuss specific recommendations (details below).

Baseline and Follow-up Assessments

At baseline, participants completed assessments of gout flare, activity limitation with HAQ (coprimary measures), diet assessment using *GoutWell* (an online FFQ), self-reported comorbidity index, smoking and alcohol use, AEs, and ULT use. Exploratory outcomes included HAQ sections/domains, FFQ, well-being, current pain intensity, and SU. Baseline blood draw for SU was performed at a closest/most convenient Quest laboratory site (details in the Results section).

Participants completed brief online questionnaires (<30 minutes total) every 3 months at 3, 6, and 9 months (HAQ, AEs, gout medication use, well-being), sent to their email address via a link, using their unique login and password. Gout flare questionnaires were completed via email every 2 weeks. Serum urate blood draws were done at the nearest Quest laboratory site at 9 months only during the follow-up (in addition to baseline assessment). We invited each study participant to join group teleconference call sessions lasting 30 to 60 minutes either at 0, 1, 4, and 7 months with study coordinators (cherry extract group) or 0, 6, and 9 months with a registered dietitian (A.L.W. or B.D.; diet modification group).

Feasibility, Acceptability, Satisfaction, Exploratory Study Outcomes, and Study Debriefing

Study and intervention acceptability were assessed at 9 months using validated questionnaires, adapted for our study.[17,18] Satisfaction with website content, function, and other aspects were assessed at 9 months using a structured website evaluation form.

Dietary assessments were done at 0, 3, 6, and 9 months using *GoutWell,* a modified gout-specific (inclusion of additional food items such as anchovies, etc.) version of VioScreen, an online, reliable, self-reported FFQ that assesses food choices and portion sizes over the past 90 days.[14]

Activity limitation assessment was done with HAQ, a validated measure, at 0, 3, 6, and 9 months.[19–21] Health Assessment Questionnaire assesses difficulty in 8 sections/domains (dressing, arising, eating, walking, hygiene, reaching, gripping, and outside activity) using 20 items; score for each section is calculated as the worst score within the section and ranges from 0 (without any difficulty) to 3 (unable to do); that is, if one question is scored 1 and another 2, then the score for the section is 2. Use of an aide or device or requiring help from another individual makes the minimum score for that section to be 2.The total score is the sum of scores of 8 sections divided by 8 and ranges from 0 (no disability) to 3 (complete disability). The minimal clinically meaningful improvement threshold for the total HAQ sore is 0.22.[22] To our knowledge, there are no Minimal Clinically Important Difference thresholds for HAQ sections.

Well-being and current pain intensity were each assessed on a 0- to 10-point scale at 0, 3, 6, and 9 months, with lower scores indicating better outcomes for both.

Assessment of barriers and facilitators to GoutWell-assisted cherry extract adherence and dietary changes was performed at 9 months (at the end of the study assessment) using a brief pretested semistructured interview guide[23] to gain at the end of the study to gain additional insights for the future hypothesis-testing trial.

Exploratory outcomes within cherry extract and diet modification groups were compared with baseline values using paired *t* tests for continuous outcomes (HAQ sections, pain intensity, well-being) and McNemar test for categorical outcomes (SU < 5 mg/dl or < 6 mg/dl). For between group comparisons, t- and chi-square tests were used.

RESULTS

Study Participant Characteristics

In this study, 84 participants with gout were randomized to cherry extract (n = 41) and diet modification (n = 43; Appendix 1,

TABLE 1. Patient Characteristics at Baseline

	All Participants (n = 84)	Cherry Extract (n = 41[a])	Diet Modification (n = 43[a])	*p* value: Difference Between the 2 Arms
	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	
Age, mean ± SD, y	55.8 ± 13.9	58.2 ± 15.5	53.6 ± 11.9	0.13
Gender, male, n (%)	61 (72%)	31 (76%)	30 (70%)	0.54
Race, n (%)				0.55
White	57 (68%)	30 (73%)	27 (63%)	
Black or African American	21 (25%)	9 (22%)	12 (28%)	
Asian/other[b]/mixed	6 (7%)	2 (5%)	4 (9%)	
Patient-reported last uric acid level, mean (SD), mg/dL	7.52 ± 3.0	7.14 ± 2.6	7.9 ± 3.3	0.39
Currently taking allopurinol, febuxostat, or probenecid[c]	30 (37%)	13 (33%)	17 (42%)	0.40
Well-being—very well to very poor (0–10; lower = better)	2.9 ± 2.6	3.1 ± 2.83	2.7 ± 2.4	0.55
Currently on special diet	24 (29%)	12 (29%)	12 (28%)	0.89
Validated gout flare at baseline[d]	24 (29%)	13 (32%)	11 (26%)	0.53
Patient-reported current gout flare: baseline	30 (36%)	18 (44%)	12 (28%)	0.13
Patient-reported warm joint	25 (30%)	15 (37%)	10 (23%)	0.18
Patient-reported swollen joint	45 (54%)	28 (68%)	17 (40%)	**0.008**
Average pain >3 in 24 h	26 (31%)	13 (32%)	13 (30%)	1.0
Pain intensity (0–10)				
Now	1.92 ± 2.7	2.17 ± 2.8	1.67 ± 2.5	0.40
Average pain 24 h	2.05 ± 2.6	2.19 ± 2.6	1.90 ± 2.6	0.62
Maximum pain 24 h	2.51 ± 3.0	2.83 ± 3.1	2.21 ± 2.9	0.34
Current gout flare severity: baseline				0.41
Mild	14 (47%)	9 (50%)	5 (42%)	
Moderate	10 (33%)	7 (39%)	3 (25%)	
Severe	5 (17%)	2 (11%)	3 (25%)	
Very severe	1 (3%)	0 (0%)	1 (8%)	
SATMED[e] subscale and total scores				
Undesirable adverse effects	14.0 ± 26.0	18.6 ± 29.7	9.6 ± 21.3	0.18
Treatment effectiveness	60.6 ± 32.9	54.8 ± 34.6	66.1 ± 30.7	0.17
Convenience of use	76.2 ± 25.1	74.7 ± 25.3	77.6 ± 25.1	0.65
Impact on daily activities	65.3 ± 32.3	57.0 ± 35.1	73.0 ± 27.7	0.05
Medical care	69.9 ± 30.4	66.3 ± 32.0	73.3 ± 28.8	0.36
Global satisfaction	68.8 ± 30.7	63.9 ± 33.5	73.4 ± 27.5	0.22
Total score	57.9 ± 18.2	55.1 ± 19.0	60.5 ± 17.3	0.25

Bold font indicates statistical significance, $p < 0.05$.

[a]Of the 84 people randomized, 41 were randomized to cherry extract and 43 to individualized diet modification.

[b]Other race includes Native Hawaiian or other pacific islander, American Indian or Alaskan native, Asian, other, and mixed.

[c]Missing frequency, n = 3.

[d]Validated gout flare was defined as the presence of 3 (or more) of the 4 following criteria: patient-reported gout flare, warm joint, swollen joint, average pain >3 in the last 24 hours, based on previously published validated gout flare definition. Physician-reported confirmation of gout diagnosis was done for all 84 subjects.

[e]Patient satisfaction with ULT was assessed by validated Treatment Satisfaction with Medications questionnaire (SATMED) at baseline only. It has 17 items; each scored from 0 to 4. SATMED has 6 dimensions/subscales. A total raw score ranges from 0 to 68, with higher score indicating more satisfaction with treatment. Both dimension and total scores are transformed 0 to 100.

http://links.lww.com/RHU/A144; CONSORT flowchart). Because cherry extract is not a drug, biologic, or device regulated by the US Food and Drug Administration, study registration was not required on Clinicaltrials.gov.

Patient characteristics have been previously described[12] and were similar across the study treatment arms. The study participants had a mean age of 56 (SD, 14) years; mean body mass index was 33 (SD, 9) kg/m^2; mean gout flares in the last year were 4 (SD, 5.4), that is, 0.33 gout flares per month. Of participants, 72% were male, 68% were white, 80% had ever had some sort of gout medication prescription, and 37% were currently on ULT. Satisfaction with ULT medications at baseline was moderate and similar for cherry extract versus diet modification. Other patient characteristics were similar between the 2 arms and are shown in Table 1.

Finalization of Key Study Procedures/Tools

GoutWell and 2-Weekly Gout Flare Assessments

We modified VioScreen, an online highly reliable FFQ tool,[14] a self-reported assessment of food choices and portion sizes over the past 30 days, into *GoutWell* to be gout specific (inclusion of additional food items such as anchovies, etc.) and used with modifications in our study (details below). It measured the 20 variables below (Appendix 2, http://links.lww.com/RHU/A144): calories, carbohydrates, protein, fat, total saturated fatty acids (SFAs), polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids (MUFAs), calcium, caffeine, alcohol consumption, cooked lean meat (beef, pork, etc.), cooked lean meat (sausage, luncheon meats), cooked lean meat from organ meats, cooked lean meat (chicken, turkey, poultry), and total fat.

GoutWell provided participants with intervention-specific personalized message regarding diet or cherry extract adherence to increase the chance of success of each intervention. *GoutWell* also sent an automated personalized email reminder to all enrolled patients regularly every 2 weeks asking them if they have had a gout flare in the last 2 weeks.

After the study participant completed the baseline FFQ, a summary report was created from *GoutWell*, and the patient entered the Interactive Behavioral Feedback module of the system to guide them to develop a customized dietary plan (Appendix 2, http://links.lww.com/RHU/A144). This report highlighted the amount and % excess/deficient intake of various diet components, and by its cross-linking to risk imparted by these factors and an individual's decision for the diet-related changes he/she was willing to make at a given time, a registered dietitian (A.L.W. or B.D.) generated an individualized and personalized diet modification plan. The plan included suggestions and assistance such as controlling food cues, priming the food environment to make beneficial food selections, increasing knowledge of positive gout-related diet changes to promote initial dietary changes, and tips on portion control of gout-related foods, advance food purchase planning, and consistency in healthy food selection for longer-term dietary adherence. The information related to diet modification recommendations was presented in easy graphics via email to enhance patient understanding[24] and enhanced during calls with dietitian.

GoutWell-assisted 2-weekly gout flare assessment was sent via an email link to each study participant every 2-weeks. High initial completion rates were noted in the first 7 surveys (>80%), with some waning of response rate by the 12th assessment (>75%) and further decline by the 18th survey (62%; Appendix 3, http://links.lww.com/RHU/A144).

Confirmation of Gout Diagnosis by Patient's Health Care Provider and Patient Self-report of Gout Classification Criteria

The diagnosis of gout was confirmed in 90% (84/93) of the participants who self-reported gout, most (>90%) within 2 weeks of the first contact with the health care provider's

TABLE 2. Satisfaction With the Intervention and of Intervention Components/Goals and Acceptability of the Study Assessed at 9-Month End-of-Study Visit

	Cherry Extract (n = 41)	Diet Modification (n = 43)	
	Mean ± SD or n (%)	Mean ± SD or n (%)	*p* value
Feasibility of and satisfaction with the study intervention, 0–100 (higher = better)			
Ease of doing the intervention	83.5 (23.5)	75.7 (22.6)	0.14
Intervention was understandable	88.2 (18.4)	74.3 (27.6)	**0.01**
Enjoyed the intervention	72.6 (27.0)	65.3 (28.7)	0.70
Intervention was helpful	73.0 (25.9)	69.8 (28.2)	0.60
Overall satisfaction with the intervention	76.6 (23.8)	70.9 (28.1)	0.33
Satisfied (very or extremely satisfied) with intervention components/goals, n (%)			
Nutritional goal of 25% reduction in seafood	N/A	16 (44%)	
Nutritional goal of 10% reduction in meat intake	N/A	17 (47%)	
Nutrition goal of 10% increase in skim milk intake	N/A	11 (31%)	
Take cherry extract with breakfast	29 (73%)	N/A	
Keep cherry bottle next to the coffee maker	15 (38%)	N/A	
Add daily reminder on cell phone for cherry	15 (38%)	N/A	
Study acceptability, 0–100 (higher = better)			
Amount of time for study was acceptable	87.2 (19.8)	80.2 (18.5)	0.11

Bold indicates a significant $p < 0.05$.

N/A indicates not applicable.

office. Diagnosis was not gout for 2 potential participants (2% [2/93]), and we were unable to get a response from health care provider office regarding the diagnosis for 7 potential participants (8% [7/93]).

We obtained patient self-reported gout classification criteria from all participants (100 [84/84]), and 92% (77/84) participants met the 1977 ACR classification criteria for gout, but reporting rates were lower for health care provider–reported gout classification criteria: 80% provided data (67/84), and 67% (45/67) met gout classification criteria (Appendix 4, http://links.lww.com/RHU/A144). The overall patient-provider concordance for satisfying the 1977 ACR classification criteria for gout was 67% (45/67) with overlap of greater than 70% for 7 gout classification criteria (Appendix 5, http://links.lww.com/RHU/A144). Mean (SD) gout classification criteria were higher for self-reported versus health care provider reported, 8.6 ± 3.1 versus 4.8 ± 2.6 (Appendix 4, http://links.lww.com/RHU/A144).

Centralized Laboratory-Assisted SU Testing

The study coordinator identified the nearest Quest laboratory site and requested all study participants to get a blood draw for baseline SU, scheduled based on their preference. A copy of the laboratory slip and confirmation slip was sent to each study participant via email to give to the laboratory personnel on arrival to the Quest facility. Participants were reminded of the appointment via email and phone call 1 day before the blood draw. The blood draw was rescheduled for those who missed it. Test results were sent to the study team in a Health Insurance Portability and Accountability Act–compliant manner over a secure server/fax and were recorded

TABLE 3. Web-Based Material Consumer Rating Form at 3-Month Follow-up to Assess Patient Satisfaction With the Web-Based Study Material and the Study Intervention

	Combined (n = 84)					Cherry Extract (n = 41)	Diet Modification (n = 43)	
Question	Not at All	Slightly	Moderately	Very Much so	Extremely	% Positive Responses	% Positive Responses	*p* value
Website interaction								
1. How easy was it to use the website overall?	7%	0%	21%	31%	42%	95%	92%	0.54
2. How easy was it to use the website tabs?	8%	1%	18%	31%	42%	91%	92%	0.83
3. How pleasant or visually appealing was the website?	9%	3%	29%	29%	31%	90%	86%	0.57
4. To what extent did the icons or "tabs" appear readable?	8%	1%	25%	31%	35%	90%	92%	0.83
5. How easy was it to follow the instructions for logging onto the website?	8%	1%	18%	37%	37%	90%	92%	0.83
Website content								
6. To what extent did the website content maintain your interest in the website?	13%	1%	35%	35%	16%	82%	89%	0.46
8. Did it seem like the content related to your experience with trying to modify your diet/self-manage cherry extract supplementation was depicted in the website?	17%	8%	33%	27%	16%	73%	78%	0.64
9. To what extend did the setting or place distract you from attending to the website?	47%	6%	27%	12%	8%	42%	53%	0.32
10. To what extent did the written content for the health materials appear readable?	12%	1%	29%	38%	21%	86%	89%	0.64
11. To what extent do you think this information would help you in managing your diet/cherry capsule intake?	16%	1%	34%	33%	17%	83%	83%	0.96
Website self-monitoring function								
12. How easy was it to use the self-monitoring function for daily food intake?	17%	3%	39%	22%	19%	78%	83%	0.56
13. How easy was it to use the self-monitoring function for daily cherry extract intake?	17%	1%	31%	27%	24%	83%	81%	0.79
Website content concordant with personalized plan								
7. Did it seem like the content related to your experience with trying to modify your diet/self-manage cherry extract supplementation was depicted in the personalized plan?	18%	5%	34%	29%	14%	76%	78%	0.83

Answer choices: not at all, slightly, moderately, very much so, extremely. Positive response implies that the respondent chose moderately, very much so, or extremely.

TABLE 4. Baseline Dietary Component for All Participants and Comparison Between Cherry Extract Versus Diet Modification Arms

	All Participants With MD Confirmed Gout (n = 84)	Randomized to Cherry Extract (n = 41)	Randomized to Diet Modification (n = 43)	
Variable Name	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	***p* value**
Body mass index, kg/m^2	32.7 ± 8.5	32.5 ± 7.9	34.0 ± 10.0	0.49
Total calories, kcal	2099.4 ± 728.7	2015.0 ± 952.9	2012.5 ± 954.7	0.99
% Calories from carbohydrate intake	44% ± 10%	43% ±10%	46% ± 11%	0.15
% Calories from fat intake	38% ± 9%	38% ±10%	37% ± 8%	0.48
% Calories from protein intake	16% ± 4%	16% ±4%	15% ± 4%	0.34
Protein, g	80.62 ± 30.7	78.2 ± 35.3	75.7 ± 35.6	0.75
Carbohydrate, g	226.70 ± 85.2	218.4 ± 123.5	225.9 ± 122.4	0.78
Fat, g	88.42 ± 38.6	83.8 ± 42.9	83.3 ± 42.5	0.95
Total SFAs, g	28.1 ± 13.5	26.4 ± 15.4	26.7 ± 14.7	0.95
MUFAs, g	32.3 ± 14.8	19.6 ± 12.0	19.8 ± 10.5	0.79
PUFAs, g	21 ± 10.8	31.1 ± 14.6	30.1 ± 17.1	0.94
Fiber, g	21.1 ± 9.6	19.9 ± 10.3	20.1 ± 9.1	0.94
Calcium, mg	957.3 ± 456.5	885.0 ± 473.7	915.8 ± 508.7	0.78
Alcohol, oz	1.2 ± 1.65	1.1 ± 1.6	1.0 ± 1.7	0.73
Caffeine, mg	201.8 ± 163.5	223.1 ± 194.3	179.8 ± 140.4	0.24
Cooked lean meat beef, pork, veal, lamb, and game, oz	1.35 ± 1.51	1.6 ± 1.6	1.1 ± 1.5	0.12
Cooked lean meat, frank, sausage, luncheon meats, oz	0.6 ± 0.6	0.6 ± 0.6	0.6 ± 0.7	0.88
Cooked lean meat from organ meats, oz	0.014 ± 0.06	0.01 ± 0.05	0.01 ± 0.06	0.72
Cooked lean meat chicken, turkey, and other poultry, oz	1.48 ± 1.2	1.3 ± 1.0	1.6 ± 1.3	0.25
HEI 2010 score	64.3 ± 10.0	64.6 ± 11.8	62.7 ± 10.7	0.42

HEI2010 indicates Healthy Eating Index (a measure of diet quality used to assess how well a set of foods aligns with key recommendations of the dietary guidelines for Americans; it uses a scoring system to evaluate a set of foods; scores range from 0 to 100).

in the study database by a trained coordinator. Participants were provided additional incentive ($40 incentive per draw) for completing the baseline and 9-month SU blood draws to account for the inconvenience. Completion rates for baseline and 9-month SU blood draw were 100% and 77%, respectively.

Satisfaction With Intervention and Study Website, Study Feasibility, and Acceptability

Participant satisfaction with the intervention was high (0- to 100-point scale), with intervention being easy, enjoyable, understandable, and helpful (Table 2). The overall satisfaction with intervention was moderate–high. No significant differences by treatment arm were noted except that cherry extract intake was more understandable than the diet modification intervention ($p = 0.01$; Table 2).

Subject satisfaction with study website was high for the overall study participants, with more than 70% of people moderately to extremely satisfied with various aspects of study website (Table 3). Participants reported high rate of concordance of website content with the personalized plan (Table 3). Satisfaction ratings were similar across the 2 active comparator arms.

The amount of time spent for study was acceptable, with nonsignificantly higher score in cherry extract versus diet modification group (Table 2).

Dietary Changes

There were no differences in baseline diet quality in cherry extract versus diet modification groups (Table 4). No between-group differences in dietary component intake were seen in cherry extract versus diet modification groups from baseline to follow-up visits, except significantly lower total calories and total carbohydrate intake at 6 months in the diet modification versus cherry extract group ($p < 0.05$) and borderline significantly lower total fat intake ($p = 0.05$; Table 5), respectively. Some increase in all 3 diet components occurred from 6 to 9 months in the diet modification group; values were still lower than those at the baseline (Table 5). There was no meaningful body mass index change in either group (Table 5).

Exploratory Outcomes: HAQ Section Scores, Current Pain, Well-being, and Proportion With Target SU

Baseline HAQ domain scores were similar for cherry extract and diet modification arms (Table 6). Comparing 9-month scores with baseline scores, 6 of the 8 HAQ domains (dressing, arising, walking, hygiene, reaching, gripping, outside activity) improved significantly from baseline to 9 months in cherry extract versus 2 HAQ domains in the diet modification group (Table 6).

There were no significant differences in pain intensity (current, last 24 hours), well-being, or target SU of less than 5 mg/dL or less than 6 mg/dL, between groups over the study follow-up (Table 7). Small within-group improvements were noted in current pain intensity or well-being from baseline to follow-up (Table 7).

Study End Qualitative Debriefing

Qualitative debriefing of study participants at study exit revealed the following main messages: (1) overall study enjoyment, (2) future study improvements, (3) the preference for little more human versus internet interaction, (4) the hassle of study assessment reminders, (5) gout flare surveys were too frequent, (6) suggestion

TABLE 5. Dietary Component Changes by Treatment Arm: Baseline and Study Follow-up Every 3 Months

	Baseline			3 mo			6 mo			9 mo			Overall *p* value
	n	Mean (SD)	*p* value	n	Mean (SD)	*p* value	n	Mean (SD)	*p* value	n	Mean (SD)	*p* value	Over 9 mo
Body mass index, kg/m^2			0.49			0.66			0.22			0.16	0.33
Cherry	41	32.5 (7.9)		40	32.5 (7.3)		35	32.2 (7.9)		31	32.0 (6.5)		
Diet	40	34.0 (10.0)		30	33.4 (8.7)		27	35.2 (11.1)		20	35.0 (8.8)		
Total calories, kcal			0.99			0.47			**0.03**			0.40	0.39
Cherry	41	2015.0 (952.9)		40	1837.9 (714.4)		35	1707.5 (754.1)		31	1765.5 (813.6)		
Diet	43	2012.5 (954.7)		32	1697.8 (914.1)		28	1307.1 (682.9)		23	1537.6 (1172.9)		
% Calories from carbohydrate intake			0.16			0.13			0.80			0.21	0.13
Cherry	41	43% (10%)		40	43% (8%)		35	45% (8%)		31	42% (8%)		
Diet	43	46% (11%)		32	47% (9%)		28	45% (10%)		23	45% (13%)		
% Calories from fat intake			0.48			0.64			0.57			0.61	0.45
Cherry	41	38% (10%)		40	36% (8%)		35	36% (7%)		31	37% (8%)		
Diet	43	37% (8%)		32	36% (9%)		28	35% (8%)		23	36% (8%)		
% Calories from protein intake			0.35			0.62			0.14			0.48	0.82
Cherry	41	16% (4%)		40	16% (3%)		35	16% (4%)		31	18% (8%)		
Diet	43	15% (4%)		32	18% (3%)		28	18% (8%)		23	16% (6%)		
Protein, g			0.75			0.58			0.16			0.42	0.41
Cherry	41	78.2 (35.3)		40	73.6 (29.6)		35	66.3 (28.7)		31	73.3 (30.9)		
Diet	43	75.7 (35.6)		32	68.8 (43.7)		28	55.5 (31.1)		23	63.7 (54.3)		
Carbohydrate, g			0.78			0.78			**0.02**			0.69	0.60
Cherry	41	218.4 (123.5)		40	198.9 (90.4)		35	193.1 (91.9)		31	186.5 (99.5)		
Diet	43	225.9 (122.4)		32	192.4 (103.2)		28	143.3 (76.9)		23	173.3 (146.8)		
Fat, g			0.95			0.38			**0.05**			0.25	0.33
Cherry	41	83.8 (42.9)		40	74.7 (33.6)		35	67.0 (30.1)		31	73.3 (36.7)		
Diet	43	83.3 (42.5)		32	67.0 (40.9)		28	51.7 (30.8)		23	60.3 (45.7)		
Total SFAs, g			0.75			0.47			**0.04**			0.25	0.36
Cherry	41	26.4 (15.4)		40	23.3 (12.9)		35	21.1 (11.5)		31	23.2 (12.8)		
Diet	43	26.7 (14.7)		32	21.1 (12.4		28	15.4 (9.1)		23	19.1 (12.5)		
MUFAs, g			0.79			0.26			*0.06*			0.21	0.25
Cherry	41	19.6 (12.0)		40	28.3 (12.2)		35	25.1 (10.8)		31	27.3 (12.7)		
Diet	43	19.8 (10.5)		32	24.4 (16.4)		28	19.4 (12.8)		23	21.9 (18.1)		
PUFAs, g			0.94			0.66			0.16			0.39	0.56
Cherry		31.1 (14.6)		40	16.9 (7.9)		35	15.3 (7.0)		31	16.8 (9.6)		
Diet	41	30.1 (17.1)		32	16.0 (10.7)		28	12.5 (8.4)		23	14.2 12.5)		
Fiber, g			0.94			0.77			0.34			0.75	0.97

Continued next page

TABLE 5. *(Continued)*

	Baseline			3 mo			6 mo			9 mo			Overall *p* value Over 9 mo
	n	Mean (SD)	*p* value	n	Mean (SD)	*p* value	n	Mean (SD)	*p* value	n	Mean (SD)	*p* value	
Cherry	41	19.9 (10.3)		40	19.0 (8.6)		35	17.8 (8.2)		31	17.1 (7.9)		
Diet	43	20.1 (9.1)		32	19.6 (10.3)		28	15.8 (8.8)		23	18.1 (14.5)		
Calcium, mg			0.78			0.88			*0.07*			0.29	0.63
Cherry	41	885.0 (473.7)		40	810.2 (394.8)		35	762.1 (385.3)		31	831.9 (462.1)		
Diet	43	915.8 (508.7)		32	828.2 (583.9)		28	588.6 (349.1)		23	684.4 (551.0)		
Alcohol, oz			0.95			0.58			0.48				
Cherry	41	1.1 (1.6)		40	1.1 (1.4)		35	1.0 (1.3)		31	1.0 (1.5)	0.67	0.59
Diet	43	1.0 (1.7)		32	1.0 (1.7)		28	0.8 (1.4)		23	0.8 (1.6)		
Caffeine, mg			0.73			0.28			0.65			0.78	0.59
Cherry	41	223.1 (194.3)		40	210.3 (172.5)		35	160.0 (142.4)		31	152.0 (147.4)		
Diet	43	179.8 (140.4)		32	167.8 (154.8)		28	178.5 (178.7)		23	162.5 (124.7)		
Cooked lean meat, frank, sausage, luncheon meats, oz			*0.12*			0.75			0.75			0.82	0.95
Cherry	41	1.6 (1.6)		40	0.7 (1.0)		35	0.6 (0.5)		31	0.6 (0.8)		
Diet	43	1.1 (1.5)		32	0.7 (0.7)		28	0.5 (0.5)		23	0.6 (0.7)		
Cooked lean meat beef, pork, veal, lamb, and game, oz			0.88			0.37			0.13			0.45	0.14
Cherry	41	0.6 (0.6)		40	1.3 (1.3)		28	1.0 (1.0)		31	1.3 (1.5)		
Diet	43	0.6 (0.7)		32	1.0 (1.2)		18	0.7 (0.8)		23	1.0 (1.4)		
Cooked lean meat from organ meats, oz	43		0.72			0.13			1.0			0.25	0.90
Cherry		0.01 (0.05)		40	0.02 (0.1)		35	0 (0)		31	0.002 (0.01)		
Diet	41	0.01 (0.06)		32	0.002 (0.01)		28	0 (0)		23	0.02 (0.04)		
Cooked lean meat chicken, turkey, and other poultry, oz	43		0.25			0.12			0.59			0.74	0.74
Cherry	41	1.3 (1.0)		40	1.5 (1.3)		35	1.3 (1.0)		31	1.2 (0.8)		
Diet	43	1.6 (1.3)		32	1.0 (1.0)		28	1.2 (1.0)		23	1.1 (1.2)		
HEI2010 score			0.42			0.58			0.25			0.50	0.99
Cherry	41	64.6 (11.8)		40	65.5 (11.6)		35	64.4 (11.9)		31	64.8 (10.7)		
Diet	43	62.7 (10.7)		32	67.1 (11.2)		28	67.7 (10.2)		23	62.6 (12.2)		

Bold font indicates statistical significance, $p < 0.05$.

TABLE 6. Baseline and 9-Month HAQ-DI Domain and Total Scores for Participants With Both Values Available

	All Participants (n = 58) Mean ± SD		Cherry Extract (n = 32[a]) Mean ± SD			Diet Modification (n = 26[a]) Mean ± SD			Cherry vs Diet *p* value	
	Baseline	9-mo FU	Baseline	9-mo FU	*p* value	Baseline	9-mo FU	*p* value	Baseline	9-mo FU
HAQ-DI domains										
Dressing	0.41 ± 0.8	0.20 ± 0.5	0.44 ± 0.8	0.22 ± 0.8	**0.05**	0.38 ± 0.8	0.15 ± 0.5	0.13	0.97	0.37
Arising	0.50 ± 0.7	0.22 ± 0.5	0.53 ± 0.8	0.28 ± 0.8	**0.04**	0.46 ± 0.6	0.15 ± 0.4	0.03	0.11	**0.02**
Eating	0.17 ± 0.5	0.10 ± 0.4	0.22 ± 0.5	0.16 ± 0.5	0.16	0.12 ± 0.4	0.04 ± 0.2	0.42	0.51	**<0.001**
Walking	0.78 ± 0.9	0.34 ± 0.7	0.84 ± 1.0	0.38 ± 0.8	**0.009**	0.69 ± 0.8	0.31 ± 0.7	**0.048**	0.33	0.61
Hygiene	0.67 ± 1.0	0.26 ± 0.7	0.66 ± 0.9	0.31 ± 0.9	**0.006**	0.69 ± 1.0	0.19 ± 0.6	**0.009**	0.42	0.29
Reaching	0.50 ± 0.8	0.29 ± 0.6	0.56 ± 0.8	0.31 ± 0.6	**0.03**	0.42 ± 0.8	0.27 ± 0.6	0.32	0.73	0.74
Gripping	0.33 ± 0.7	0.17 ± 0.5	0.31 ± 0.6	0.16 ± 0.5	0.06	0.35 ± 0.7	0.19 ± 0.5	0.25	0.44	0.82
Outside activity	0.79 ± 1.0	0.47 ± 0.9	0.84 ± 1.0	0.44 ± 0.9	**0.003**	0.73 ± 1.0	0.50 ± 0.9	0.30	0.77	0.76
HAQ-DI score	0.52 ± 0.6	0.26 ± 0.7	0.55 ± 0.7	0.28 ± 0.5	**0.001**	0.48 ± 0.6	0.23 ± 0.4	**0.047**	0.61	0.13

[a]Of the 58 people with paired HAQ data at baseline and 9-months, 32 in the cherry extract group and 26 in the diet modification group had HAQ data.
Higher HAQ scores are worse and indicate more disability. Bold font indicates statistical significance, $p < 0.05$.
DI indicates disability index; FU, follow-up.

to have larger number of people participate in each diet and cherry phone session, and (7) time commitment to the study (Appendix 6, http://links.lww.com/RHU/A144). Overall, patients reported a positive study experience and constructive feedback regarding the frequency of assessments and the reminders and their preference to use a laboratory at their health care provider rather than the Quest laboratory (more convenient).

DISCUSSION

This report of patient-centered outcomes and key study procedure finalization adds to our previous report of primary and secondary study outcomes from our pilot internet gout RCT, mini-GOUCH.[12] A CONSORT checklist provides the key details of the randomized trial (Appendix 7, http://links.lww.com/RHU/A144). Study limitations included open-label design, no placebo arm, possible regression to the mean, limited generalizability to non-internet gout cohorts, and loss to follow-up. A low proportion of patients in our internet study (37%) were currently on ULT, consistent with poor adherence with ULT in gout[25–27] and possibly may be due to selection bias among people being recruited in the study, who might be less interested in pharmacological therapies and more interested in alternative therapies. Poor adherence to gout therapy and suboptimal gout outcomes[25–27] have generated interest in testing behavioral interventions, most notably a nurse-led gout management program.[28] The nurse-led gout management program dramatically improved allopurinol adherence and gout outcomes. Studies focusing on improving gout outcomes

TABLE 7. Exploratory Outcomes

	Baseline			3 mo			6 mo			9 mo		
	n	Mean (SD)	*p* value	n	Mean (SD)	*p* value	n	Mean (SD)	*p* value	n	Mean (SD)	*p* value
Current pain intensity, 0–10												
Cherry extract	41	2.17 (2.82)	0.40	41	1.27 (2.37)	0.87	37	1.22 (2.17)	0.67	32	1.03 (1.93)	0.71
Diet modification	43	1.65 (2.52)		37	1.35 (1.98)		31	1.00 (1.98)		26	0.85 (1.80)	
Average pain in last 24 h, 0–10												
Cherry extract	41	2.19 (2.60)	0.62	41	1.27 (2.31)	0.69	37	1.11 (2.09)	0.72	32	0.84 (1.44)	0.99
Diet modification	43	1.91 (2.64)		37	1.08 (1.79)		31	0.94 (1.78)		26	0.85 (1.69)	
Well-being (0–10; lower = better)												
Cherry extract	41	3.10 (2.83)	0.89	41	1.85 (2.57)	0.40	37	1.86 (2.45)	0.64	32	1.91 (2.51)	0.50
Diet modification	43	2.70 (2.40)		37	2.35 (2.67)		31	1.61 (1.84)		26	1.46 (2.44)	
% With SU <6 mg/dL												
Cherry extract	41	11 (26.8%)	0.43		N/A			N/A		34	7 (20.6%)	0.62
Diet modification	43	15 (34.9%)			N/A			N/A		31	8 (25.8%)	
% With SU <5 mg/dL												
Cherry extract	41	6 (14.6%)	0.84		N/A			N/A		34	2 (5.9%)	0.18
Diet modification	43	7 (16.3%)			N/A			N/A		31	5 (16.1%)	

N/A indicates not applicable because SU was assessed at baseline and at 9 months only; SU, serum urate.

motivated us to search examine complementary therapies that could potentially improve gout outcomes. Several findings deserve further discussion.

We found that the internet study procedures including the study interventions were feasible and acceptable to study participants, who were also satisfied with the internet website content, function, and interaction. This indicated that an internet study design is acceptable and feasible to conduct trials of dietary supplements and dietary modification in gout. Qualitative debriefing of study participants at study exit revealed overall high satisfaction with study procedures by participants and provided important insights and improvements for the next step hypothesis-testing trial. These included redesigning study assessment reminders and gout flare surveys, more human interaction (instituting a baseline and 3 monthly coordinator phone calls), having larger numbers of participants in each diet and cherry phone session, and clarifying time commitments for the study participation.

We noted a reduction in the intake of total calories and carbohydrates in both groups and a greater reduction in the diet modification group at 6 months (nonsignificant at 9 months). Notably, our 0-, 3-, and 6-month dietitian telephone sessions with participants were designed to motivate participants and potentially address this well-described phenomenon of short-term efficacy of dietary changes in observational or randomized trials.[29] However, the reduction in effect size noted between 6 and 9 months indicated that some loss of response was evident. This has implications for the future trials of diet modification in gout. More frequent diet sessions, larger groups for the calls with an opportunity for more interaction, a different timing of diet sessions, a more frequent contact by the study coordinator via phone and/or email, or inclusion of more behavioral components to keep participant involved might help increase the durability of the effect of diet modification intervention. Some improvements in the cherry extract group might be attributable to diet changes that patients might have made (on their own). Inclusion of a placebo arm and instructions to patients not to change their diet in the future placebo-controlled RCT of cherry extract will help reduce or eliminate the effect related to dietary changes.

We also finalized key study procedures including the modification of VioScreen, an online dietary assessment tool, into a gout-specific FFQ, *GoutWell*, gout flare surveys, gout diagnosis confirmation by participant's health care provider, collection of patient-reported gout classification criteria, and the SU collection by a centralized national laboratory. *GoutWell* also sent gout flare assessments and reminders. Prospective collection of validated gout flares[30,31] has been challenging in previous trials in patients with gout. In the current pilot study, we demonstrated successful prospective gout flare assessment; that is, 82% in cherry extract and 69% in the diet modification groups completed these assessments overall with higher completion rates in the beginning compared with the end of the study. We performed 18 such assessments per participant, and based on constructive feedback in qualitative debriefing, we will modify the frequency of these assessments and modify use of technological solutions to improve response rates.

Physician confirmation of presence/absence of gout diagnosis was achieved in 92% of interested participants, indicating that this approach is practical for our future trial. Success in obtaining data on gout classification criteria from patients (100%) was higher than that from the health care provider offices (80%). More people met the classification criteria for gout in patient-reported (92%) versus provider-reported criteria (67%). This could indicate either higher inaccuracy versus better recall by patients versus providers, and their relative contributions cannot be determined with the current data. Physician-assessed classification criteria are usually the criterion standard in typical pharmaceutical trials, but this study suggests that patient-reported criteria may be a practical alternative, because most gout classification criteria represent patient experience and are obtained with history rather than physical examination. We considered using the 2015 ACR gout classification but decided in favor of the 1977 gout classification criteria because of their simplicity. The details needed to document the 2015 ACR gout classification (time course and bursa involvement) and the use of new technology (ultrasound and dual-energy computed tomography) made this inappropriate for our study, because we were seeking historical documentation of these criteria as per the patient or health care provider report. A reasonably high rate of SU blood draw completion was noted at baseline (100%) and 9-month (77%) SU blood draw, indicating that this is a practical approach when additional study incentive is provided because of long driving distance and the inconvenience.

Our study provides data on exploratory outcomes including HAQ sections, current pain, well-being, and dietary changes. Six of the 8 HAQ sections improved notably in the cherry extract group versus 2 HAQ sections in the diet modification group. This finding, in conjunction with our previous finding of improvement in overall HAQ score and gout flares with cherry extract,[12] provides further insight into the mechanism of improvement of HAQ scores with cherry extract use. Health Assessment Questionnaire is an OMERACT-endorsed valid measure of function for clinical trials in gout.[21] This study provides insights into changes in HAQ section scores. We previously reported that the total mean HAQ scores significantly improved from baseline to 9 months, to 0.28 versus 0.55 in cherry extract ($p = 0.001$), but not in the diet modification group, 0.23 versus 0.48 ($p = 0.06$).[12] Small, insignificant differences in pain intensity (current and last 24 hours) and well-being between treatment arms are consistent with observations for maximum pain intensity in our previous report.[12]

In summary, this report of patient-centered outcomes including study/intervention feasibility and acceptability and finalization and implementation of key study procedures provides further evidence that the internet gout trials are possible for studies of complementary and alternative treatment strategies. Given the evidence of potential improvement of gout flares and HAQ scores in the cherry extract arm in our previous report,[12] an adequately-powered hypothesis-testing trial of cherry extract versus placebo is needed to assess whether cherry extract is efficacious in gout and to understand the underlying mechanisms. Borderline improvements in mean HAQ scores and gout flares in diet modification[12] and a strong patient preference for studies of diet as the top research agenda[9] indicate that a future assessment of diet modification versus usual care or intensification of diet modification with behavioral intervention versus usual care may also be needed. Such studies can help us understand the role of diet and dietary supplements in the management of gout and fill knowledge gaps highlighted by gout treatment guidelines.[10]

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