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Core Set of Domains for Outcome Measures in Behçet's Syndrome

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Objective. An unmet need exists for reliable, validated, and widely-accepted outcome measures for randomized clinical trials in Behçet's syndrome. The Outcome Measures in Rheumatology (OMERACT) Behçet's Syndrome Working Group, a large, multidisciplinary group of experts in Behçet's syndrome and patients with Behçet's syndrome, had an objective of developing a core set of data-driven outcome measures for use in all clinical trials of Behçet's syndrome.

Methods. The core domain set was developed through a comprehensive, iterative, multistage project that included a systematic review, a focus group meeting and qualitative patient interviews, a survey among experts in Behçet's syndrome, a Delphi exercise involving both patients and physician experts in Behçet's syndrome, and use of the data, insight, and feedback generated by these processes to develop a final core domain set.

Results. All steps were completed and domains were delineated across the organ systems involved in this disease. Since trials in Behçet's syndrome often focus on specific manifestations and not on the disease in its entirety, the final proposed core set includes 5 domains mandatory for study in all trials in Behçet's syndrome (disease activity, new organ involvement, quality of life, adverse events, and death) with additional subdomains mandatory for study of specific organ–systems. The final core set was endorsed at the 2018 OMERACT meeting.

Conclusion. The core set of domains in Behçet's syndrome provides the foundation through which the international research community, including clinical investigators, patients, the biopharmaceutical industry, and government regulatory bodies can harmonize the study of this complex disease, compare findings across studies, and advance development of effective therapies.

INTRODUCTION

Behçet's syndrome is a multisystem, variable-vessel vasculitis with a relapsing and remitting disease course with high morbidity, depending on the organ system involved. It causes oral and genital ulcers, erythema nodosum-like lesions and papulopustular lesions, arthralgia or arthritis, posterior or panuveitis with retinal vasculitis, arterial aneurysms, thrombosis in arteries and veins of all sizes, parenchymal brain lesions, cerebral sinus thromboses, and intestinal ulcers (1). Skin, mucosa, and musculoskeletal

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SIGNIFICANCE & INNOVATIONS

- The heterogeneity in the outcomes and outcome measures used in clinical trials of Behçet's syndrome has made it difficult to compare results of trials with different agents or from different centers, conduct meta-analyses, or create combined data sets for additional analyses.
- The core set of domains for clinical trials in Behçet's syndrome has been developed by the Outcome Measures in Rheumatology (OMERACT) Behçet's Syndrome Working Group with the aim of improving disease assessment in trials of Behçet's syndrome by providing a critical framework for use of outcome measures.
- The core set was developed through a multiyear, data-driven, iterative process following the rigorous standards of the OMERACT filter 2.0, resulting in consensus among patients, physicians, and researchers from several countries about what to measure in clinical trials for Behçet's syndrome. The core set received strong endorsement by the OMERACT community.
- An important innovation with this core set is that instead of a single domain set for use in all trials, there is a mandatory set of domains to be used in all trials of Behçet's syndrome and separate sets of subdomains specific for each type of organ or system involvement for use in trials seeking to specifically assess that type of involvement. This approach may provide a model for outcomes assessment in other multisystem diseases.

involvement can be associated with significant impairment in quality of life when lesions are present without causing permanent damage, whereas ocular, vascular, nervous, and gastrointestinal system involvement can result in serious disability and may even be life-threatening. Clinical findings show important heterogeneity across patients, which makes trial design and disease assessment complicated (2).

Each patient with Behçet's syndrome has only some of the disease manifestations over their lifetime and typically only a few of the manifestations are active at the same time (1). This lack of uniformity creates challenges in developing a therapeutic modality for the entire disease. Due to these difficulties, clinical trials for Behçet's syndrome are usually designed to evaluate a single type of system involvement. Conducting studies in populations of patients with Behçet's syndrome with heterogeneous manifestations using overall disease assessment instruments as primary endpoints may not be the most optimal. Some manifestations may improve while others worsen, so the change in overall disease activity scores may not be a reliable indicator of therapy efficacy. This fact is especially important for trials with agents that have shown differences in drug response across types of organ involvement. Variation in the frequency and severity of relapses of different organ manifestations is another challenge in overall composite disease assessment in Behçet's syndrome. Additionally, the severity of relapses may vary, causing damage and disability in some patients and only a transient impairment of quality of life in others. Finally, impairment of function due to damage can be difficult to discern from active disease.

Although a number of trials have been conducted in Behçet's syndrome with different agents, disease assessment has not been optimal. Standardized outcome measures that are widely accepted and commonly used in Behçet's syndrome trials do not exist. This lack of standardization has been problematic in the study of Behçet's syndrome, with difficulty in comparing results of randomized controlled trials with different agents or results of studies from different centers, combining results of studies with the same agent in meta-analyses, or combining data sets for additional analyses (3,4). In summary, there are multiple challenges due to the heterogeneity of the disease that impede successful drug development.

These challenges led the Outcome Measures in Rheumatology (OMERACT) Behçet's Syndrome Working Group (Appendix A) to work with a large multidisciplinary group of experts in Behçet's syndrome, most of whom are members of the International Society for Behçet's Disease, and patients with Behçet's syndrome, to develop a core set of data-driven outcome measures for use in all clinical trials. The first phase of this project that has been completed and is described in this article is the core set of domains for clinical trials in Behçet's syndrome, which was endorsed by OMERACT.

MATERIALS AND METHODS

The core set of domains was created following the methodology endorsed by OMERACT (5,6), with the final aim of developing a core set of outcome measures to be used in all clinical trials in Behçet's syndrome. This was an iterative, multistage, multiyear project that involved a systematic review, a survey among experts, an outcome measures focus group meeting including all stakeholders, qualitative patient interviews, a Delphi exercise involving both physician experts in Behçet's syndrome from different specialties and countries and patients with Behçet's syndrome, and ultimately endorsement through voting at the OMERACT 2018 meeting. The study was approved by the Ethics Review Committee of Istanbul University–Cerrahpasa Medical Faculty (83045809/604.01).

Systematic review. A systematic literature review was conducted to identify which domains were adopted as outcomes and outcome measures in previous studies of Behçet's syndrome (7). All randomized controlled trials, nonrandomized clinical trials, longitudinal or retrospective cohort studies, case series, biomarker studies, and genetic association studies that involved patients with Behçet's syndrome were included. The domains

and subdomains that were found in the included studies were identified as candidate items for the Delphi exercise.

Interest group meeting. To start collaborative work with a large group of experts in Behçet's syndrome, an outcome measures special interest group meeting was held during the 16th International Conference on Behçet's Disease (8). Multiple stakeholders were invited to this meeting. Participants included physicians and/or researchers from all specialties who were experts in the care of Behçet's syndrome (rheumatologists, ophthalmologists, dermatologists, neurologists, gastroenterologists, and oral health medicine specialists), patients with Behçet's syndrome, and physicians from the biopharmaceutical industry experienced in designing trials for Behçet's syndrome. The ideas and feedback generated during the meeting helped the group leaders better understand the scope of the project and shape the next steps in the project.

Survey among experts. An initial survey was conducted among experts in Behçet's syndrome who were rheumatologists, dermatologists, ophthalmologists, gastroenterologists, internists, or dentists from 13 countries to get their opinion on the domains that needed to be addressed and the instruments that are used to evaluate each of these domains in trials of Behçet's syndrome (2). An online tool (SurveyMonkey) was used to conduct the survey and collect responses. A total of 51 physicians were invited by electronic mail and received up to 3 reminders. The survey included 11 questions about the endpoints that are relevant for trials in Behçet's syndrome, the validity and reliability of the 4 overall disease activity assessment instruments for Behçet's syndrome that were identified through the systematic review, the weight of potential items to be assessed in trials of Behçet's syndrome, and whether organ-specific tools in addition to an overall disease assessment instrument are necessary to evaluate disease activity in Behçet's syndrome.

Qualitative patient interviews. In-depth, semistructured individual patient interviews were conducted with 20 patients with Behçet's syndrome from Turkey (15 men, 5 women, mean ± SD age 35 ± 6 years) (9). These patients were selected to represent the heterogeneous disease spectrum of Behçet's syndrome, and patients had various types of organ and system involvement. In addition to skin and mucosa lesions (all), 10 had eye involvement, 8 had vascular involvement, 6 had arthritis, 5 had nervous system involvement, 3 had gastrointestinal involvement, and 2 had only skin and mucosa involvement. Patients were interviewed about the impact of Behçet's syndrome on their daily activities, physical function, social and family life, psychological well-being, and coping strategies. Seven conceptual components (disease onset, diagnostic experience, treatment history, disease remission, disease flare, quality of life, and mental health impact) were covered using 41 open-ended questions. Interviews were audiorecorded, transcribed, translated into English, and entered into a qualitative data analysis computer software package (NVivo 11). A grounded theory approach was employed in thematic analysis of translated interviews (10,11). In addition to better understanding the patients' perspective of Behçet's syndrome, these interviews helped generate candidate domains and subdomains important to patients that would be included in the Delphi exercise.

Delphi process. The candidate domains that were retrieved through the systematic review, survey among experts in Behçet's syndrome, qualitative patient interviews, and the focus group meeting among multiple stakeholder groups were incorporated into a Delphi questionnaire. Item selection for the questionnaire was influenced by the framework of OMERACT filter 2.0 and by input from the OMERACT community (5).

Since organ systems are often studied separately in Behçet's syndrome due to possible differences in treatment response, the questionnaire was designed in 7 sections, based on the trial question about what needs to be measured in: 1) all trials of Behçet's syndrome, 2) trials for mucocutaneous involvement, 3) trials for eye involvement, 4) trials for vascular involvement, 5) trials for central nervous system involvement, 6) trials for gastrointestinal involvement, and 7) trials for joint involvement.

The questionnaire included an explanation on how the domains in the first section would be assessed in all trials and how in addition to these domains, in the sections on specific organ systems, those domains will only be assessed in trials of that organ or system involvement, according to the trial question. Patients and physicians completed the same questionnaire. Medical terms were explained for the patients. RedCap was used for distribution of the questionnaires and collecting responses in the 2 Delphi rounds. The invitation to participate was sent to 130 patients and 123 physicians. The Turkish version for patients was validated by forward and backward translation. Items that were agreed on by at least 70% of either patients or physicians at the end of the first round were included in the questionnaire for the second round of the Delphi exercise.

All of the items were agreed to by at least 70% of the physicians and/or the patients in the first round of the Delphi exercise. Therefore, to decrease the number of domains and subdomains, the participants were asked during the second round of the Delphi exercise to rank the domains that should be assessed in each of the sections. The highest-ranked items in each section were selected without weighting according to the number of patients and experts that responded.

Due to the high level of agreement, running a third round of the Delphi exercise using the same methods was not necessary. However, a different approach was used due to the specific expertise needed for some of the categories. Lists of the highest-ranked items in the first section (overall disease) and the

highest-ranked items in the section related to each specialty were sent to experts of that specialty. A total of 37 physician experts in Behçet's syndrome were invited, the majority of whom had participated in the first 2 rounds. The experts were asked for their opinion on the mandatory domains that should be assessed in all trials, mandatory domains that should be assessed in trials concerning their specialty, the conditional domains that are important, but not mandatory, and the exploratory domains that could be assessed in specific trials. The responses were discussed among the OMERACT Behçet's Syndrome Working Group, and the core set of domains for clinical trials in Behçet's syndrome was created. Presentation and voting of the core set took place during the OMERACT 2018 meeting. Both physicians and patients participated in the voting.

RESULTS

Results of the systematic review. The following steps were completed and the core set of domains was developed, voted upon, and endorsed by the OMERACT community, beginning with the results of the systematic review, which were previously published in detail (7). This review explored both the domains of illness studied in Behçet's syndrome and the instruments used in research in Behçet's syndrome. The instruments chosen for use and emphasis provided insight into the domains of illness felt to be of primary importance to investigators. The systematic review revealed that 139 outcomes or outcome measures were reported on in a total of 249 articles. Some of these instruments were specifically developed for Behçet's syndrome, such as the Behçet's Disease Current Activity Form (12), the Behçet's Syndrome Activity Scale (13), and the Behçet's Disease Quality of Life Measure (14). Other instruments were non-disease-specific (generic), such as the Short Form 36 health questionnaire, which are frequently used in other rheumatic and nonrheumatic diseases, but were also used in Behçet's syndrome trials. The third group of instruments were single-organ measures developed for other diseases that share similar features with Behçet's syndrome, such as the Crohn's Disease Activity Index that was used in trials of intestinal involvement of Behçet's syndrome (15). However, some of these instruments in the last group have not been validated for use in Behçet's syndrome.

Thus, the systematic review showed that substantial variability occurred in the domains studied and the outcome measures used for assessing these domains. Despite the large number of outcome measures used in trials of Behçet's syndrome, at the time the trial was conducted, few were properly validated or widely used. The use of different outcome measures within any 1 domain, such as disease activity, makes it impossible to compare or bring together the results of clinical trials. In addition, no standard definition for disease states exists, such as for relapse or remission, or for other key concepts, such as response.

Results from the interest group meeting. Results of the systematic review were presented to the participants of the expert group, and a thorough discussion regarding the difficulties of disease assessment was held. The heterogeneity in the clinical presentations of Behçet's syndrome, differences in drug response across manifestations, difficulty in defining disease states such as relapse or remission, difficulty in separating disease activity from damage, and the inadequacy and lack of instruments to assess outcomes important to patients were the main challenges. Paper cases with different clinical manifestations were presented, and what to measure in these clinical scenarios was discussed, as were the shortcomings of the available outcome measure instruments. Suggestions were made on how to develop better instruments. Participants generally agreed that generic instruments or instruments developed for other diseases could be used as long as they were validated. The group agreed that collaborative work of all stakeholders, including patients with Behçet's syndrome, physicians, researchers from all specialties taking care of patients with Behçet's syndrome, and representatives from the biopharmaceutical industry, is needed to accomplish the development of a broadly acceptable, data-driven core set of outcome measures for Behçet's syndrome.

Results of the survey among experts. A total of 51 experts from different specialties were invited and 35 (69%) responded. The results of this survey were previously reported in detail (2). In summary, the levels of agreement among experts about which domains should be measured in clinical trials of Behçet's syndrome were as follows: disease activity (100% agreement), health-related quality of life (97%), physical function (83%), mortality (74%), disease-related damage (71%), disease severity (66%), fatigue (46%), and overall damage (45%). Experts were also asked whether they agreed that the 4 most commonly used disease activity assessment instruments are valid and reliable, with the following levels of agreement: Behçet's Disease Activity Index (46% agreement), the Behçet's Syndrome Activity Scale (43%), the Clinical Manifestations Index (22%), and the Iranian Behçet's Disease Dynamic Activity Measure (22%).

When experts were asked about the necessity of a new instrument for assessing overall disease activity, 89% agreed that such an instrument is necessary and 97% agreed that this instrument should include different weighted elements for each clinical manifestation, such as oral ulcers, genital ulcers, other skin lesions, arthritis, uveitis, vascular disease, nervous system lesions, or gastrointestinal lesions. The experts were also asked about the necessity of organ-specific instruments, with the following results by organ system: uveitis activity (92% agreement), neurologic activity (82%), vascular activity (73%), oral ulcer activity (73%), gastrointestinal activity (70%), genital ulcer activity (59%), and other cutaneous (papulopustular and nodular lesions) activity (50%).

Table 1. Physicians' and patients' rank order of importance of domains and subdomains for inclusion in clinical trials for each category of disease manifestation for Behçet's syndrome*

Physicians	Patients	Physicians and patients†
Overall		
Overall BeS disease activity	Overall BS disease severity	Overall BeS disease activity
Flare of existing organ involvement	Damage	Flare of existing organ involvement
New organ involvement	New organ involvement	Overall BeS disease severity
Overall BS disease severity	Flare of existing organ involvement	New organ involvement
Overall function	Overall BeS disease activity	Overall function
Physician global assessment of BeS	Quality of life	Damage
Patient global assessment of BeS	Overall function,	Quality of life
Quality of life	Psychological well-being	Patient global assessment of BeS
Damage	Patient global assessment of BeS	Physician global assessment of BeS
Acute phase response	Fatigue	Psychological well-being
Fatigue	Acute phase response	Fatigue
Psychological well-being	Physician global assessment of BeS	Acute phase response
Skin and mucosa involvement		
Mucocutaneous activity	Pain of oral ulcers	Mucocutaneous activity
Mucocutaneous severity	Mucocutaneous activity	Pain of oral ulcers
Number of oral ulcers	Number of oral ulcers	Number of oral ulcers
Pain of oral ulcers	Pain of genital ulcers	Mucocutaneous severity
Number of genital ulcers	Mucocutaneous severity	Pain of genital ulcers
Pain of genital ulcers	Pain of nodular lesions	Number of genital ulcers
Mucocutaneous function	Number of genital ulcers	Mucocutaneous function
Number of nodular lesions	Mucocutaneous function	Pain of nodular lesions
Pain of nodular lesions	Number of papulopustular lesions	Number of nodular lesions
Number of papulopustular lesions	Number of nodular lesions	Number of papulopustular lesions
Joint involvement		
Joint involvement activity	Joint involvement severity	Joint involvement activity
Swollen joint count	Pain	Joint involvement severity
Tender joint count	Joint involvement activity	Swollen joint count
Joint involvement severity	Tender joint count	Tender joint count
Pain	Swollen joint count	Pain
Eye involvement		
Ocular involvement activity	Ocular involvement severity	Ocular involvement activity
Visual acuity	Visual acuity	Visual acuity
Ocular involvement severity	Ocular involvement activity	Ocular involvement severity
Retinal vasculitis	Retinal vasculitis	Retinal vasculitis
Number of ocular attacks	Retinal infiltrates	Number of ocular attacks
Retinal infiltrates	Capillary leak	Retinal infiltrates
Cystoid macular edema	Number of ocular attacks	Cystoid macular edema
Glucocorticoid cessation/tapering	Cystoid macular edema	Capillary leak
Capillary leak	Glucocorticoid cessation/tapering	Glucocorticoid cessation/tapering
Vascular involvement		
New/extending venous thrombus	New arterial aneurysm	New arterial aneurysm
New arterial thrombus	New arterial thrombus	New/extending venous thrombus
New arterial aneurysm	New/extending venous thrombus	New arterial thrombus
Superficial thrombophlebitis	Superficial thrombophlebitis	Superficial thrombophlebitis
Central nervous system involvement		
New/flare of existing involvement	New/flare of existing involvement	New/flare of existing involvement
Progression on MRI	Progression on MRI	Progression on MRI
Cognitive functioning	Mood disorders	Cognitive functioning
Headache	Headache	Headache
Mood disorders	Cognitive functioning	Mood disorders
Gastrointestinal involvement		
Gastrointestinal activity	Flare of existing involvement	Gastrointestinal activity
Flare of existing involvement	Gastrointestinal activity	Flare of existing involvement
Abdominal pain	Perforation/surgery	Perforation/surgery
Perforation/surgery	Diarrhea	Abdominal pain
Diarrhea	Hematochezia	Diarrhea
Hematochezia	Weight loss	Hematochezia
Weight loss	Hematemesis	Weight loss
Hematemesis	Abdominal pain	Hematemesis
Nausea	Nausea	Nausea

* BeS = Behçet's syndrome; MRI = magnetic resonance imaging.
† The order of the items in the third column was arrived at by combining the preferences of physicians and patients.

Results of qualitative patient interviews. The results of the semistructured qualitative patient interviews have been reported in detail elsewhere (9). Several subdomains were identified through these interviews under the 4 main domains, which were symptoms, impact on function, psychological impact, and social impact. Skin problems, pain, vision problems, fatigue and sleep disturbances, and gastrointestinal concerns and weight loss were the most common subdomains within the symptom domain. The impact on function could be grouped in the categories of impact on speech and vision, mobility, energy for tasks, adaptations, and self care. Fear, anxiety, stress, depression, and anger were the most frequently discussed emotions in the psychological impact domain. A decreased ability to socialize and negative impact on social duties, especially on family life and work, were stressed in the social impact domain. These were useful in identifying domains important to patients to be sought for agreement during the Delphi exercise. The data collected through these interviews may also help in developing a Behçet's syndrome–specific, patient-reported outcome measure.

Delphi exercise. Among the 130 patients and 123 physicians who were invited to participate in the first round of the Delphi exercise, 59 patients (45%) and 74 physicians (60%) participated in round 1. Physicians were experts in Behçet's syndrome from different specialties in 21 countries over 3 continents, and most were members of the International Society for Behçet's Disease. Eighty-six percent of the physicians were from academic institutions. Their specialties were rheumatology (50%), dermatology (16%), ophthalmology (12%), internal medicine (12%), gastroenterology (3%), and neurology (1%).

The majority of the patients were from Turkey, Italy, US, UK, and France. The clinical manifestations experienced by the patients during their disease course were oral ulcers in 96%, skin lesions in 87%, genital ulcers in 76%, uveitis in 52%, vascular

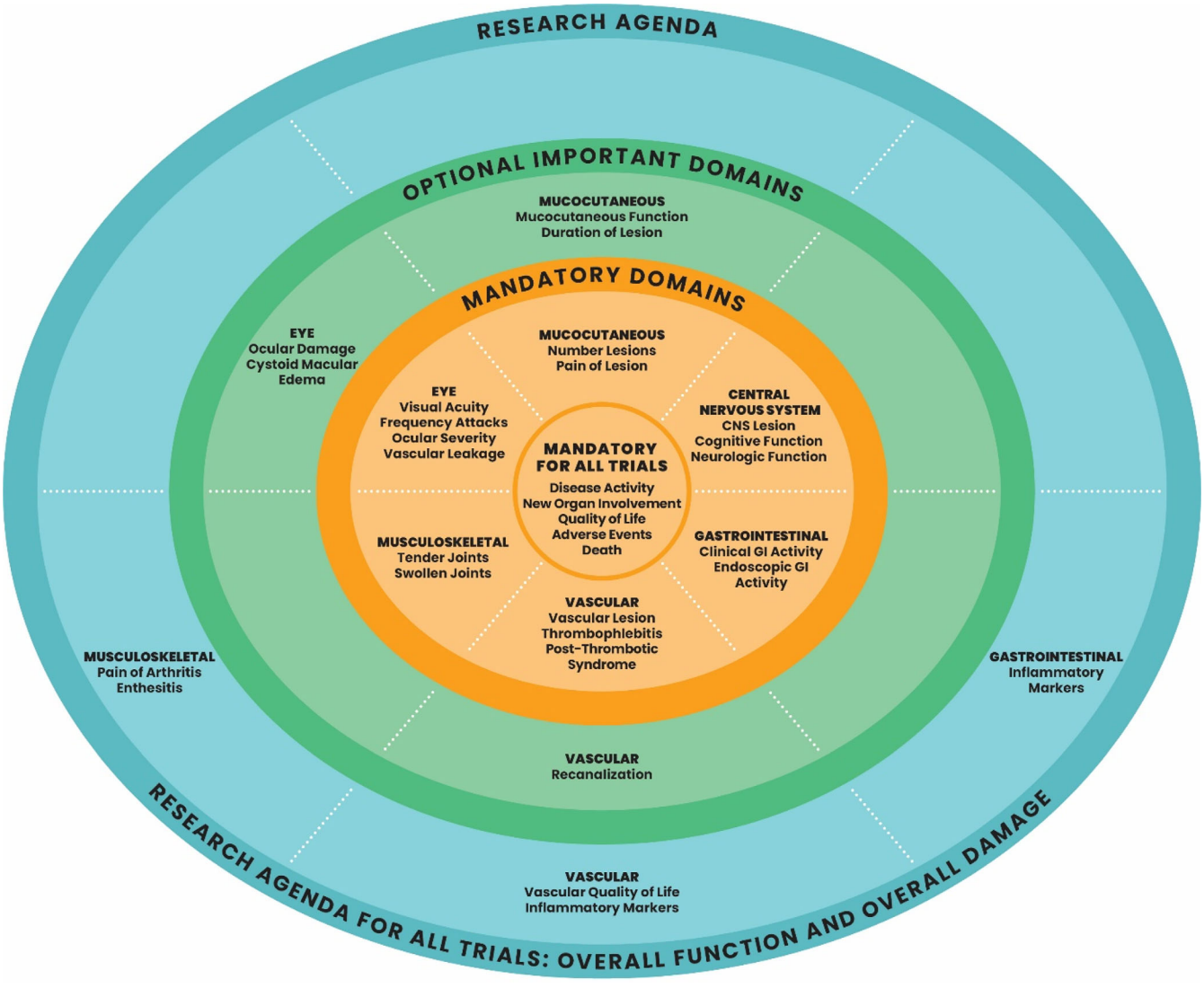

Figure 1. Core set of domains for study in clinical trials of Behçet's syndrome. CNS = central nervous system; GI = gastrointestinal.

involvement in 44%, nervous system involvement in 32%, and gastrointestinal involvement confirmed by endoscopy in 14%.

All of the 56 domains/subdomains that were sent during round 1 were endorsed by physicians and/or patients. All of the domains endorsed by physicians were also endorsed by patients. Additionally, patients endorsed fatigue, sleep, sexual functioning, psychological functioning, and acute phase reactants. To reduce the number of domains and subdomains to a number that could be feasibly assessed during a trial, the participants were asked to rank the items in the second round of the Delphi exercise. Results of the ranking by physicians and patients for overall assessment and each type of organ involvement are shown in Table 1.

To get a review and validation of the highest-ranked candidate domains in each category, the domains were sent to experts from the related specialty, together with the overall domains that would be assessed in all trials. Thirty of the 37 experts responded. Among these, 12 were rheumatologists, 5 were ophthalmologists, 5 were dermatologists, 4 were neurologists, 3 were gastroenterologists, and 1 was a vascular surgeon. Based on their responses and discussions among the OMERACT Behçet's Syndrome Working Group, the core set of domains was developed (Figure 1).

The core set consists of 5 domains that should be assessed in all trials in Behçet's syndrome (mandatory for all trials). These domains are overall disease activity, new organ involvement, quality of life, adverse events, and death. In addition to these, there are subdomains that should be assessed in trials for a specific organ involvement (mandatory per subset), as follows: 1) mucocutaneus: number and pain of lesions; 2) eye: visual acuity, frequency of ocular attacks, ocular severity, and vascular leakage; 3) vascular: vascular lesions, superficial thrombophlebitis, and post-thrombotic syndrome; 4) central nervous system: central nervous system lesion, cognitive function, and neurologic function; 5) gastrointestinal: clinical gastrointestinal activity and endoscopic activity; and 6) musculoskeletal: tender joint count and swollen joint count. Important but optional subdomains could be assessed according to the purpose of the trial (optional important domains); these are mucocutaneous function and duration of lesions for mucocutaneous involvement, ocular damage and cystoid macular edema for eye involvement, and recanalization for vascular involvement. Finally, the research agenda contains domains and subdomains, including overall function and overall damage for potential use in all trials in Behçet's syndrome, pain of arthritis and enthesitis for musculoskeletal involvement, vascular quality of life and inflammatory markers for vascular involvement, and inflammatory markers for gastrointestinal involvement.

OMERACT voting. A total of 111 participants who attended the OMERACT 2018 meeting voted. The core set was endorsed by 100 of the voters (90.1%), a remarkably high percentage for any vote at OMERACT, especially for a core set.

DISCUSSION

The development of a core set of domains for use in clinical trials in Behçet's syndrome was achieved using the methodology set forth by OMERACT, and through a consensus of patients, physicians, and researchers about what to measure in clinical trials for Behçet's syndrome. The final core set was the result of a multiyear, data-driven, iterative process. The defined domains provide a critical framework for use of outcome measures in Behçet's syndrome and as a guide for design of future trials in Behçet's syndrome. The domain core set will help reduce the heterogeneity of trial designs in Behçet's syndrome and harmonize research in this complex disease.

This core set of domains includes an important difference from core sets previously developed for most other diseases such as rheumatoid arthritis or antineutrophil cytoplasmic antibody–associated vasculitis (16,17). Instead of a single domain set for use in all trials, there is a mandatory set of domains to be used in all trials of Behçet's syndrome and separate sets of subdomains specific for each type of organ or system involvement for use in trials seeking to specifically assess that type of involvement. This novel approach to domain selection addresses 2 key issues: 1) a need to generate outcomes data comparable across all trials of Behçet's syndrome; and 2) recognition that Behçet's syndrome affects many different organ systems that are often studied separately and for which responses to treatments and the treatments themselves may differ. Thus, the proposed core set provides a practical framework for harmonizing clinical trial designs in this multisystem disease.

A few examples of the variable disease courses, life impacts, and approaches to treatment are illustrative of the challenges in outcome assessment in Behçet's syndrome. Mucocutaneous lesions and joint involvement follow a relapsing and remitting course, with symptoms that may impair the quality of life of patients, but do not result in permanent physiologic damage. In contrast, active involvement of the brain, eyes, gastrointestinal tract, or vasculature each carries a risk of long-term damage, organ failure, and in some cases, death. With varying timing, severity, and impact of relapses, current treatment strategies are often quite different for these types of involvement; thus, disease assessment is often different. These variations in course and outcomes in Behçet's syndrome have led to the proposed set of core domains for each main organ system. In addition to organ-specific subdomains, having domains that should be assessed in all trials is important, to avoid missing any new manifestations or the potential impact of an agent in preventing or worsening of those systems not the primary target of the clinical trial.

There were several strengths in the approach to developing this core set of domains. The work followed each aspect and the rigorous standards of the OMERACT filter 2.0 process. The perspectives of patients, physicians, investigators, and methodologists were all strongly taken into consideration, with international

representation among each stakeholder group. Additional strengths of the work were the inclusion of patients with each type of organ system involvement in both the qualitative interviews and the Delphi process, and the inclusion of experts from all relevant specialties. Consensus and international buy-in was reached at each stage, and the final core set was overwhelmingly endorsed by the OMERACT community.

Some limitations of the project included those inherent in the study of many relatively rare diseases, including potential overrepresentation by stakeholders from 1 or more regions and the relatively small number of participants within each group; however, the study involved participants from multiple countries and several continents.

The proposed approach to domain selection in Behçet's syndrome sets a new precedent within OMERACT and provides a paradigm for similar work in other multisystem rheumatic diseases, such as systemic lupus erythematosus and systemic sclerosis (scleroderma), and for diseases in other fields.

Developing this core set of domains for trials in Behçet's syndrome is an important step in harmonizing clinical trials and data collection in this complex disease, with the ultimate aim of enhancing the conduct and comparability of new trials, leading to better management and outcomes for patients with Behçet's syndrome.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Hatemi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Hatemi, Meara, Özgüler, Direskeneli, Mahr, Shea, Cam, Gul, Y. Yazici, H. Yazici, Merkel.

Analysis and interpretation of data. Hatemi, Meara, Özgüler, Shea, H. Yazici, Merkel.

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APPENDIX A: RESEARCH COLLABORATORS FOR THE OMERACT BEHÇET SYNDROME WORKING GROUP

The members of the Behçet Syndrome Working Group are: Canada: Nataliya Milman, Beverly Shea, Peter Tugwell; Denmark: Robin Christensen; France: Bahram Bodaghi, Julien Gaudric, Isabelle Koné-Paut, Alfred Mahr, David Saadoun; Germany: Andreas Altenburg, Christopher Deuter, Ina Kötter, Nicole Stuebiger, Manfred Zierhut, Christos Zouboulis; Greece: Petros Sfikakis; Iran: Fereydoun Davatchi, Alireza Khabbazi, Farhad Shahram; Iceland: Gunnar Tomasson; Italy: Massimo Accorinti, Salvatore D'Angelo, Giacomo Emmi, Claudio Fabiani, Ignazio Olivieri, Nicolo Pipitone, Carlo Salvarani; Japan: Shunsei Hirohata, Yoshiaki Ishigatsubo,

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