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Title: Outcome Measures for the Evaluation of Treatment Response in Hidradenitis Suppurativa for Clinical Practice: A HiSTORIC Consensus Statement

Nicole Mastacouris, MS,[1] Rachel Tannenbaum, MD,[1] Andrew Strunk, MA,[1] Jonathan Koptyev, BA,[1] Pim Aarts, MD,[2] Raed Alhusayen, MBBS, MSc,[3] Falk G. Bechara, MD,[4] Farida Benhadou, MD, PhD,[5] Vincenzo Bettoli, MD,[6] Alain Brassard, MD, FRCPC,[7] Debra Brown, RN,[8] Siew Eng Choon, MBBS, FRCP,[9] Patricia Coutts, RN,[10] Dimitri Luz Felipe da Silva, MD,[11] Steven Daveluy, MD,[12] Robert P. Dellavalle, MD,[13,14] Veronique del Marmol, MD, PhD,[15] Lennart Emtestam, MD,[16] Kurt Gebauer, MBBS, FACD, FACP, OAM,[17] Ralph George, MD, FRCSC, [18] Evangelos J. Giamarellos-Bourboulis, MD, PhD,[19] Noah Goldfarb, MD,[20] Iltefat Hamzavi, MD,[21] Paul G Hazen, MD,[22] Barbara Horvath, MD, PhD,[23] Jennifer Hsiao, MD,[24] John R. Ingram, MD, PhD,[25] Gregor B. E. Jemec, MD, DMSc,[26] Joslyn Kirby, MD, MS, Med,[27] Michelle A. Lowes, MBBS, PhD,[28] Angelo Marzano, MD,[29] Lukasz Matusiak, MD, PhD,[30] Haley B. Naik, MD, MHSc,[31] Martin M. Okun, MD, PhD,[32] Hazel Oon, MD,[33,34] Lauren Orenstein, MD, MSc,[35] So Yeon Paek, MD,[36] José C. Pascual, MD,[37] Pablo Fernandez-Peñas, MD, PhD,[38] Barry Resnik, MD, FAAD,[39] Christopher Sayed, MD,[40] Linnea Thorlacius, MD, PhD,[41] Hessel H. van der Zee, MD, PhD,[42] Kelsey R van Straalen, MD, PhD,[42] Amit Garg, MD[1]

1 Northwell Health, New Hyde Park NY

2 Department of Dermatology, Erasmus University Medical Center, Rotterdam, The Netherlands.

3 Sunnybrook Research Institute, Division of Dermatology, University of Toronto, Toronto, ON, Canada

4 Department of Dermatology, Venereology and Allergology, Ruhr-University, Bochum, Germany.

5 Université libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B.), CUB Hôpital Erasme, Department of Dermatology, Brussels, Belgium.

6 Department of Medical Sciences, O.U. of Dermatology, Azienda Ospedaliera – University of Ferrara, Italy.

7 University of California Davis, Sacramento, CA.

8 Medical Dermatology Guy's and St Thomas' NHS Foundation Trust.

9 Hospital Sultanah Aminah and Clinical School Johor Bahru, Monash University Malaysia, Malaysia.

10 Independent Consultant.

11 University Santo Amaro (UNISA), São Paulo, Brazil.

12 Wayne State University Department of Dermatology, Detroit, MI.

13 Department of Dermatology, University of Colorado Anschutz School of Medicine, Aurora, CO.

14 Dermatology Service, US Department of Veterans Affairs, Eastern Colorado Health Care System, Aurora, CO.

15 Department of Dermatology, Erasme Hospital, Universite Libre de Bruxelles, Brussels, Belgium.

16 Section of Infectious Diseases and Dermatology, Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden.

17 University of Western Australia, Perth, Western Australia.

18 Department of Surgery, University of Toronto, Toronto, Canada.

19 Department of Internal Medicine, National and Kapodistrian University of Athens, Greece.

20 Departments of Medicine and Dermatology, University of Minnesota, Minneapolis, MN.

21 Department of Dermatology, Henry Ford Health System, Detroit, MI.

22 Case-Western Reserve University School of Medicine, Cleveland, OH.

23 Department of Dermatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

24 Department of Dermatology, University of Southern California, Los Angeles, CA.

25 Division of Infection & Immunity, Cardiff University, Cardiff, UK.

26 Department of Dermatology, Zealand University Hospital, Roskilde, Denmark.

27 Penn State Milton S Hershey Medical Center, Hershey, PA.

28 The Rockefeller University, New York, NY.

29 Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

30 Department of Dermatology, Venereology and Allergology Wroclaw Medical University, Wroclaw, Poland.

31 Department of Dermatology, University of California, San Francisco, CA.

32 Fort HealthCare, Fort Atkinson, WI.

33 National Skin Centre, Singapore, Singapore City, Singapore.

34 Lee Kong Chian School of Medicine, Singapore City, Singapore.

35 Emory University School of Medicine, Department of Dermatology, Atlanta, GA.

36 Baylor University Medical Center, Dallas, Texas A&M College of Medicine, Dallas, TX.

37 Dermatology Department, Alicante University General Hospital, Alicante Institute for Health and Biomedical Research (ISABIAL), Alicante, Spain.

38 The University of Sydney, Westmead Hospital, Department of Dermatology, Westmead, New South Wales, Australia.

39 Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL.

40 University of North Carolina School of Medicine Department of Dermatology, Chapel Hill, NA.

41 Department of Dermatology, Zealand University Hospital, Roskilde, Denmark.

42 Department of Dermatology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands.

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Corresponding Author:
Amit Garg, MD
Department of Dermatology
Donald and Barbara Zucker School of Medicine at Hofstra/Northwell
1991 Marcus Ave, Ste. 300
New Hyde Park, New York 11042
Phone: 516-321-8543
Email: amgarg@northwell.edu
ORCID iD is 0000-0003-0886-6856

Reprint requests: Amit Garg, MD, ORCID iD is 0000-0003-0886-6856

Authors:
Nicole Mastacouris; nmastacouris@northwell.edu
Rachel Tannenbaum; rtannenbaum@northwell.edu
Andrew Strunk; astrunk1@northwell.edu
Jonathan Koptyev; jk1614@rwjms.rutgers.edu
Pim Aarts; p.aarts@erasmusmc.nl
Raed Alhusayen; raed.alhusayen@sunnybrook.ca
Falk G. Bechara; f.bechara@klinikum-bochum.de
Farida Benhadou, dr.farida.benhadou@gmail.com
Vincenzo Bettoli; vincenzo.bettoli@gmail.com
Alain Brassard; abrassard@ucdavis.edu
Debra Brown; Debra.brown@gstt.nhs.unk
Siew Eng Choon; choonse@yahoo.co.uk
Pat Coutts; patmcoutts@rogers.com

Steven Daveluy; sdaveluy@med.wayne.edu
Robert P Dellavalle; robert.dellavalle@cuanschutz.edu
Veronique del Marmol, v.marmol@skynet.be
Lennart Emtestam; lennart.emtestam@ki.se
Dimitri Luz Felipe da Silva; dimitriluzfs@gmail.com; ORCID 0000-0003-0869-9330
Kurt Gebauer; kurt@fremantledermatology.com.au
Ralph George; ralph.george@unityhealth.to
Evangelos J. Giamarellos-Bourboulis; egiamarel@med.uoa.gr
Noah Goldfarb; gold0414@umn.edu
Iltefat Hamzavi; iltefat@hamzavi.com
Paul Hazen; paulhazen@aol.com
Barbara Horvath; b.horvath@umcg.nl
Jennifer Hsiao; j.hsiao.publications@gmail.com
John R. Ingram; ingramjr@cardiff.ac.uk, ORCID 0000-0002-5257-1142
Gregor B. E. Jemec; gbj@regionsjaelland.dk
Joslyn Kirby; jkirby1@pennstatehealth.psu.edu
Michelle Lowes; lowesm8@gmail.com
Angelo Marzano; angelo.marzano@unimi.it
Lukasz Matusiak; luke71@interia.pl
Haley B Naik; haley.naik@ucsf.edu
Martin M Okun; mmokun@yahoo.com
Hazel Oon; derm@hazeloon.com
Lauren Orenstein; lauren.orenstein@emory.edu
So Yeon Paek; doctor.paek@gmail.com
Jose Pascual; jcpascualramirez@hotmail.com
Pablo Fernandez Penas; pablo.fernandezpenas@sydney.edu.au
Barry Resnik; bir@drresnik.com
Christopher Sayed; christopher_sayed@med.unc.edu
Linnea Thorlacius; linneath@gmail.com
Hessel van der Zee; h.vanderzee@erasmusmc.nl
Kelsey R van Straalen; kelseyvanstraalen@gmail.com
Amit Garg; amgarg@northwell.edu, ORCID iD is 0000-0003-0886-6856

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Abbreviations:
HS: Hidradenitis Suppurativa
HiSTORIC: Hidradenitis Suppurativa Core Outcomes Set International Collaboration

PRP: Patient Research Partners
COS: Core Outcome Set
C3: CHORD COUSIN Collaboration
ClinRO: Clinician-reported outcome measure
PRO: Patient-reported outcome measure
CREDES: Conducting and Reporting of Delphi Studies
SQUIRE: Standards for Quality Improvement Reporting Excellence
HS-IGA: Hidradenitis Suppurativa Investigator Global Assessment
HS-PGA: Hidradenitis Suppurativa Physician Global Assessment
IHS-4: International HS Severity Score System
HiSCR: Hidradenitis Suppurativa Clinical Response
HiSQOL: Hidradenitis Suppurativa Quality of Life
HSIA: Hidradenitis Suppurativa Impact Assessment
HSSA: Hidradenitis Suppurativa Severity Assessment

Abstract

Importance: Although several clinician and patient-reported outcome measures have been developed for trials in hidradenitis suppurativa (HS), there is currently no consensus on which are best suited for use in clinical practice. Identifying validated and feasible measures applicable to the practice setting has the potential to optimize treatment strategies and generate real-world evidence that may inform treatment guidelines.

Objective: To establish consensus on a core set of clinician and patient reported measures recommended for use in clinical practice, and to establish the appropriate interval within which these measures should be applied.

Evidence Review: Clinician and patient-reported HS measures and studies describing their psychometric properties were identified through literature reviews. Identified measures comprised an item-reduction survey and subsequent e-Delphi consensus rounds. In each consensus round, a summary of outcome measure components and scoring methods was provided to participants. Experts were provided with feasibility characteristics of clinician measures to aid selection. Consensus was achieved if at least 67% of respondents agreed with use of a measure in clinical practice.

Findings: Among all stakeholders, response rates for item-reduction, e-Delphi I, and e-Delphi II survey rounds were 74.6% (59/79), 93.2% (55/59), and 89.8% (53/59), respectively. In the final e-Delphi round, HS experts and patient research partners (PRPs) agreed with use of the HS Investigator Global Assessment (71.8%) and HS Quality of Life score (92.9%), respectively. The most preferred assessment interval in which to apply these measures was 3-months (69.2%).

Conclusions and Relevance: An international group of HS experts and PRPs from HiSTORIC achieved consensus on a core set of HS measures suitable for use in clinical practice. Consistent use of these measures may lead to more accurate assessments of HS disease activity and life impact, facilitating shared treatment decision making in the practice setting.

Introduction:

Among inflammatory skin diseases, hidradenitis suppurativa (HS) may be the most heterogeneous in its presentation and disease course. There are several distinct morphologic lesions in HS, including nodules, abscesses and tunnels. Patients experience a broad range of symptoms including fatigue, drainage, odor, itch and most notably, pain. Disease course is rather unpredictable, as patients experience flares in addition to chronic activity. Response to treatment is also highly variable, and few therapies demonstrate consistently high and sustained efficacy.[1] Nearly half of HS patients express dissatisfaction with their medical treatments.[2,3]

In this context, assessment of disease activity and treatment response is also complex. Standardized and regular application of outcome measures in clinical practice may facilitate bidirectional discussion between the dermatologist and patient on whether treatment goals are being met and whether timely adjustments to the overall therapeutic strategy may be warranted.[4] This approach has led to improved outcomes for patients with a number of chronic inflammatory diseases including rheumatoid arthritis and psoriatic arthritis.[5-7] Longitudinal recording of clinical outcomes may also support analyses of real-world treatment effectiveness, which provides insights into treatment impact in the broader HS population that clinical trial data cannot.[8] Further integration of patient-reported measures allows capture of treatment effect on symptoms and life quality, which patients may hesitate to discuss due to fear of stigmatization[9], and which may otherwise be underestimated by clinicians.[10-12] The objective of this study was to provide expert and patient consensus-based recommendations on the application of validated, HS-specific outcome measures that are feasible for clinical practice.

Methods

The Hidradenitis Suppurativa Core Outcomes Set International Collaboration (HiSTORIC) is an international multi-stakeholder group comprised of experts, patient research partners (PRP), methodologists, and industry partners with a background in health outcomes whose objective is to develop a core outcome set (COS) for interventional trials in HS, and for clinical practice.[13] Along with approximately 20 COS groups, HiSTORIC operates under the CHORD COUSIN Collaboration (C3), an

umbrella research organization whose mission is to develop, disseminate and implement COS for clinical trials and routine practice for dermatologic conditions with the goal of standardizing valid and reliable measurement of disease activity and treatment response, and of comparing effectiveness.[14] In 2018, HiSTORIC established consensus on the Core Domain Set ('what to measure') for interventional clinical trials in HS which included the following: 1) Pain, 2) Physical signs, 3) HS-specific Quality of Life, 4) Global assessment, 5) Progression of course (flare and recurrence after surgery), and 6) Symptoms.[15] To date, HiSTORIC has developed and/or validated a number of clinician-reported outcome measures (ClinROMs) and patient-reported outcome measures (PROMs) mapped to these core domains.[16-22]

A total of 55 HS Experts (consisting of dermatologists, internists, surgeons, and nurses) and 24 PRPs from the HiSTORIC group were invited to participate in the present study which was comprised of the following three phases: 1) literature search to identify candidate outcome measures in HS; 2) an online item reduction survey; and 3) an e-Delphi to establish consensus on a set of HS measures that should be applied to clinical practice. **(Figure 1)** Consensus surveys pertaining to the most suitable clinician and patient-reported outcome measures for practice were completed separately by HS Experts and PRPs, respectively, between September, 2022 and February, 2023. To prioritize feasibility for application to clinical practice, it was determined *a priori* that no more than one ClinROM and one PROM could be recommended at the conclusion of the consensus process. This project was conducted in compliance with the Conducting and Reporting of Delphi Studies (CREDES) standards [23] and the Standards for Quality Improvement Reporting Excellence (SQUIRE) reporting guideline.[24]

Identification of Candidate Treat to Target Measures

A literature search was performed to identify HS outcome measures that have been evaluated for psychometric properties including convergent validity, inter-rater reliability, intra-rater reliability, and responsiveness. This resulted in a total of 10 ClinROMs and 13 PROMs. Following initial review, two ClinROMs and eight PROMs were removed from consideration due to lack of specificity to HS, insufficient psychometric properties, or inadequate feasibility for the practice setting **(Supplementary eTable 1)**. We restricted outcome measurement instruments to those that were disease-specific, as these

289 measures capture disease impact with depth and tend to be more sensitive in detecting changes in the
290 patient's condition compared to general measures.[25]

291 *Item Reduction survey*

292 A single-round item reduction survey was conducted among HS experts and among PRPs
293 separately to eliminate measures that were unlikely to achieve consensus due to low feasibility or limited
294 relevance to patients' perception of treatment response. Information provided to participants included the
295 following: 1) rationale for the application of HS measures to clinical practice; 2) summary of the
296 components and scoring methodology of candidate measures;[16,18,19, 26-33] and 3) feasibility characteristics
297 of measures for clinical practice. **(Supplementary eTables 2 and 3)**

298 Experts were asked to select four of eight candidate ClinROMs that were most feasible for use in
299 clinical practice. In addition, experts were asked to select the most appropriate assessment interval within
300 which to apply the measures. The PRPs were asked to rank each of the five PROMs according to their
301 ability to capture information most relevant to determining whether a treatment is working adequately.
302 The four ClinROMs with the highest number of votes and the three PROMs receiving the highest
303 aggregate ratings (based on a weighted scale) were selected for consideration in consensus rounds.

304 *Consensus on HS Measures For Clinical Practice*

305 Consensus rounds were conducted separately among experts and PRPs on the most preferred
306 ClinROMs and PROMs applicable to practice. Participants who completed the item reduction survey
307 were eligible to participate in consensus rounds. Information provided to participants included the
308 following: 1) summary of the components and scoring methodology of candidate measures; 2) feasibility
309 characteristics of measures for routine practice; and 3) psychometric properties of the measures.[16-18, 26-28,
310 34-42] Background materials provided to participants are provided in **Supplementary eTables 2-4**.

311 Experts were asked to rate level of agreement with the following standardized statement for
312 ClinROMs included in the consensus exercise: "'Measure Name' *is a feasible measure that I am willing*
313 *to utilize in my routine clinical practice to assess treatment response."* We use the term "treatment
314 response" to refer to a change in the value of a particular outcome measure after the initiation of a

treatment. In addition, experts were asked to select the most appropriate assessment interval within which to apply the measure. The PRPs were asked to rate level of agreement with the following standardized statement for PROMs included in the consensus exercise: "'Measure Name' *captures aspects of HS impact that are relevant to me, and it should be used routinely to evaluate response to treatment."*

Experts and PRPs were asked to score each standardized statement using a 5-point Likert scale, which allowed participants to specify their level of agreement (strongly agree to strongly disagree). In accordance with the Delphi method, experts and PRPs were provided with aggregate data and anonymized comments from the previous Delphi round prior to making selections in the subsequent round.

Thresholds and definitions of consensus were based on previously cited values and were designated a priori.[43] Consensus In was defined as at least 67% of total participants agreeing or strongly agreeing with use of the measure in clinical practice. Consensus Out was defined as at least 67% of total participants disagreeing or strongly disagreeing with use of the measure. Instruments that did not meet either of these definitions were deemed to have no consensus. Prior to survey distribution, we specified that if multiple measures reached consensus, the measure with the highest percent agreement would be recommended.

Descriptive statistics were calculated to evaluate the demographic characteristics of clinicians and patients responding to each survey round. All statistical analysis was performed using Excel, version 16.70. This study was approved by the human subjects research committee of the Feinstein Institutes for Medical Research at Northwell Health.

Results

Demographic characteristics of experts and PRPs participating in item reduction and e-Delphi rounds are shown in **Tables 1 and 2**, respectively. Across these rounds, the majority of experts were practicing dermatologists (92.9 to 94.9%) with a median of 18 to 19 years of clinical experience following training. Most PRPs were female (76.5 to 85.7%), between the ages of 30-49 years (74.3 to 80.6%) and had moderate disease (52.9 to 57.1%). Response rates were 42/55 (76.4%), 38/42 (90.5%), and 39/42

(92.9%) in the item-reduction, e-Delphi I, and e-Delphi II rounds, respectively, among experts. Among PRPs, response rates were 17/24 (70.8%), 17/17 (100%), and 14/17 (82.4%) in the item reduction, e-Delphi I, and e-Delphi II rounds, respectively.

Item-reduction survey

The four ClinROMs that received the highest number of votes among experts were the following: HS-Investigator Global Assessment (HS-IGA) (63%), HS-Physician Global Assessment (HS-PGA) (63%), International HS Severity Score System (IHS-4) (56.5%), and HS Clinical Response (HiSCR) (54.3%). Among PROMs, the HS Quality of Life score (HiSQOL) (weighted ranks=60), HS Impact Assessment (HSIA) (51), and HS Severity Assessment (HSSA) (50) were scored by PRPs as most relevant to capturing therapeutic response. The remaining ClinROMs and PROMs were not selected for consideration in consensus rounds due to low agreement among experts and PRPs, respectively. Results of the item reduction survey round are shown in **Supplementary eTable 5**.

Consensus on Outcome Measures and Assessment Interval

Results for expert consensus rounds are shown in **Figure 2**. After the second round, the HS-IGA met criteria for Consensus In, with 71.8% of experts agreeing to its utility in clinical practice. None of the remaining ClinROMs achieved ≥ 67% agreement after e-Delphi II. Use of the IHS-4, HS-PGA, and HiSCR in clinical practice was supported by 56.4%, 51.3%, and 30.7% of experts, respectively, after e-Delphi II. More than half (53.8%) of experts disagreed with the use of HiSCR in clinical practice. Most experts agreed to apply the selected measures at 3-month (69.2%) or 4-month (17.9%) intervals.

Results for PRP consensus rounds are shown in **Figure 3**. After the second round, the HiSQOL met criteria for Consensus In, with 92.9% of PRPs agreeing to its application in clinical practice. No other PROMs achieved ≥ 67% agreement. Use of the HSSA and HSIA in clinical practice was agreed upon by an equal percentage (50.0%) of PRPs.

Discussion

An objective framework within which to evaluate disease status and response to treatment, both medical and procedural, is a necessary component to determining whether timely changes to the treatment strategy

during the 'window of opportunity' in HS may be warranted.[44] In this study, HiSTORIC achieved consensus on outcome measures in HS that are recommended to be applied in clinical practice. These included the HS-IGA, a ClinROM selected by HS experts, and the HiSQOL, a PROM selected by patients. Most respondents endorsed a 3-month assessment interval. The HS-IGA was developed using a Phase 3 clinical trial dataset [PIONEER I (NCT01468207), AbbVie] with input from experts, PRPs, and methodologists within HiSTORIC.[16] The measure was validated using a replicate Phase 3 clinical trial dataset [PIONEER II (NCT01468233), AbbVie] as well as a separate more recent Phase 2 clinical trial dataset [HS0001, UCB].[16,17] As a global assessment, the HS-IGA is a simple-to-use measure which demonstrates very strong test-retest reliability, good convergent validity with known disease activity anchors, and responsiveness to change (**Supplementary eTable 6**).[16,17] The HS-IGA utilizes the familiar construct of a 6-point ordinal scale with response defined as 2-point improvement from baseline. **(Supplementary eTable 7)** The HS-IGA is scored as a number between 0 and 5 based on the sum of abscess, nodule (inflammatory and non-inflammatory), and tunnel (draining and non-draining), in either the upper or lower body regions. Specification of qualifying lesion types and distinction among difficult-to-discern lesion types (i.e., inflammatory nodule vs abscess, or draining abscess vs draining tunnel) are not required by the clinician, which may support measurement accuracy. Papules, plaques, pustules, comedones, and scars are not counted in the score. The score limits counting to 21 qualifying lesions. These features of the HS-IGA may allow for feasibility and ease of use in clinical practice.

The HiSQOL, a disease-specific quality of life measure for adults with HS, captures the unique features of HS that are not directly measured with general skin quality of life measures. The measure consists of 17 items, each with a 7-day recall period, that assesses a wide range of symptoms related to HS, including pain, itch, odor, and drainage, as well as psychosocial impact, and activities that may be impacted by HS.[19] Each item is scored using an ordinal scale, ranging from 'not at all' to 'extremely' with a score ranging from 0 to 4, respectively. Some items have a response option of 'unable to do, due to HS' that is scored with the highest number of points (4), indicating high impact on quality of life. The total score ranges from 0 to 68, with higher scores indicating worse quality of life. **(Supplementary eFigure**

1) The HiSQOL has been translated into approximately 20 languages, which will support its broader application.[45,46] The HiSQOL has also been converted into an electronic version, which showed acceptability and usability regardless of age, gender, or device familiarity, as well as ease of use.[47] The HiSQOL was developed by an international steering group that included patients, thereby enhancing its content validity and ability to comprehensively capture the impact of HS on quality of life. As a result, it may be more sensitive to changes in the status of an HS patient with treatment.[10] Previous studies on the HiSQOL have demonstrated excellent reliability, including test-retest and internal consistency, and very strong convergent and known-groups validity.[19,21] Analysis from a recent phase II trial defined minimal important difference on the HiSQOL as an 18-point or 58% reduction in total score from baseline.[48] Additional studies with the HiSQOL are underway to evaluate responsiveness and application to adolescents with HS, as well as to create a reduced, or 'mini', set of items.

It is important to underscore that recommendations on use of disease measures for HS in practice represent one component of a comprehensive evaluation strategy. Adherence to recommendations also does not ensure an improved outcome for every patient. Ultimate judgment on assessment and treatment should be made by the physician in partnership with the patient. The intent of these recommendations is to provide an objective framework with both clinician and patient input that can facilitate bidirectional discussion, trust building, and decision-making on the current treatment strategy and the need to adjust or escalate treatment in an appropriate timeframe. Defining feasible HS measures that can be utilized in routine practice provides the foundation on which targets of treatment may be established and treatment outcomes may be assessed. While HiSTORIC has achieved consensus on the HS measures which should be applied in practice, the thresholds that should be achieved on each as an indication of treatment adequacy is not yet defined. For this reason, payers should not require use of this framework for access or continuation of treatments. As additional and more effective treatment options become available, the Treat to Target benchmark will have more meaningful application in practice. Indeed, similar Treat to Target frameworks that guide treatment decisions through shared decision-making have improved

418 outcomes for patients with other chronic diseases including diabetes mellitus, hypertension, rheumatoid
419 arthritis, and psoriatic arthritis.[49-53]

420 There are limitations to the present study which merit consideration. While we aimed to optimize
421 global participation, most experts and HS patients represented countries in North America and Europe,
422 where historically HS has been a significant research focus. The HS expert consensus results may have
423 been influenced by differing regional practices in HS management. Neither the HS-IGA nor the HiSQOL
424 have been studied in the practice setting. However, experts and patients have agreed that both validated
425 measures are simple to use and evaluate concepts relevant to the practical care of HS patients. Lastly,
426 while we encourage application of the proposed HS disease activity and impact measures in practice, we
427 recognize the inherent variability in individual practice time, staffing and workflows which may limit
428 implementation. Potential implementation challenges include the need to train clinicians in outcome
429 measure scoring, interpretation, as well as the staff in routine administration and collection of data. Given
430 some challenges to practice implementation, outcome measurement may need to be prioritized for
431 patients with diseases, such as HS, for which treatment outcomes are frequently suboptimal. This study
432 also had several strengths. Experts were primarily dermatologists with approximately 20 years of clinical
433 experience and expertise in medical management of HS patients. In addition, the e-Delphi method had
434 several benefits, including (1) asynchronous survey distribution (2) anonymity of survey responses and
435 (3) presentation of anonymized comments to aid decision making. The PROM was selected by patients
436 with HS and experience in participating in consensus processes on HS measures. We also employed an
437 iterative process of consultation and feedback to ensure development of a high-quality survey instrument
438 for each round.

439 In conclusion, HiSTORIC has achieved consensus on the application of HS-IGA and HiSQOL
440 measures to evaluate HS patient outcomes in clinical practice. The measures are recommended to be
441 applied at three-to-four-month intervals during treatment. Application of HS outcome measures in
442 practice may facilitate shared decision making on treatments with the goal of optimizing treatment
443 strategies, controlling symptoms, and slowing disease progression. Use of these measures in practice may

also generate real-world evidence that may inform HS treatment guidelines. Future consensus studies will establish targets of treatment in practice as well as a definition of minimal disease activity which may be applied in clinical trials and in practice as more efficacious treatments in HS are developed.

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Figure I Title: Methods Overview
Figure I Legend: Abbreviations and Acronyms – HS: Hidradenitis Suppurativa, ClinROM: Clinician-reported outcome measure, PROM: Patient-reported outcome measure, HS-IGA: Hidradenitis suppurativa Investigator Global Assessment, HiSQOL: Hidradenitis Suppurativa Quality of Life

Figure II Title: e-Delphi Results, Clinician Reported Outcome Measures
Figure II Legend: Abbreviations and Acronyms – HS-IGA: Hidradenitis suppurativa Investigator Global Assessment, IHS-4: International Hidradenitis Suppurativa Severity Score System, HS-PGA: Hidradenitis Suppurativa Physician Global Assessment, HiSCR: Hidradenitis Suppurativa Clinical Response

Figure III Title: e-Delphi Results, Patient Reported Outcome Measures
Figure III Legend: Abbreviations and Acronyms – HiSQOL: Hidradenitis Suppurativa Quality of Life, HSIA: Hidradenitis Suppurativa Impact Assessment, HSSA: Hidradenitis Suppurativa Symptom Assessment

Table I Title: Characteristics of Experts in Hidradenitis Suppurativa
Table I Legend: Abbreviations and Acronyms: Q1/Q3: Quartile 1 (25^{th} percentile)/ Quartile 3 (75^{th} percentile)

Table II Title: Characteristics of Hidradenitis Suppurativa Patient Research Participants
Table II Legend: Abbreviations and Acronyms: Q1/Q3: Quartile 1 (25^{th} percentile)/ Quartile 3 (75^{th} percentile)
a - Missing for some participants

Table I. Characteristics of Experts in Hidradenitis Suppurativa

	Item-reduction survey	**e-Delphi Round I**	**e-Delphi Round II**
Total # of participants	42	38	39
Response Rate	42/55 (76.4%)	38/42 (90.5%)	39/42 (92.9%)
Geographic Region			
USA	17 (40.5)	15 (39.5)	15 (38.4)
Europe	16 (38.1)	15 (39.5)	16 (41)
Canada	3 (7.1)	3 (7.9)	3 (7.7)
SE Asia	3 (7.1)	2 (5.3)	2 (5.1)
Australia	2 (4.8)	2 (5.3)	2 (5.1)
South America	1 (2.4)	1 (2.6)	1 (2.6)
Primary Specialty			
Dermatology	39 (92.9)	36 (94.7)	37 (94.9)
Surgery	1 (2.4)	1 (2.6)	1 (2.6)
Other (Internal Medicine)	2 (4.8)	1 (2.6)	1 (2.6)
Years in Practice (post-training completion)			
Median (Q1, Q3)	18.5 (10, 28.75)	19 (9.25, 25.75)	18 (10.25, 29.5)
Practice Setting			
Academic/ University	34 (81)	29 (76.3)	32 (82.1)
Community-based	7 (16.7)	8 (21.1)	7 (17.9)
Research	1 (2.4)	1 (2.6)	0 (0)

Abbreviations and Acronyms: Q1/Q3: Quartile 1 (25^{th} percentile)/ Quartile 3 (75^{th} percentile)

Table II. Characteristics of Hidradenitis Suppurativa Patient Research Participants

	Item reduction survey	e-Delphi Round I	e-Delphi Round II
Total # of participants	17	17	14
Response Rate	17/24 (70.8%)	17/17 (100%)	14/17 (82.4%)
Geographic Region			
USA	6 (35.3)	6 (35.3)	5 (35.7)
Europe	9 (52.9)	9 (52.9)	6 (42.9)
Canada	2 (17.6)	2 (11.8)	2 (14.3)
Age Category			
18-29	0 (0)	0 (0)	0 (0)
30-39	4 (23.5)	4 (23.5)	3 (21.4)
40-49	9 (52.9)	9 (52.9)	8 (57.1)
50-59	2 (11.8)	2 (11.8)	2 (14.3)
60+	2 (11.8)	2 (11.8)	1 (7.1)
Female Sex	15 (88.2)	13 (76.5)[a]	12 (85.7)
Race			
White	17 (100)	17 (100)	14 (100)
Years since HS symptom onset			
Median (Q1, Q3)	28 (24, 34)	27 (23, 33)	27.5 (22.5, 33.5)
Years since HS diagnosis			
Median (Q1, Q3)	16 (10, 23)	17 (11, 23)	14.5 (10.25, 22.25)
HS Disease Severity			
Mild	3 (17.6)	3 (17.6)	4 (28.6)
Moderate	9 (52.9)	9 (52.9)	9 (57.1)
Severe	5 (29.4)	5 (29.4)	2 (14.3)

Abbreviations and Acronyms: Q1/Q3: Quartile 1 (25^{th} percentile)/ Quartile 3 (75^{th} percentile)

a- Missing for some participants

Figure 1. Methods Overview

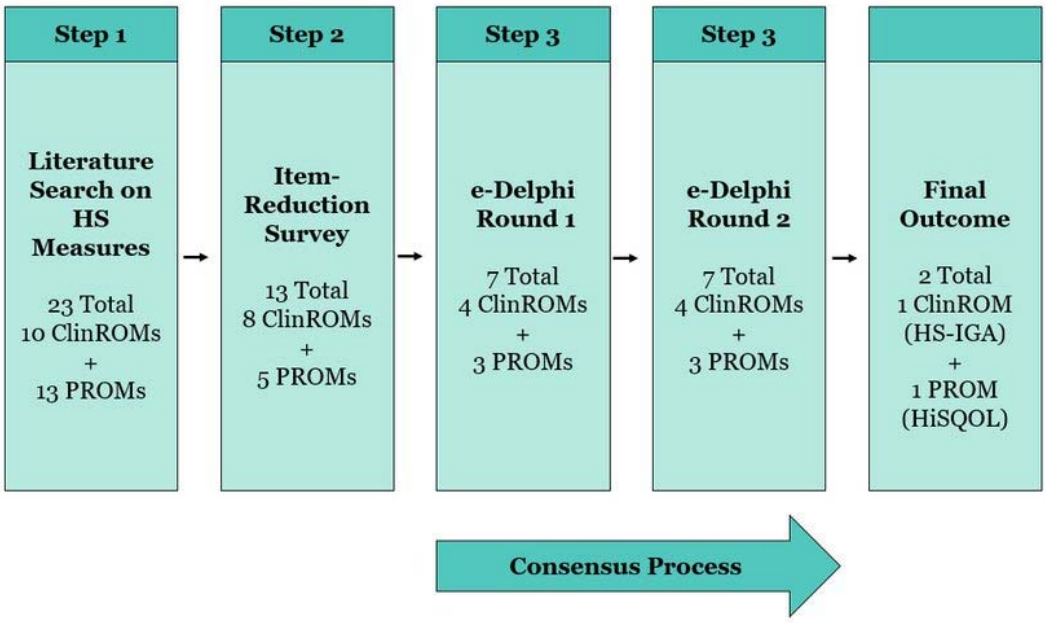

Figure 1 Legend: Abbreviations and Acronyms – HS: Hidradenitis Suppurativa, ClinROM: Clinician-reported outcome measure, PROM: Patient-reported outcome measure, HS-IGA: Hidradenitis suppurativa Investigator Global Assessment, HiSQOL: Hidradenitis Suppurativa Quality of Life

Figure 2. e-Delphi Results, Clinician Reported Outcome Measures

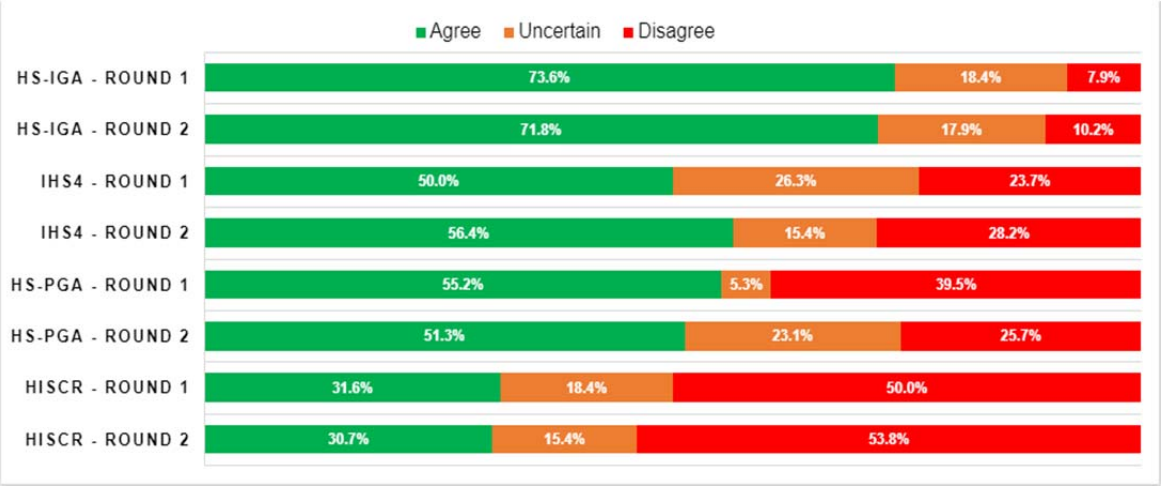

Figure 2 Legend: Abbreviations and Acronyms – HS-IGA: Hidradenitis suppurativa Investigator Global Assessment, IHS-4: International Hidradenitis Suppurativa Severity Score System, HS-PGA: Hidradenitis Suppurativa Physician Global Assessment, HiSCR: Hidradenitis Suppurativa Clinical Response

Figure 3. e-Delphi Results, Patient Reported Outcome Measures

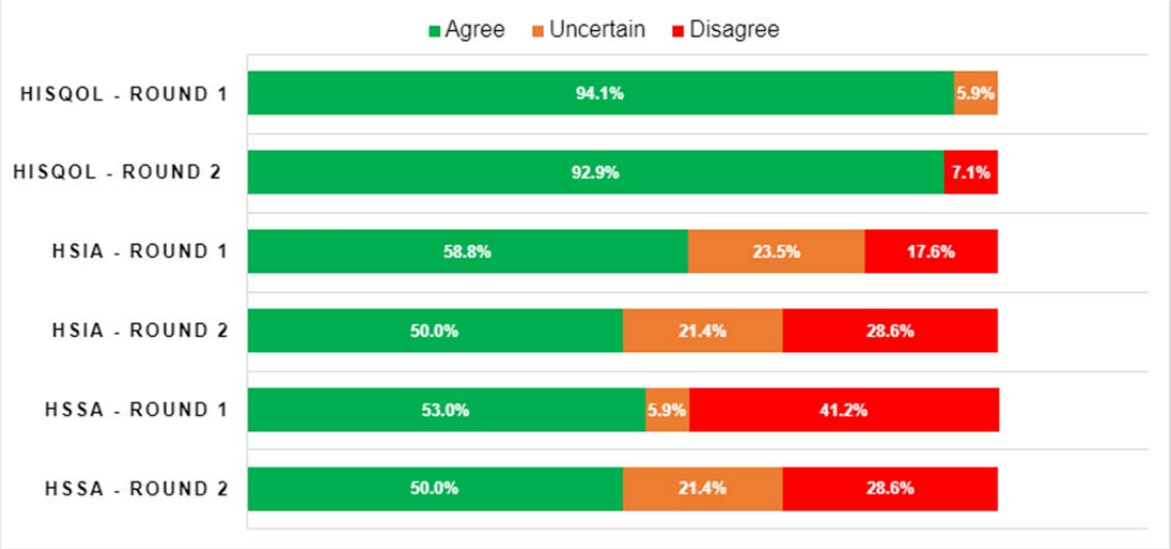

Figure 3 Legend: Abbreviations and Acronyms – HiSQOL: Hidradenitis Suppurativa Quality of Life, HSIA: Hidradenitis Suppurativa Impact Assessment, HSSA: Hidradenitis Suppurativa Symptom Assessment