

PAPER**International consensus for a definition of disease flare in lupus**

N Ruperto¹, LM Hanrahan², GS Alarcón³, HM Belmont⁴, RL Brey⁵, P Brunetta⁶, JP Buyon⁷, MI Costner⁸, ME Cronin⁹, MA Dooley¹⁰, G Filocamo¹, D Fiorentino¹¹, PR Fortin¹², AG Franks Jr⁷, G Gilkeson¹³, E Ginzler¹⁴, C Gordon¹⁵, J Grossman¹⁶, B Hahn¹⁶, DA Isenberg¹⁷, KC Kalunian¹⁸, M Petri¹⁹, L Sammaritano²⁰, J Sánchez-Guerrero²¹, RD Sontheimer²², V Strand¹¹, M Urowitz¹², JM von Feldt²³, VP Werth^{23,24}, JT Merrill²⁵

for the Lupus Foundation of America, Inc. International Flare Consensus Initiative

¹Gaslini Pediatria II, Reumatologia, PRINTO, Genova, Italy; ²Lupus Foundation of America, Inc., Washington, DC, USA; ³University of Alabama at Birmingham, Birmingham, AL, USA; ⁴New York University Hospital for Joint Diseases, New York, NY, USA; ⁵University of Texas Health Science Center at San Antonio School of Medicine, San Antonio, TX, USA; ⁶Genentech, San Francisco, CA, USA; ⁷New York University School of Medicine, New York, NY, USA; ⁸UT Southwestern Medical Center, Dallas, TX, USA; ⁹Medical College of Wisconsin, Milwaukee, WI, USA; ¹⁰University of North Carolina at Chapel Hill, USA; ¹¹Stanford University School of Medicine, Stanford, CA, USA; ¹²Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada; ¹³Medical University of South Carolina, Charleston, SC, USA; ¹⁴State University of New York Downstate Medical Center, Brooklyn, NY, USA; ¹⁵University of Birmingham Medical School, Edgbaston, Birmingham, UK; ¹⁶University of California at Los Angeles, Los Angeles, CA, USA; ¹⁷University College London, Bloomsbury, London, UK; ¹⁸University of California, San Diego School of Medicine, La Jolla, CA, USA; ¹⁹Johns Hopkins Medical Institutions, Baltimore, MD, USA; ²⁰Hospital for Special Surgery, New York, NY, USA; ²¹Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán México, Distrito Federal, México; ²²University of Utah School of Medicine, Salt Lake City, UT, USA; ²³University of Pennsylvania School of Medicine, Philadelphia, PA, USA; ²⁴Philadelphia VA Medical Center, Philadelphia, PA, USA; and ²⁵Oklahoma Medical Research Foundation, Oklahoma City, OK, USA

The Lupus Foundation of America (LFA) convened an international working group to obtain a consensus definition of disease flare in lupus. With help from the Paediatric Rheumatology International Trials Organization (PRINTO), two web-based Delphi surveys of physicians were conducted. Subsequently, the LFA held a second consensus conference followed by a third Delphi survey to reach a community-wide agreement for flare definition. Sixty-nine of the 120 (57.5%) polled physicians responded to the first survey. Fifty-nine of the responses were available to draft 12 preliminary statements, which were circulated in the second survey. Eighty-seven of 118 (74%) physicians completed the second survey, with an agreement of 70% for 9/12 (75%) statements. During the second conference, three alternative flare definitions were consolidated and sent back to the international community. One hundred and sixteen of 146 (79.5%) responded, with agreement by 71/116 (61%) for the following definition: “A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment.” The LFA proposes this definition for lupus flare on the basis of its high face validity. *Lupus* (2011) 20, 453–462.

Key words: autoimmune disease; flare; systemic lupus erythematosus

Introduction

Lupus is a chronic, remitting and relapsing autoimmune disorder characterized by unpredictable disease flares and remissions. Although a host of

new, rational biologic treatments are in the development pipeline, the heterogeneity of the patients has led to formidable challenges in clinical trial design and interpretation. The rate and the severity of flares during a year-long course of treatment are important predictors of disease outcome. However, different clinical trial designs have utilized various definitions of flare, each with pitfalls in logic that were sometimes only recognized in retrospect. In 2006, the LFA convened an International Consensus Panel to evaluate unmet needs in defining and measuring lupus flares. As the first step in

Correspondence to: Joan T Merrill, M.D., Member and Head Clinical Pharmacology Research Program, Oklahoma Medical Research Foundation, 825 Northeast 13th Street, Oklahoma City, OK 73104, USA

Email: Joan-Merrill@omrf.org

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creating or modifying major flare indices, the panel agreed that a single, community-accepted definition for flare is required as an underpinning for instruments being developed to measure this outcome.

Previous definitions for disease flare have usually included a combination of results from activity indices and serologic measures.¹⁻⁴ Several instruments have been developed to measure acute disease activity, and have been adapted, using serial measurements, to approximate flare indices. These have included the SLEDAI 2000, the revised Systemic Lupus Activity Measures (SLAMR), the European Consensus Lupus Activity Measurement (ECLAM), the British Isles Lupus Assessment Group (BILAG), and the Cutaneous Lupus Disease Area and Severity Index (CLASI).⁵⁻¹¹ Investigators in the National Institutes of Health-sponsored studies of Safety of Estrogens in Lupus National Assessment (SELENA) published a specific flare instrument linked to a modified version of the SLEDAI (SELENA SLEDAI).^{10,12} However, specific pitfalls in the application of all of these instruments to flare outcomes have been recognized. These include problems in determining the relative importance of missing elements in each instrument, problems in differentiating new organ flares from worsening within an organ, differentiating mild from moderate flare, and, very importantly, difficulties with all of the instruments in distinguishing between significant flares and small increases in disease activity which barely cross threshold definitions between mild and moderate or between moderate and severe disease ("the threshold effect").

The clinical challenges in quantifying flares in a disease that is heterogeneous between patients, and waxes and wanes unpredictably within each patient, are formidable. Additionally, patients with lupus may have clinical flares without serologic flare and vice versa.³ However, no previous community-wide input has been obtained to facilitate understanding of clinical flares in lupus patients. To ensure that flare measurement in future lupus clinical trials reflects a broad community understanding of the clinical and treatment implications of differing degrees of flare, the LFA utilized the expertise of the international lupus clinical community to gather input on these issues. The 9-10 May 2006 conference, titled "Definition and Validation of Lupus Flares," was convened to plan this process.¹³

At this meeting it was acknowledged that current instruments were insufficient to measure flare optimally. It was also determined that, before this problem could be addressed, a single, community-accepted, clinically meaningful overall definition of

flare was required to fully clarify whether variables such as threshold effects, random variation of clinical and serologic measurements, waxing and waning disease activity, or additional novel insights from the community would emerge as significant enough to impact a flare definition. The overriding goal was to elicit, from a wide range of knowledgeable lupus clinicians, a robust and generally accepted framework for differentiating and quantifying degrees of flare.

Following this preliminary planning conference, an international collaborative process was launched in 2007, with the technical help of the Paediatric Rheumatology International Trials Organization (PRINTO),¹⁴ a group experienced in consensus-building methods. The first objective was to survey the global lupus clinical community to obtain an unbiased view on how flares are defined in clinical practice. Secondly, further understanding of issues that arose during this polling process was sought, as well as problems in flare measurement that had been recognized in the context of clinical trials. The final goal was to integrate community-wide input into a consensus definition that could reflect important variables in daily medical practice and thus provide a meaningful rationale for outcome measures in clinical trials. The objective of this paper is to report the work done to achieve community-wide agreement on a flare definition that is considered meaningful by clinicians and addresses the ambiguities that have been recognized in clinical trials.

Patients and methods

The online polling project was conducted using the Delphi Technique, a well-recognized consensus formation methodology, specifically designed to combine judgments from a group of experts in a particular field.¹⁵ The Delphi Technique utilizes a series of well-defined questionnaire-based surveys and has been used to develop outcome measures for several chronic rheumatic diseases, including rheumatoid arthritis,¹⁶ juvenile arthritis,^{17,18} juvenile systemic lupus erythematosus,¹⁹⁻²¹ and idiopathic inflammatory myopathies.²²⁻²⁵ Consensus formation methodology is designed so that each subsequent step is based on the results of the previous steps.

Three Delphi surveys and a LFA consensus conference, convened between the second and third surveys, were performed. The surveys were

implemented via a web-based system, with user-name and password access through the secured PRINTO web site on an https platform. E-mails, faxes, or telephone reminders were used to ensure a response rate of at least 70% for the survey.

Web survey 1

Prior to the first survey, the LFA Flare Steering Committee, including representatives of various specialty areas that treat patients with lupus, identified a roster of 120 clinicians from around the world with significant experience treating lupus patients. Potential participants, including rheumatologists, nephrologists, and representatives from pharmaceutical companies from 11 countries (see Appendix), were first asked if they were interested in participating in the survey. After a positive reply, responders were asked to answer 13 open-ended questions proposed by the Steering Committee of the LFA in order to obtain community-wide understanding of how clinicians define lupus flare in practice, how its threshold, time course, duration, and severity are assessed, and whether there are problems differentiating lupus flare from other clinical conditions.

For the analyses of the results, and in order to avoid bias, a two-step procedure was used. First, all responses were reviewed and collated independently by the PRINTO team, and a "preliminary definition" was derived from the most characteristic responses to each question. Then, the community responses and PRINTO definitions were further reviewed by the Steering Committee of the LFA to ensure that the web-based community would have access to initial input that was either characteristic of or potentially conflicting with other statements. The results of this process constituted the material for the second web survey.

Web survey 2

In the second round of the survey, these refined draft statements were presented to the participants, who were asked to either revise the draft definitions or agree to them. The percentage of agreement/disagreement for each question was calculated (Table 1). Definitions with an agreement over 70% were considered acceptable by the Steering Committee for further discussion. Similarly to the previous step, the definitions with an agreement below 70% were therefore first reworded by PRINTO and subsequently by the LFA Steering Committee to take into account the range of comments from all the responders.

Second international Lupus Flare Conference

In June 2008, the LFA convened a second international consensus conference²⁶ in Washington, D.C., which was attended by more than 80 experts in lupus research and clinical practice from around the world, drawn from academia, the pharmaceutical industry, and the U.S. government.

The areas of expertise represented were rheumatology (adult and pediatric), dermatology, immunology, nephrology, neurology, pulmonology, clinical epidemiology, and biostatistics. Plenary session presentations and meeting-wide discussions reviewed the progress of the group. The goals of this meeting were to finalize a consensus definition of flare for final ratification by the community, identify possible ways to use or adapt existing lupus disease indices, and propose methods for validating flare measurement tools for future clinical trials.

Web survey 3

The conference participants recommended that three versions of the definition of flare be sent back to the Delphi survey participants who had participated in the development of the original definitions. The Steering Committee agreed that, since this was the last round of the web survey, it should have been sent to a larger list of 146 participants (the respondents to the first two surveys plus other participants of the Second International Lupus Flare Conference). Since participants were asked to express a preference among three different definitions of lupus flare (Table 2), which represented minor changes to the same definition, a majority of votes was considered sufficient to select the final definition.

Descriptive analyses of the questionnaire-based surveys were performed.

Results

Web survey 1

A total of 69/120 (57.5%) responded to the invitation to participate in the first web survey. Two of these respondents answered that they were not interested in participating. Of the remaining 67, 54 participants indicated interest and completed the survey, five indicated interest and partially answered the survey, and eight indicated interest but did not participate in the survey. The total number of responses available for analysis was 59.

Table 1 Questions proposed by the Steering Committee of the Lupus Foundation of America, Inc. with the results of the second survey and final statements derived from community input. A total of 87/118 (74%) completed the second survey

<i>List of original questions with the proposed definitions</i>	<i>Agree N (%)</i>	<i>Disagree N (%)</i>
1. What is a flare? A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical findings, laboratory measurements and/or changes in ADL. It must be considered clinically significant by the assessor and usually there would be at least consideration of an increase in treatment.	75 (86%)	12 (14%)
Final statement A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical findings, laboratory measurements. It is a temporary event and must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment.		
2. Is there a difference between disease activity and flare? If so, what is it? Yes, disease activity reflects any signs, symptoms or laboratory abnormalities due to lupus, without reflection on previous activity. A flare is an increase in disease activity as compared to a previous assessment.	77 (89%)	10 (11%)
Final statement Yes. Disease activity encompasses all the signs and symptoms or laboratory abnormalities related to lupus pathophysiology. It is determined at one point in time and is unrelated to the prior amount of disease activity. A flare is an increase in disease activity as compared to a previous assessment and usually there would be at least consideration of a change or increase in treatment modality.		
3. When does flare begin? The flare begins at the first sign of change in disease activity, (when clinical status begins to worsen) whether or not the flare has reached its maximal disease activity at that point.	53 (61%)	34 (39%)
Final statement The flare begins at the first sign or laboratory measurements of an increase in disease activity, whether or not the flare has reached its maximal disease activity at that point.		
4. When does flare end? When the disease activity returns to the level it was at before the flare, not necessarily fully quiescent disease.	77 (89%)	10 (11%)
Final statement A flare ends when disease activity returns to the pre-flare level, not necessarily fully quiescent disease or the disease activity has been stable for a given period of time.		
5. Is there a minimal threshold of disease activity to define mild, moderate, or severe flare? Yes. Severe disease implies a threat to an organ or to life. However, this is not easy to define, and may be different for different organ systems. The BILAG and/or SLEDAI could be used to define the thresholds and a consensus is needed to build these definitions.	68 (78%)	19 (22%)
Final statement A flare can occur at any level of disease activity. These definitions will require a combination of "change" and "total activity." Severe flare implies a threat to an organ or to life. However, this is not easy to define, and may be different for different organ systems. Several instruments (BILAG, SLEDAI, SLAMR, CLASI) could be used to define the thresholds and studies are needed to quantify these definitions.		
6. Is the degree of change important in defining mild, moderate, or severe flare? Yes, a small degree of change might be a mild flare, even at high disease activity levels, but if there is a change in the intention to treat this might define a severe flare even without major change in disease activity level.	54 (62%)	33 (38%)
Final statement The degree of change may associate with the degree of flare over a broad range of disease activity levels. A change in the intention to treat, even without major change in disease activity level, should be considered to define the severity of flare.		
7. Are there examples of thresholds in which a small change could signify a severe flare? Yes, if it leads to hospitalization or institution of aggressive immune suppression.	59 (68%)	28 (32%)
Final statement Yes, if it leads to institution of aggressive immune suppression.		
8. Do both degree of change and threshold of flare need to be defined? Yes, but there may be some examples where one or the other would suffice to designate a severe flare.	75 (86%)	12 (14%)
Final statement Yes, but there may be some examples where one or the other would suffice to designate a severe flare. The approach should be pre-specified in clinical trials.		
9. Is it important to distinguish between mild flare and moderate flare? Yes, mild flares usually do not lead to medication changes yet still might be important to quality of life. They might also be important in clinical trials. Physicians and patients would not accept the same degree of toxicity from treatments for mild versus severe flares.	64 (74%)	23 (26%)
Final statement To distinguish between severe and non-severe flares is clinically more important than to distinguish between mild and moderate. Mild flares usually do not lead to medication changes yet still might be important to quality of life and they might also be important in clinical trials. Moderate flares need to be recognized opportunely in order to be properly treated and controlled. These terms need more precise definition even though it also depends on the organ involved.		

(continued)

Table 1 Continued

<i>List of original questions with the proposed definitions</i>	<i>Agree N (%)</i>	<i>Disagree N (%)</i>
10. Is there a way to define a mild flare that would not be confused with symptoms not attributable to lupus? Yes, but it is not easy. This is a major problem. It depends on careful differential diagnosis by the clinician and excellent clinical skills and even then will not be infallible.	70 (80%)	17 (20%)
Final statement Probably, this is a major problem. It depends on careful differential diagnosis by the clinician and clinical skills. Specific biomarkers help to indicate the presence or absence of lupus disease activity.		
11. How do you differentiate a flare from ongoing clinical disease? A flare represents a change, a worsening.	70 (80%)	17 (20%)
Final statement A flare is a change, an increase of disease activity or a worsening in symptoms that were not present previously that is temporary, while ongoing clinical disease is a continuum worsening and would not be considered a flare.		
12. How do you differentiate flare from progressive organ damage? Although sometimes this is clear, it can be problematic. It may require better biomarker development. Currently available laboratory values can be helpful. Optimally, the assessor will be using multiple kinds of assessments, history, physical exam, laboratories, biopsies, imaging studies. Clinical acumen is critical and the picture may clear up over time since flares are reversible and damage is not.	70 (80%)	17 (20%)
Final statement A flare represents a potentially reversible increase in disease activity resulting from immunologic or inflammatory activity. Progressive organ damage occurs secondary to treatment toxicity or as a consequence of scarring from inflammatory insults. Clinical acumen is critical to distinguish between the two entities and currently available assessment may be useful. The identification of future biomarkers should facilitate our ability to differentiate a flare from progressive organ damage.		

Table 2 Results of the third web survey with the agreement on the three final definitions of lupus flare. A larger group of 146 physicians were involved in the third survey and the response rate was 116/146 (79.5%)

<i>Definitions of lupus flare</i>	<i>Responses N (%)</i> <i>116/146 (79.5%)</i>
1. A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment.	71 (61%)
2. A flare is a measurable, clinically significant increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor.	29 (25%)
3. A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical findings, laboratory measurements and/or changes in activity of daily living ADL. It must be considered clinically significant by the assessor and usually there would be at least consideration of an increase in treatment.	15 (13%)

As detailed in the methods, the PRINTO team and the LFA Steering Committee reviewed the responses and drafted 12 new statements to be used for the second survey, as detailed in Table 1, including two of the original statements, which were collapsed into one. The definitions numbered 3, 5, 6, 7, and 9 had an agreement below 80% among responders. These questions were then reworded by PRINTO and the Steering Committee to take into account comments from the respondents who were rejecting the statements as originally written.

Web survey 2

A total of 118 candidates were asked to participate in the second survey (two were removed from the

list after expressing no interest in the first round). Eighty-seven of 118 (74%) completed the second survey. Agreement <70% was reached for questions 3 (“When does flare begin?”), 6 (“Is the degree of change important in defining mild, moderate or severe flare?”), and 7 (“Are there examples of thresholds in which a small change could signify a severe flare?”). There was an agreement at a level of ≥70% (9/12 or 75%) for all remaining definitions refined in the first web survey. Community consensus was thus obtained for several ancillary issues important in the detection and measurement of lupus flares, extending beyond the final definition that was reached.

By integrating the common points in the responses to the first question (“What is a flare?”)

in the first web survey, it was apparent that the respondents thought the flare definition should encompass two key concepts: (1) a measurable increase in disease activity attributable to lupus pathophysiology; and (2) the physician's (or assessor's) consideration of a change in therapy as a response to the change in the patient's clinical status. Based on these two concepts, and some more detailed comments from the responders, PRINTO and the LFA Steering Committee provided the following draft definition of flare for the second web questionnaire in order to gauge the degree of agreement to a consolidated definition among the participants:

"A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical findings, laboratory measurements, and/or changes in activities of daily living (ADL). It is a temporary event and must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment." This definition was accepted by 75/87 (86.2%) of respondents in the second web survey.

Second international Lupus Flare Conference

The results of the first two web surveys were examined at a second international face-to-face conference of lupus experts. There was extended discussion of some of the minority statements, particularly those suggesting that deterioration in quality of life or activities of daily life might be a very important aspect of determining flare, whether temporal boundaries are needed to define flare, and some issues about whether flares require a change of treatment or whether treatment might be refused, withheld or delayed for legitimately flaring patients.

After the June 2008 LFA consensus conference, a decision was made to take the draft definitions presented at the International Lupus Flare Conference, plus two additional variations debated at the meeting, back to the global lupus community. The purpose was to weigh all definitions in order to see whether a final consensus could be reached.

Web survey 3

A larger group of 146 physicians were involved in the third survey and the response rate was 116/146 (79.5%); the participants included the 118 who had been included in the second survey plus additional people who participated in the Second International Lupus Flare Conference. The results

are presented in Table 2. Lupus Flare definition number 1 received 71/116 (61%) of the vote and was considered ratified: "A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment."

Discussion

The Guidance for Industry issued by the Food and Drug Administration in March 2005²⁷ has become an unofficial template for lupus drug development protocols. This document included flare as a potential outcome for clinical trials, and subsequently it has become evident that, even when improvement serves as the primary outcome, assessment of the durable efficacy of a treatment depends on a valid, clinically meaningful and reproducible measurement of flares. The current project was undertaken to address problems arising in clinical trials when attempts have been made to include flare measurements in definitions of response.

Among the several instruments that have been in widespread use as Disease Activity Measures, only the SELENA SLEDAI and the BILAG index have templates suitable for measuring flares.^{10,28} However, the following issues have been identified when using these instruments for flare: 1) the SELENA SLEDAI flare instrument does not differentiate mild from moderate flare. Intent to treat or acceptability of response may differ within this spectrum of disease; 2) the SELENA SLEDAI flare instrument defines an increase in the SLEDAI score to greater than 12 as a severe flare, regardless of whether the actual change in disease activity to reach this landmark was either numerically or clinically significant ("the threshold effect"). Similarly, the BILAG index thresholds between mild, moderate, and severe activity might also define flare in some instances of minimal increase in clinical disease. Furthermore, the BILAG designation of "B" or moderate disease describes a wide range of symptoms from relatively mild to moderately severe activity. Differentiating mild from moderate flares, then, might be problematic in clinical trials using either of these instruments.

For these reasons, it was deemed important to elicit, from a wide range of experienced clinicians, a meaningful definition of flare that would allow

clinical trials to measure events with significant clinical impact. Questions such as whether it is important to distinguish between mild and moderate flare, how to determine when a flare begins and ends, whether laboratory data must support a flare, and whether disease thresholds and/or treatment changes are necessary or sufficient to define various degrees of flare, had never previously been agreed upon by the clinical community. Although the final definition of flare may appear to be deceptively simple, it in fact serves to provide a community consensus on all of these issues.

The final definition of flare that evolved from the Delphi process is as follows: "A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment." When the intermediate questions in Table 1, along with this statement, are reviewed, community opinion appears to support the following conclusions, which may be relevant in designing outcome measures for clinical trials: 1) although a flare may involve small, intermediate or severe changes, the increase must be "measurable" and the assessor must agree that the change that has occurred to meet the threshold of flare is clinically significant. Flare measurements, then, should not specify increases in disease as flare without consideration of their clinical impact; 2) answers to questions 3 and 4 in Table 1 support measuring flare from the beginning of increased symptoms ("start of flare") to the point at which it returns at least to the baseline disease activity but not necessarily to quiescent disease ("end of flare"). This would allow clinical trials to be designed around baseline landmarks such as the point of entry to the trial or the point of best disease improvement after protocol treatment and measurement of time to flare or numbers of flares using reproducible definitions. When measuring flare activity from visit to visit, a new flare would not necessarily be recorded when there is persistent activity from a previous flare extending past the visit interval. In studies, these decisions could be protocol-specific; 3) answers to questions 5–8 in Table 1 further illuminate that both a threshold amount of disease and a degree of change may need to be factored into definitions of mild, moderate, and severe flare, and that there may be specific instances in which either would supersede the other. Despite concerns about the threshold effects seen in previous flare measurements, the community does not believe that the

threshold can be eliminated from a flare assessment, but a significant degree of change would still often be required to define a severe flare (as opposed to severe, ongoing disease activity or milder flare). A specific exception to this might be a smaller change that results in a decision threshold such as an aggressive change in treatment, and would be, to most observers, acceptable as a severe flare. Thus, the threshold effect could be eliminated by requiring either a defined significant change in disease activity or a significant change in treatment plan.

Answers to Question 9 in Table 1 suggest that the practicing community is more concerned with differentiating moderate from severe flare than with defining the difference between mild and moderate flare. However, all three gradations may be important to distinguish in clinical trials, since mild flares may have impact on a patient's quality of life, whereas moderate flares might need to be distinguished with a more aggressive intent to treat. The final statement on this point suggests that all three should be better defined, and there are additional cautions from the clinical community that the definitions may vary from organ to organ. Questions 10–12 (Table 1) suggest that challenges may still remain in distinguishing mild flares from non-specific (non-lupus) symptoms and that progressive organ damage may mimic a flare in some rare circumstances. The answers highlight the ongoing importance of clinical acumen and the need for new biomarkers to clarify these gray areas, both in practice and, potentially, in clinical trials.

Finally, in arriving at a final definition of flare, there was an original community consensus in support of the first, more extensive, definition proposed in Table 1. This included both a patient-reported outcome of ADL and a physician's intent to treat in the flare definition. The final statement was derived from a significant minority report against these two features. Strong opinions were manifested that intention to treat, although usually involved in moderate to severe flares, can overly restrict the definition of flare, especially when given for ongoing persistent activity. There were equally strong concerns that ADL changes might not be due to an increase in lupus disease activity and could potentially introduce false-positive flares. At the second face-to-face meeting, it was decided to re-poll the community using three alternative definitions of flare with and without these controversial elements. By a clear margin, the simpler definition of flare, which excluded the ADL, was preferred by the

community when given a choice, and has been selected as the final flare definition derived through this process. It should be stressed that this would not rule out ADL as an important, indeed critical, measurement for the impact of flare on the patient, but might promote caution in the attribution of these data to flare as opposed to either the cumulative personal toll of an ongoing disease burden or indirect effects of disease burden, such as treatment side effects or progressive organ damage, all of which are important measures in their own right in the evaluation of treatment impact.

This work should be viewed in the light of certain limitations, which include some Delphi response rates that were below the expected cut-off of 70% and the possibility of selection bias in the preparation of the list of experts.

In conclusion, the LFA proposes this community consensus definition of lupus flare on the basis of its high face validity. Further work is underway to refine, select, and validate specific clinical flare measurement instruments to grade and quantify flares.

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Conflict of interest

None declared.

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Appendix: Members of the Lupus Foundation of America, Inc.

International Flare Consensus Initiative

Members of the Lupus Foundation of America, Inc. International Flare Consensus Initiative, in addition to the authors of this article, are as follows: Joseph Ahearn, MD (Pittsburgh, PA), Mohammed Akil, MD (Sheffield, UK), Michael D Amos, PhD (Gaithersburg, MD), Jennifer Anolik, MD, PhD (Rochester, NY), Gerald Appel, MD (New York, NY), Cynthia Aranow, MD (Manhasset, NY), Tadej Avcin, MD, PhD (Ljubljana, Slovenia), Anna Novotney Barry, MS (Smyrna, GA), Damon Bass, DO (King of Prussia, PA), Jean-Claude Becker, MD (Princeton, NJ), Timothy W Behrens, MD (San Francisco, CA), Michael W Beresford, MBChB, PhD (Liverpool, UK), Susan Boackle, MD (Aurora, CO), Dimitrios Boumpas, MD (Heraklion, Greece), Ian Bruce, MD (Manchester, UK), Hermine Brunner, MD, MSc (Cincinnati, OH), Rubén Burgos-Vargas, MD (Mexico City, Mexico), Shunle Chen, MD (Shanghai, China), Marc Chevrier, MD, PhD (Millersville, MD), Rolando Cimaz, MD (Florence, Italy), Ann Clarke, MD, MSc (Montreal, Canada), Mary K Crow, MD (New York, NY), Rubén J Cuttica, MD (Buenos Aires, Argentina), Gregory Dennis, MD (Rockville, MD), Betty A Diamond, MD (Manhasset, NY), Jorn Drappa, MD, PhD (San Francisco, CA), Mary Foster, MD (Durham, NC), William W Freimuth, MD, PhD (Rockville, MD), Richard Furie, MD (Lake Success, NY), Jay Garg, MD (Menlo Park, CA), Edward Giannini, MSc, DrPH (Cincinnati, OH), Deirdre Gillespie, MD (San Diego, CA), Dafna D Gladman, MD (Toronto, Ontario, Canada), Rick Goulburn (Basking Ridge, NJ),

Mark Gourley, MD (Bethesda, MD), Bridget Griffiths, MD (Newcastle upon Tyne, UK), André Groenewegen, MD (Monheim, Germany), John Hanly, MD (Halifax, Canada), Olivier Harari, MD, PhD (Slough, UK), John Harley, MD, PhD (Cincinnati, Ohio), E Nigel Harris, MD (Mona, Jamaica), Evelyn V Hess, MD (Cincinnati, OH), Robert W Hoffman, DO (Indianapolis, IN), Douglas Hough, MD (Rockville, MD), Lisa F Imundo, MD (New York, NY), Judith James, MD, PhD (Oklahoma, City, OK), Meenakshi Jolly, MD, MS (Chicago, IL), Diane Kamen, MD (Charleston, SC), David R Karp, MD, PhD (Houston, TX), Robert Katz, MD (Chicago, IL), Lexy Kelley, MD (Smyrna, GA), Munther Khamashta, MD, PhD (London, UK), Robert Lahita, MD (Jersey City, NJ), Kevin Latinis, MD, PhD (Kansas City, KS), Thomas JA Lehman, MD (New York, NY), S Sam Lim, MD, MPH (Atlanta, GA), Matthew D Linnik, PhD (San Diego, CA), Daniel J Lovell, MD, MPH (Cincinnati, OH), Gerald McGwin, MS, PhD (Birmingham, AL), Michael P Madaio, MD (Augusta, GA), Daniel Magilavy, MD (South San Francisco, CA), Leslie Magnus, MD (Basking Ridge, NJ), Susan Manzi, MD, MPH (Pittsburgh, PA), Alberto Martini, MD (Genova, Italy), Barbara Mittleman, MD (Bethesda, MD), Barry L Myones, MD (Houston, TX), C Michael Neuwelt, MD (San Leandro, CA), Ola Nived, MD, PhD (Lund, Sweden), Nancy J Olsen, MD (Hershey, PA), Theodore Phillips, MD (Gaithersburg, MD), Stanley Pillemer, MD (Rockville, MD), Chaim Putterman, MD (Bronx, NY), Anisur Rahman, PhD (London, UK), Rosalind Ramsey-Goldman, MD, DrPH (Chicago, IL), Angelo Ravelli, MD (Genoa, Italy), Westley H Reeves, MD (Gainesville, FL), John D Reveille, MD (Houston, TX), Jose Roldan, MD, MS (San Antonio, TX), Brad H Rovin, MD (Columbus, OH), Jane Salmon, MD (New York, NY), Iñaki Sanz, MD (Rochester, NY), Peter Schur, MD (Boston, MA), Kenneth E Schwartz, MD (San Mateo, CA), Jeffrey N. Siegel, MD (Silver Spring, MD), Leonard Sigal, MD (Princeton, NJ), Earl Silverman, MD (Toronto, Canada), Sudhakar Sridharan, MD (Collegeville, PA), Gunnar Sturfelt, MD, PhD (Lund, Sweden), Charla Tambourine, RN (Basking Ridge, NJ), James Tumlin, MD (Atlanta, GA), Kathleen Uhl, MD (Rockville, MD), Paul J Utz, MD (Stanford, CA), Ronald Van Vollenhoven, MD, PhD

(Stockholm, Sweden), Daniel J Wallace, MD (Los Angeles, CA), Barbara White, MD (Gaithersburg, MD), David Wofsy, MD (San Francisco, CA), Pat Woo, MD, PhD (London, UK), Chee-Seng Yee,

PhD (Edgbaston, Birmingham, UK), David Zhang, MD (San Francisco, CA), John Zhong, PhD (Rockville, MD), Asad A Zoma, MB (East Kilbride, Lanarkshire, UK).