MCID/Low Disease Activity State Workshop: Summary, Recommendations, and Research Agenda

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ABSTRACT. The OMERACT 6 Minimal Clinically Important Difference/Low Disease Activity Workshop was organized with the aim of meeting the many challenges that exist in determining a low disease activity in rheumatoid arthritis (RA). This article presents an overview of that workshop, including results of the voting, a summary of associated discussions, recommendations, and a proposed research agenda. (J Rheumatol 2003;30:1115–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS　　　　　　　　　　OUTCOME AND PROCESS ASSESSMENT
　　　　　　　　　　　DISEASE ACTIVITY

Introduction

In preparation for the workshop, 2 background papers were available for workshop participants: an introduction to and rationale for the definition of a low disease activity state (LDAS), and methods and procedures for deriving an operational definition of a LDAS.

The workshop began with a plenary session introducing the objectives and reviewing concepts and terminologies. Participants were then divided into 4 breakout groups: Group 1 considered low disease activity from a patient perspective; Group 2 considered methods and the consensus process that can be used for developing an operational definition of low disease activity; Group 3 reviewed measures that could be used in the definition of low disease activity; and Group 4 reviewed actual formulations of definitions of a LDAS. A *rapporteur* from each group presented a report from their breakout session to the closing workshop plenary. The reports of the breakout groups were merged and a summary presented at the conference plenary. A series of questions on key issues associated with LDAS were presented and voted on by conference participants.

This article presents the results from the voting, summarizes the associated discussions, identifies the recommendations, and suggests a research agenda.

Breakout Group Results

The patient participants in breakout Group 1 were asked to write down "what they felt like" when they considered themselves in a LDAS. Each patient then read aloud what they had written and the results were listed and grouped accordingly. In the first instance, patients described their state in terms of change. They were then requested to think about the lowest or highest value accordingly for the various outcomes when they were doing well. Again they read aloud their notes, and results were listed and grouped. Pain was considered relevant, and less than 20 mm on the visual analog scale (VAS) was considered an important cutoff. Low energy/fatigue was considered to be extremely important, as was sleep, with 5 hours of uninterrupted sleep an important cutoff. Except for pain, swollen joint counts were considered irrelevant, and only certain tender joints such as the knee were considered relevant. Patient and physician global assessment VAS scores of under 20 mm were noted, but the latter was not considered to be as relevant. Finally, function was considered difficult to assess and needed to be used better, whereas radiographs were considered irrelevant. Features were listed along with corresponding measures,

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and participants voted and ranked them. Patients reviewed the core set of measures and added or removed measures accordingly.

Participants in breakout Group 2 were to consider a wide range of possible judgmental and statistical approaches as the basis for a comprehensive methodological strategy to develop an operational definition of LDAS. There was a long and detailed discussion of disease activity versus disease severity and concerns with the concept of a LDAS. The various approaches that could be considered were renamed: opinion-based and observation-based.

Opinion-based approach. This approach depends on obtaining information via a survey and/or Delphi groups and would need to include a wide range of rheumatologists and patients. A direct and indirect approach can be distinguished. In a *direct* opinion-based approach, the definition is obtained explicitly from participants who are asked to define low disease activity in terms of a range within each of the measures relevant for disease activity. In an *indirect* approach, the definition is obtained implicitly from assessments that the participants make when presented with patient profiles that describe actual levels of measures relating to each of the relevant features. The set(s) of patient profiles should represent data from real patients selected to span potential cutpoints on each feature. The observation-based approach depends on analysis of clinical visit data on patients with RA, where low disease activity is inferred from a proxy variable (e.g., clinician decisions to reduce/not to increase drug treatment or patient behavior in titrating analgesic use).

Participants in breakout Group 3 reviewed measures that could be used in the definition of a LDAS. Starting with core measures used in indexes such as the American College of Rheumatology remission criteria (ACR 20) and the Disease Activity Score, participants discussed the measures and an initial polling; subsequent discussions indicated the following key domains or features, in order: pain, function, inflammation, health related quality of life, and structure/damage.

For the various features discussed, participants identified corresponding indicators/instruments. In particular, for the key features the indicators/instruments identified were: pain (tender joints, pain VAS); function (Health Assessment Questionnaire, HAQ); inflammation (morning stiffness, nocturnal awakening, swollen joints, C-reactive protein/erythrocyte sedimentation rate); health related quality of life (Medical Outcome Study Short Form-36, EQ5D); and structure/damage (radiography, magnetic resonance imaging, range of motion).

Participants in breakout Group 4 assumed that the component measures used in the operational definition were given, and they concentrated on the task of determining levels and aggregation, as well as the structure of the aggregate outcome. They considered methods where levels, or cutoffs, for low disease activity for each component measure were first determined and then the component measures were aggregated using one of several methods. Alternatively, component measures were first aggregated using different methods and a level for low disease activity for the aggregate outcome determined. Different "straw-man" definitions for a LDAS were introduced and discussed by the participants. For Straw-man 1, a matching system was used in which the WHO/ILAR core measures were considered and a low disease activity cutoff for each measure was identified. The LDAS was then identified as achieving a given number of cutoffs for the core measures. Different versions of this straw-man were considered by varying the number of measures needed and the cutoff value. For Straw-man 2, a point system was used in which the range of values for each WHO/ILAR core measure was categorized into a number of levels, and points were awarded to each level, with the lower points indicating a better outcome. The points would then be summed to provide an indication of disease activity. For Straw-man 3, an unweighted summated single score was used in which the WHO/ILAR core measures were used with their values transformed to a common scale. The sum across all the measures would then yield a score providing an indication of disease activity. For Straw-man 4, a weighted summated single score was used in which each component measure was weighted and the weighted scores summed. A cutoff for this weighted score would be defined to indicate low disease activity. For Straw-man 5, a tree-like format using a logical flow through the component measures was considered.

Responses to Plenary Questions

Four questions were posed and voted on by all the conference participants in the final plenary session. The questions were based on the key points of discussions that took place among the participants in each of the 4 breakout sessions. The goal was to help formulate an overview on a research agenda.

Question 1. The following outcomes should be included in a research agenda for consideration in the definition of a low disease activity state:

Pain	VAS, tender joints
Function	HAQ
Inflammation	Tender joints, swollen joints, CRP /ESR
HRQoL	SF36, patient global assessment
Structure/damage	Imaging, swollen joints
Toxicity and comorbidity	Adverse events and comorbidity list

Results. Yes 80%; No 19%; Don't know 1%

The first issue concerned the candidate measures for defining LDAS. The first question provided a number of candidate measures that the conference participants were asked to vote on as a comprehensive list to consider for the definition of LDAS. It was determined a priori that if less than 80% of participants agreed with the list, then each candidate variable would be voted on separately in order to determine the specific measures to be considered in the research agenda. The vote by all the conference participants in the final plenary session resulted in exactly 80% supporting the suite of candidate measures proposed. As a result, the questions concerning each of the individual candidate measures were not voted on separately.

Question 2. A research agenda needs to be formulated for measuring the following outcomes so that these can be considered in the definition of low disease activity state:

Sleep
Energy/fatigue

Results. Yes 87%; No 11%; Don't know 2%

The second question concerning candidate measures for defining LDAS evolved from discussions in the breakout session on patient perspectives. In particular, the patients noted two factors, sleep and energy, that they believed were important but were not well measured or properly considered in assessing disease activity. This question was posed to and voted on by all the conference participants at the final plenary session, with a resulting 87% in agreement.

Question 3: What approach should be used for developing an operational definition of low disease activity state?

Results. Opinion-based 8%; Observation-based 15%; Both opinion and observation-based 75%; Don't know 2%

The next issue concerned the methods and procedures for deriving an operational definition of a LDAS. Two broad approaches were posed for consideration. The first was an opinion-based approach involving a survey method and/or Delphi process using direct or indirect procedures: using a direct procedure, participants are presented with profiles describing actual levels of measures relating to each feature of disease activity; and using an indirect approach, participants are presented with each disease activity feature one at a time. The second approach is an observational-based approach involving the analysis of existing RA data and inferring low disease activity from a proxy variable, such as a clinician's decision to reduce/not increase drug treatment.

The question on which approach should be used for developing an operational definition of LDAS was posed to and voted on by all conference participants at the final plenary session, with a resulting 75% indicating that a combined opinion and observational approach should be considered.

Question 4. A research agenda needs to be formulated to compare the attributes of a weighted, unweighted, and tree approach for formulating a low disease activity state.

Results. Agree 85%; Disagree 12%; Don't know 3%

The last issue concerned the actual formulation for expressing the LDAS: more specifically, whether a research agenda was needed to compare the attributes of a weighted, unweighted, and tree approach for formulating a LDAS. For the unweighted approach, a cutoff is defined for each outcome measure and each measure is given an equal weight as the number of measures satisfying the cutoff are counted. With the weighted approach, actual outcome measures are weighted and aggregated. A simple example involving the 3 outcome measures pain VAS, patient global VAS, and HAQ illustrates the difference in the 2 approaches. For the unweighted, success is defined as satisfying at least 2 out of 3 criteria: pain > 20 mm, patient global > 20 mm, and HAQ > 1. For the weighted approach, an equation is generated and success is defined if:

$$A \times \text{Pain} + B \times \text{Patient Global} + C \times \text{HAQ} < D,$$

where A, B, C, and D have numeric values. The final formulation is a tree-like format providing a step-by-step path through the outcome measures constituting the definition, and with branching at any conditional point. An example is the OARSI responder criteria. The question on whether a research agenda was needed to compare the attributes of the 3 approaches was posed to and voted on by all conference participants at the final plenary session, with a resulting 85% in agreement.

Research Agenda Overview
1. Review and obtain consensus on the specific outcomes that should be considered in the definition of low disease activity state for RA
2. Design and conduct an assessment of evaluating the outcomes sleep and energy/fatigue using valid and reliability-measuring instruments
3. Design and conduct an opinion-based and observation-based approach for determining a low disease activity state for RA
4. Design and conduct a study to compare the attributes of a weighted, unweighted, and tree approach for formulating a low disease activity state for RA.

Conclusion

The objectives of this workshop were to meet the challenges that exist in determining a low disease activity state by reviewing the concepts and terminologies associated with a LDAS, and to determine the processes for developing an operational definition of LDAS. Progress has been made and a research agenda has been agreed to by the conference participants. An outline of the research plan has been formulated and over the next 2 years the different phases of the plan will be designed, implemented, and conducted.