EULAR points to consider for conducting clinical trials in systemic lupus erythematosus

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ABSTRACT

Objective: Systemic lupus erythematosus (SLE) is a complex multi-organ disease, characterised by relapses and remissions. Designing a high-quality randomised controlled trial poses many challenges. We have developed evidencing-based recommendations for points to consider in conducting clinical trials in patients with SLE.

Methods: The EULAR Task Force on SLE comprised 19 specialists and a clinical epidemiologist. Initially, the evidence for clinical trial end-points in SLE was evaluated and this has been reported separately. A consensus approach was developed by the SLE Task Force in formulating recommendations for points to consider when conducting clinical trials in SLE.

Results: The literature review revealed that most outcome measures used in phase 2/3 trials in SLE have not actually been validated in clinical trials, although other forms of validation have been undertaken. The final recommendations for points to consider for conducting clinical trials in SLE address the following areas: study design, eligibility criteria, outcome measures including adverse events, concomitant therapies for SLE and its complications.

Conclusions: Recommendations for points to consider when conducting clinical trials in SLE were developed using an evidence-based approach followed by expert consensus. The recommendations should be disseminated, implemented and then reviewed in detail and revised using an evidence-based approach in about 5 years, by which time there will be further evidence to consider from current clinical trials.

Systemic lupus erythematosus (SLE) is a complex multifaceted autoimmune disease that can present at any age but is most common in women during the reproductive years. Certain ethnic groups are predisposed to develop this disease more frequently than others, and some, such as those of Afro-American or Afro-Caribbean descent, are more likely to have a poor prognosis.1 2 Currently antimalarials, corticosteroids and cytotoxic agents are the mainstay of therapy but these treatments have many complications. There are particular concerns about the risks of infertility from cyclophosphamide therapy.3 4 Consequently, there is increasing interest in developing more specific therapies with improved efficacy and safety profiles over traditional drug treatments for SLE.5 6

There have been previous attempts at defining the type of outcome measures (end-points) that should be used in clinical studies in SLE but no formal recommendations for conducting clinical trials have been published. Concerns have been raised about the poor quality of SLE trial design and reporting.7 The first initiative was by the Systemic Lupus International Collaborating Clinics (SLICC) in 1996. This defined the concepts of assessing, disease activity, chronic damage and quality of life.8 These recommendations were endorsed by the Omeract IV conference in 1998.9 11 The individual disease activity and damage indices and measures for recording quality of life and health status in SLE have recently been reviewed.12 Potential renal outcome measures have been extensively reviewed and renal response criteria for lupus nephritis trials have been proposed but await validation.13 The FDA have published issues for the pharmaceutical industry to consider when planning clinical trials (http://www.fda.gov/cder/guidance/6496dft.pdf).

EULAR has developed standard operating procedures for reviewing the evidence base for medical practice.14 Under the auspices of EULAR, we undertook the task of developing guidelines for the management of various aspects of SLE15 and points to consider for conducting clinical trials in SLE. Here we provide recommendations for points to consider when conducting clinical trials using a combination of research-based evidence and expert consensus.

METHODS

The expert committee and selection of questions for literature review

An expert committee was formed that comprised 19 specialists, one clinical epidemiologist (JPAI) and one research fellow (GB), representing 12 European countries. EULAR standardised operating procedures were followed for the elaboration and evaluation of the evidence for conducting clinical trials14 16 with the aim of devising recommendations for dissemination and implementation. The target population was defined as all practising physicians concerned with planning or evaluating clinical trials in SLE, the pharmaceutical industry, the licensing authorities. Eight questions addressing the evidence for clinical trial methodology in SLE using a modified Delphi technique were selected and a systematic search of PubMed and the Cochrane library was performed as described previously.17 The results of the literature search...
were summarised and eight final statements about end-points for clinical trials in SLE were agreed.17

**Expert opinion approach and strength of statements**

There is a paucity of high-quality randomised clinical trials in SLE, particularly for lupus manifestations other than lupus nephritis. The literature review revealed that most outcome measures used in phase 2/3 trials in SLE have not actually been validated in clinical trials, although other forms of validation have been undertaken. A consensus building process was used therefore to derive a set of recommendations for points to consider when conducting clinical trials in SLE, based on the limited currently available literature combined with expert opinion. The resulting recommendations are therefore for “points to consider” when conducting clinical trials in SLE. Members of the Task Force were asked to state their strength of agreement with each statement in the tables, to the best of their ability and experience, as for the recommendations for the management of SLE19 on a scale of 1–10 (10 being full agreement and 1 being total disagreement). Finally, the expert committee proposed topics for a Research Agenda (box 1).

**RESULTS**

**Recommendations for points to consider in conducting clinical trials in systemic lupus erythematosus**

Using a consensus approach the SLE Task Force formulated points to consider for conducting clinical trials in SLE. We recommend considering the following topics when planning a clinical trial: end-points (outcome measures) including adverse events, study design and analysis, eligibility criteria and concomitant medications.

1. End-points for clinical trials in systemic lupus erythematosus

It is essential to define clearly the most appropriate primary end-point and additional secondary end-points relevant to the objective(s) of a trial. Table 1 summarises clinical end-points that can be considered and the mean level of agreement with their use of the Task Force members.

1.1 Lupus disease activity

Although not validated for use in clinical trials, the SLE Task Force agreed that standardised disease activity indices are preferable to completely untested outcome measures for capturing disease activity (item 1.1, table 1). The most appropriate primary end-point may be a defined level of disease activity or a change in a specific organ manifestation. It is anticipated that more than one measure of disease activity may be used in a trial to capture changes in the manifestations of lupus present at baseline and the development of any new features of lupus during the trial. For example, a system-based approach such as the British Isles Lupus Assessment Group (BILAG) index10 and/or a global scoring method such as the SLE Disease Activity Index (SLEDAI)19 (or one of its variants such as SLEDAI-200020) and/or European Consensus Lupus Activity Measure (ECLAM)21 and/or SLE Activity Scoring System (SIS)22 and/or Systemic Lupus Activity Measure (SLAM),12 or a disease activity index and a biomarker. A number of previously used renal end-points have already been reviewed23 and a proposal for response criteria in lupus nephritis trials have been suggested24 but these should be used in conjunction with a method for capturing non-renal disease such as the BILAG index,25 26 SLEDAI,20 21 SLAM,22 SIS23 or the SELENA (Safety of Estrogens in Lupus Erythematosus National Assessment)-SLEDAI flare tool25 24. The glossary definitions for items that may appear to be the same, such as arthritis, vary between some of the indices. It is essential that only items thought to be due to lupus are recorded and that confounders such as proteinuria or red cells due to urinary infection are excluded. Similarly, fatigue, arthralgia or myalgia due to fibromyalgia or osteoarthritis must not be recorded in a lupus activity assessment but they should be recorded as adverse events or pre-existing comorbid conditions.

1.2 Chronic damage

The prevention of the development of damage (both global and organ specific) is a worthy target for any new therapeutic approach. Accumulated multisystem chronic damage (as measured by the SLICC/ACR damage index25) is only definitely suitable as an end-point in studies using newly or recently diagnosed patients without pre-existing damage and in studies with sufficient duration of follow-up for damage to occur. Damage items are usually recorded if the clinical item has been present for over 6 months.25 Damage may be due to the effects of previous disease activity, the side-effects of treatment and/or co-morbid conditions. The genetic background of the patients may influence the development of these conditions, for example, diabetes and ischaemic heart disease in South Asian patients26 27 and hypertension, including stroke and cardiomyopathy in patients of black African origin.28 29 Increased exposure to steroids is associated with an increased risk of accumulating damage30 and cyclophosphamide is associated with an increased risk of premature menopause.4 Patients with early damage (within 1 year of diagnosis) are more likely to develop further damage with a worse prognosis.31 32 Damage may be more suitable as a stratification measure, as a positive SLICC/ACR damage index score indicates patients at increased risk of severe disease with complications.33

Doubling of serum creatinine is an example of a damage-related laboratory end-point that has been used in clinical trials in lupus nephritis.34 35 There is currently increasing interest in using changes in estimated glomerular filtration rate as an end-point in trials of lupus nephritis as this is felt to be more reliable than measurement of serum creatinine.35 It is important to consider only stable changes in renal function as end-points (that is repeated abnormal values at 1–3-month intervals). Single measures that may be subject to bias due to fluctuation from co-morbid conditions should be avoided.

1.3 Quality of life and health status

The use of health status and quality of life measures as primary end-points in clinical trials is attractive as it reflects the patient’s view of their illness.37 Most studies have used generic measures such as the Short-Form (SF)-36 health survey38 39 although more lupus-specific measures are being developed.40 41 However, there are very few data on meaningful change with any of the measures used. Composite end-points, including improvement in disease activity measures with improvement, stabilisation or at least no deterioration in quality of life measures have been proposed. However, observational studies have shown that these measures often reflect the psycho-social background of the patient42 43 though a few trials have suggested that a little improvement between the start and end of a study is possible in patients on active drug that is not seen in the controls.44 The SLE Task Force supported the use of such measures much less strongly than other end-points (item 1.3, table 1), though these have been recommended as outcome measures for lupus trials in

the past.\textsuperscript{5–11} At present, we recommend that health status and quality of life should remain secondary end-points in a clinical trial.

### 1.4 Adverse events and reporting of harms

There are no lupus-specific methods of reporting harm (adverse events) that occur during a trial but the CONSORT (Consolidated Standards of Reporting Trials) recommendations should be followed.\textsuperscript{48} Standardised reporting methods for assessing toxicity, safety and tolerability of drugs should be used such as the National Cancer Institute common terminology criteria for adverse events (CTCAE). A proposal for trials in rheumatic diseases in general has been made by OMERACT 7.\textsuperscript{44–45} These drug safety module criteria could also be used in lupus trials. It is important to try and distinguish the causes of any harmful event.

### 1.5 Cost-effectiveness

Given the high cost of developing many biological therapies and the cost of running multicentre trials to demonstrate appropriate efficacy and safety for new drugs, there is increasing interest in looking at health economics.\textsuperscript{37} Some initial work on direct and indirect costs of lupus disease in the UK, USA and Canada have been reported.\textsuperscript{46–47} This is a rapidly evolving field and although not all members of the SLE Task Force agreed with the need to consider health economics or cost-effectiveness as an end-point in clinical trials (item 1.5, table 1), this is likely to become more important in the future.

### 1.6 Changes in drug therapy

As an alternative to disease activity, measuring the amount of drugs (such as the steroid dose) used to treat the disease activity might serve as an end-point. The concept of steroid-sparing drugs is not new, but few lupus trials have used steroid dosing as a primary outcome measure, though it has been included as a secondary outcome.\textsuperscript{68} However, this may be a useful end-point for some trials, particularly for those drugs being considered as a maintenance therapy to prevent flares. Any trial assessing disease activity as an end-point will need to ensure that the use of immunosuppressive drugs that influence disease activity is controlled during a study, as there is an inverse relationship between the amount of immunosuppressive therapy and the disease activity in most patients.

### 1.7 Mortality

Mortality on its own is not usually a primary end-point for clinical trials in lupus these days but it is likely to continue to be used as part of a composite end-point, particularly when comparing two drugs that are thought to be of equal efficacy. It is essential that cause(s) of death are established. In the past, death and end-stage renal failure were used as a composite primary end-point.\textsuperscript{26} In the future, reduction in certain types of adverse event and death together may be the primary end-point (improved safety) in trials of therapies that are expected to have equal efficacy.

### 2. Study design and analysis

It is assumed that the CONSORT guidelines for undertaking and reporting clinical trials\textsuperscript{50–52} will be followed in addition to Good Clinical Practice guidelines.\textsuperscript{53} It is essential to define the objective(s) of trial, including the hypothesis(es) being tested and especially the type of trial (ie, superiority versus non-inferiority). The duration of the trial should be adequate for its objectives, the known pharmacological properties of the drug to be assessed, and the end-points to be used. The end-points used should capture all relevant aspects of disease that the drug is expected to affect in the time-frame studied.

The methods used to stratify patients (eg, ethnic/racial group, presence of damage as measured by the SLICC/ACR damage index\textsuperscript{28} or the minimisation techniques should be clearly defined and justified in the protocol before the study starts. Statistical analyses must be planned in advance and designed to minimise bias.\textsuperscript{7} The minimum clinically significant difference in the end-points to be used should be stated. With a complex disease, such as SLE, studies must be adequately powered to allow for drop-outs (loss to follow-up and deaths). Methods for dealing with missing data will be required and should be specified.

Whatever method of disease activity assessment is used, training of investigators is essential before the start of a trial and reminders/updates should be provided in the form of written
materials, further investigator meetings, CD, DVD and/or web-based instruction. It is critical to determine what is lupus activity as opposed to damage, co-morbid disease or possible adverse events due to trial drug or other drugs.

2.1 Definitions of efficacy

The efficacy of a drug can be described in a number of possible ways depending on the end-points used (table 1). These include: (1) reduction in lupus disease activity, specific organ criteria and/or biomarker measurement; (2) prevention of disease flare, as defined by a disease activity index, specific organ criteria and/or change in biomarker measurement (eg, rise in anti-double-stranded (ds)DNA antibodies); (3) prevention of the onset of damage or the progression of damage, as defined by the SLICC/ACR damage index; specific organ dysfunction (eg, renal impairment), results of biopsy or imaging; (4) improvement or stabilisation of health status and quality of life; and (5) reduction in steroid dose.

2.2 Definitions of remission, response and treatment failure

For clinical trials assessing improvement in lupus disease activity, it is important to define what a “major clinical response” or “complete response” is. These terms are usually preferable to the term “complete remission” but can encompass the concept of complete remission. A “major clinical response” or a “complete response” can include no disease activity in the presence of a low level of acceptable therapy (eg, prednisolone/prednisone of 5–10 mg or less and stable other immunosuppressant and/or hydroxychloroquine). The term “major clinical response” may also include defined low levels of disease activity. For example, certain levels of disease activity measured by specific tests (eg, proteinuria <0.25 g in 24 h or equivalent) or levels of disease activity measured by indices that are not considered worrying or sufficient to increase therapy (BILAG index system scores of C, SLEDAI score ≤2 or SIS ≤4). In some cases, a certain percentage improvement in parameters such as proteinuria, glomerular filtration rate or disease activity score may be used to define response. Major clinical response may also include or be defined by the concept of prevention of lupus flares. The time-point at which these assessments are to be undertaken must be stated and it is wise to include a concept of duration of sustained improvement for a major clinical response to have been achieved.

A “partial clinical response” can then be defined as a level of improvement that would be considered significant but not sufficient for the definition of major clinical response. This definition may include a delay in time to flare and/or a certain reduction in steroid dose by the appropriate time point(s). “Non-responders” and “treatment failures” are those patients that do not achieve major or partial response. In some cases a treatment failure will be based specifically on the development of flare (new activity, particularly if it requires additional therapy).

3. Eligibility criteria

Eligibility criteria should be defined in advance and relevant data collected at baseline to allow comparisons between studies and planned subgroup analyses. The SLE Task Force showed broad agreement with the criteria to be considered, as shown in table 2. Studies should aim to include as broad a spectrum of patients as is compatible with the objectives of the trial given the diverse nature of the patients and the disease. It is important to identify all the relevant inclusion/exclusion criteria that might affect the outcome of the trial and to elaborate on specific features if necessary. All of these items should appear as baseline data when the trial is reported.

3.1 Disease definition (item 1 in table 2)

It is necessary to define what features of SLE a patient should have for entry to any given trial. Examples of disease-related entry criteria that may be used as inclusion criteria are 4 or more of the revised ACR classification criteria for SLE; a specific organ manifestation (eg, discoid rash), pre-defined criteria on biopsy for lupus nephritis; a specific biomarker or autoantibody (eg, anti-dsDNA antibodies) or the presence of any one autoantibody from a group, including antinuclear, anti-dsDNA, anti-Ro or anti-RNP antibodies.

3.2 Demographics (item 2 in table 2)

Demographic features that are relevant to the inclusion and exclusion criteria should be predefined. Lupus is a disease predominantly of females. Any limits on minimum and maximum age should be stated as disease manifestations, outcome and complications of the disease and its treatment may vary with age. Given the variation in disease expression and outcome related to ethnic and racial background, it should be noted if all groups can be recruited, and if any specific limits on the proportion from a given background is advisable. Ethnicity/race may be used as a stratification factor.

3.3 Duration of disease since diagnosis (item 3 in table 2)

It may be important to define the duration of the lupus manifestations used as inclusion/exclusion criteria. Examples might include patients newly diagnosed within last 12 months, or a minimum or maximum duration of active disease manifestations currently.

3.4 Other eligibility criteria and baseline data to be recorded (items 4–8 in table 2)

It is important to define any inclusion and exclusion criteria in terms of disease activity and severity, specifying how these are to be measured (disease activity index, SLICC/ACR damage index score or specific organ manifestations). Patients with certain complications (eg, antiphospholipid syndrome), comorbid conditions, previous disease conditions or current drug treatments (as shown in table 2) may be considered unsuitable for the study as they would be hard to evaluate or might be at particular risk of harm from the drug under study. Therefore, it is usually necessary in trials to specify exclusion criteria, for example no damage as measured by SLICC/ACR damage index at baseline; no infection requiring treatment within the last 7 days; no previous thrombosis; no malignancy within the last 10 years.

4. Concomitant medications

It is important to establish what drugs (immunosuppressives and other drugs) are allowed at entry into a trial, which should determine that the patient should be excluded, and which drugs might affect the outcomes of the study if dosing is changed (as shown in table 3). If certain drugs are not allowed during the study, the drug-free interval must be specified, and any washout procedure, as in the case of leflunomide, should be defined. If drugs are allowed, the acceptable dose range must be stated, and the time since the drug was started should be specified.
4.1 Immunosuppressives (items 1–3 in table 3)  
A patient who has recently started a new immunosuppressive may be susceptible to toxicity that will be confused with toxicity from the trial medication, and the beneficial effects of the therapy may not be seen until after the trial starts, potentially causing bias with the results of the study. Thus patients should be on a stable dose of immunosuppressive for at least 8 weeks before the commencement of the study. In reality this may restrict recruitment and a compromise has to be found. The concomitant use of hydroxychloroquine needs also to be specified. The doses of immunosuppressive drugs should be kept constant throughout the trial and reduction or cessation of treatment should only occur if there is suspected toxicity or if it is part of the protocol.

4.2 Corticosteroid therapy (items 4 and 5 in table 3)  
The use of corticosteroids during a trial should be defined. The dose of corticosteroids may be part of the primary end-point, or a secondary outcome measure. Except in trials in which the steroid dose is to remain constant, steroid reduction is likely to be part of the protocol and adherence to this must be documented. Administration of other forms of steroid (such as intramuscular, intravenous and intra-articular injection) should not be allowed unless specified in the protocol.

4.2 Other drugs (items 6–10 in table 3)  
Other drugs that may affect the end-points must also be kept stable during a trial. For example, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs and cyclo-oxygenase inhibitors may all affect renal parameters, blood pressure control and cardiac function, as well as certain disease activity measures. Anticoagulation and antiplatelet agents may influence the development of organ-specific damage. Hormone replacement therapy has been shown to increase the risk for mild to moderate flares.9 Although oral contraceptives are not considered to influence disease activity in stable patients with mild/moderate lupus disease, their effects on patients with more severe disease have not been studied.

Table 2  Eligibility criteria to be considered and baseline data to be recorded in clinical trials

<table>
<thead>
<tr>
<th>No.</th>
<th>Items to be considered and recorded</th>
<th>Definition/example</th>
<th>Mean level of agreement (scale 1–10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Disease definition</td>
<td>SLE by classification criteria, eg, ACR criteria25</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Organ manifestation, eg, lupus nephritis defined by renal biopsy25</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biomarker manifestation, eg, anti-ds DNA antibodies</td>
<td>7.7</td>
</tr>
<tr>
<td>2</td>
<td>Demographics</td>
<td>Age</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ethnicity/race</td>
<td>9.6</td>
</tr>
<tr>
<td>3</td>
<td>Duration of disease since diagnosis</td>
<td>Specify if by clinical diagnosis or ACR criteria26 or duration of specific item</td>
<td>8.8</td>
</tr>
<tr>
<td>4</td>
<td>Disease activity</td>
<td>Validated disease activity index</td>
<td>9.5</td>
</tr>
<tr>
<td>5</td>
<td>Disease severity</td>
<td>Damage score or organ manifestation</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Specific complications</td>
<td>Antiphospholipid syndrome</td>
<td>8.9</td>
</tr>
<tr>
<td>7</td>
<td>Co-morbid disease</td>
<td>Steroid-dependent asthma</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infections or malignancy</td>
<td>8.9</td>
</tr>
<tr>
<td>8</td>
<td>Current treatment with immunosuppressives and concomitant drugs</td>
<td>Steroids</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antimalarials</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunosuppressives</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anticoagulation</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antiplatelet agents</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACE inhibitors</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Table 3  Concomitant therapies to be considered/recorded during trials

<table>
<thead>
<tr>
<th>No.</th>
<th>Therapy</th>
<th>Examples</th>
<th>Mean level of agreement (scale 1–10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acceptable immunosuppressives</td>
<td>Which drugs, what doses and for what duration before study</td>
<td>9.7</td>
</tr>
<tr>
<td>2</td>
<td>Unacceptable immunosuppressives</td>
<td>Specify time interval free of certain drugs</td>
<td>9.5</td>
</tr>
<tr>
<td>3</td>
<td>Need for washout prior to study</td>
<td>eg. Lefluonamide</td>
<td>9.1</td>
</tr>
<tr>
<td>4</td>
<td>Corticosteroid treatment prior to study</td>
<td>Specify steroid type and dose over given time</td>
<td>8.7</td>
</tr>
<tr>
<td>5</td>
<td>Corticosteroid dose reduction</td>
<td>Define regimen and time before assessment</td>
<td>9.5</td>
</tr>
<tr>
<td>6</td>
<td>ACE inhibitors</td>
<td>Important in all studies with renal/cardiac/BP end-points</td>
<td>9.3</td>
</tr>
<tr>
<td>7</td>
<td>Anticoagulation and anti-platelet agents</td>
<td>Specify what is allowed or has been used</td>
<td>8.9</td>
</tr>
<tr>
<td>8</td>
<td>NSAIDs and COXIBs</td>
<td>Specify what is allowed or has been used</td>
<td>8.5</td>
</tr>
<tr>
<td>9</td>
<td>Contraception and HRT</td>
<td>Specify what is allowed or has been used</td>
<td>8.5</td>
</tr>
<tr>
<td>10</td>
<td>Other drugs</td>
<td>Specify any that might interfere with the results</td>
<td>8.5</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; ACR, American College of Rheumatology; SLE, systemic lupus erythematosus.
DISCUSSION

Recommendations for points to consider for conducting clinical trials have been proposed. These recommendations were developed using the EULAR standardised operating procedures for the elaboration, evaluation, dissemination and implementation of recommendations. As the systematic literature search revealed that there have been few high-quality randomised clinical trials in SLE, particularly for lupus manifestations other than lupus nephritis, and as end-points used in phase 2/3 trials in SLE have not actually been validated in clinical trials, it was felt appropriate to make suggestions for points to consider rather than firm recommendations for conducting clinical trials.

The SLE Task Force anticipates that these suggestions will provide a useful structure for investigators planning clinical trials in SLE. It is planned to disseminate these recommendations for points to consider widely and to evaluate their usefulness in the design and conduct of clinical trials. They will be reviewed in 5 years by which time it is anticipated that a number of new trials will have been published that should help to inform the discussion. A research agenda has been proposed that lists some of the unresolved issues (box 1).

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