

Current challenges in the development of new treatments for lupus

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1 **Current Challenges in the Development of New Treatments for**
2 **Lupus**

3

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1 **Abstract**

2 Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a
3 considerable impact on patients' quality of life. Despite the plethora of clinical trials
4 for SLE since the turn of the millennium, only one new treatment has been approved
5 for the condition and the overall pace of successful drug development remains slow.
6 Nevertheless, the myriad of clinical studies has yielded insights that have informed
7 and refined our understanding of eligibility criteria, outcome measures and trial
8 design in SLE. In this review, we highlight the achievements of clinical trials as well
9 as the major pitfalls that have been identified in drug development for SLE and, in
10 doing so, identify areas where collaboration and consensus will be important to
11 facilitate progress.

12

13

1 INTRODUCTION

2 Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that follows a
3 relapsing-remitting course. It is characterized by the production of autoantibodies
4 against a range of autoantigens including nuclear components, immune-mediated
5 inflammation in a variety of organs, and the accrual of organ damage over time.[1]
6 Despite its prevalence (approximately 70 cases per 100,000 people)[2-6] and
7 considerable impact on quality of life,[7, 8] treatment options remain inadequate and
8 the development of novel therapies has been slow.

9 Only one new drug, belimumab, has been approved for the treatment of SLE in more
10 than 60 years.[9-11] While numerous other drugs and biologics have entered clinical
11 trials for SLE since the turn of the millennium, development of most has been halted
12 at various stages.[12-14] Although some of these failures may be related to
13 inefficacy of the investigational product or adverse events, there is general
14 consensus in the community that problems with trial design and operation may have
15 contributed to the unsuccessful outcomes. Notably, however, a number of recent
16 phase IIb trials (each investigating agents with different modes of action) have
17 reported positive outcomes,[15, 16] suggesting that new treatment options may be
18 on the horizon, though the recent failure of a phase III anifrolumab trial to meet its
19 primary endpoints, reported in the lay press, suggests that there is more to learn.

20 Although the majority of trials in SLE have failed to meet their primary endpoints,
21 many of these studies have offered valuable insights that have advanced the field
22 considerably, including the evolution of thinking about eligibility criteria and outcome
23 measures. Nevertheless, several important issues remain unresolved, and progress in
24 these areas will require consensus among the relevant stakeholders. The aim of this
25 review is to highlight pitfalls in drug development for SLE and identify areas where
26 collaboration and consensus will be important to facilitate progress.

27 LESSONS LEARNED FROM PREVIOUS CLINICAL TRIALS IN SLE

28 Formal clinical trials in SLE have been carried out for nearly two decades, although
29 many failed to meet their primary endpoints.[12] Post-hoc analyses of these studies
30 have identified numerous issues related to trial design,[12, 17] prompting
31 investigators, pharmaceutical companies and regulatory agencies to standardize
32 aspects, such as entry criteria (by defining thresholds for disease activity and

1 autoantibody positivity), outcome measures, preferences for trial duration, and the
2 choice of background therapy (including regimens for steroid use and tapering).

3 Many of these issues have been decided pragmatically, often in discussions between
4 pharmaceutical/biotech companies and regulatory agencies.[12] Whether the final
5 negotiated approach is the most scientifically valid has often not been determined,
6 but operationally a “standard” SLE therapeutic trial design has emerged.[9, 10]
7 Despite previous trial failures, many companies continue to have a strong
8 commitment towards developing new drugs for SLE. In some cases, this may relate
9 to promising trends in the trial data that differentiate potential responders from
10 nonresponders.[18] Other times, it is learning from another company's successes
11 and failures.[14] Regardless, the pace of clinical trials in SLE remains brisk.

12 Some of the failed trials in SLE might have tested agents that were truly ineffective.
13 However, in other cases it was reasonable to expect success, such as when testing
14 agents related to compounds that had previously been successful (belimumab versus
15 tabalumab), agents with strong evidence of efficacy from clinical experience
16 (rituximab), or agents with extensive pre-clinical experience (abatacept plus
17 cyclophosphamide). These experiences suggest that the current trial paradigm for
18 SLE may not be capable of convincingly testing the efficacy of a compound, or
19 definitively deciding whether or not to advance a compound into phase III.

20 **Disease activity as an entry criterion**

21 One of the earliest trials in SLE examined the efficacy of dehydroepiandrosterone
22 (DHEA) in 381 patients.[19] Although this study did not meet its primary endpoint,
23 valuable insights were obtained into the design of clinical trials in SLE. Specifically, a
24 post-hoc analysis indicated that the primary endpoint was only met in patients with a
25 baseline SLE Disease Activity Index (SLEDAI) score >2 . As such, this was the first
26 trial demonstrating the potential utility of disease activity as an entry criterion.

27 Subsequent trials have confirmed the importance of recruiting patients with
28 moderate-to-high disease activity in order to discern a treatment effect. This has
29 generally been achieved by specifying disease activity beyond a certain threshold for
30 inclusion (e.g. SLEDAI ≥ 6 , or a British Isles Lupus Assessment Group (BILAG) score
31 of B or A, indicating active organ involvement).[14] Post-hoc analysis of the BLISS
32 trials revealed additional benefits of belimumab treatment in patients with higher

1 disease activity (SLEDAI ≥ 10) at baseline.[20] Notably, this increased benefit
2 seemed to rely on decreased responsiveness in patients receiving standard of care
3 only. Thus, the absolute difference in response between the group receiving
4 standard of care plus belimumab, and the group receiving standard of care alone,
5 was increased. This observation suggests that standard of care therapy can be
6 effective in the setting of a clinical trial, and could be especially effective in patients
7 with mild disease upon entry (despite having apparently failed standard of care
8 before enrollment). Discerning a response to an experimental agent appears to be
9 more likely in patients with more active disease, in whom the response to
10 background therapy is diminished.

11 **Geographic location**

12 International SLE trials have demonstrated major differences in treatment response
13 according to geographical region. Specifically, sites in developing countries generate
14 data that indicate a better response to placebo (plus standard of care) compared to
15 results obtained in the United States or western Europe.[21] The reason for this
16 discrepancy is uncertain, but might relate to patients' access (or lack thereof) to
17 standard of care therapies before entering the trial, and the requirement to
18 consistently take these medications in the trial setting. A second concern is the
19 increased frequency of infection[22] as well as trial-related deaths[23, 24] in studies
20 conducted in developing countries. Part of this may relate to higher rates of certain
21 infections in these countries, coupled with the lack of access to standard and
22 emergency medical care. Thus, whilst there are major attractions to recruiting
23 patients from developing countries (including low expense, rapid enrolment and the
24 prevalence of active disease), there is a clear need to guard against a greater
25 placebo response, and to mitigate the intrinsic risk of serious adverse events, in
26 these regions.

27 **Ancestry/ethnicity**

28 A number of SLE trials have suggested preferential response to treatment in certain
29 ancestral subsets. The comparative trial of mycophenolate mofetil (MMF) versus
30 cyclophosphamide (CYC) in lupus nephritis suggested that MMF might be more
31 efficacious in a primarily African-Ancestry (AA)/Hispanic trial population.[25] In
32 contrast, the induction phase of the Aspreva Lupus Management Study (ALMS) trial,
33 with patients of predominantly European Ancestry (EA) did not show any significant

1 difference between the two drugs.[26] However, post-hoc analysis suggested an
2 improved response to MMF in the AA/Hispanic group.[27] These findings were
3 sufficiently convincing that the 2012 ACR Lupus Nephritis Treatment Guidelines
4 recommend MMF over CYC as first-line treatment for AA and Hispanic
5 populations.[28] Results from the pivotal trials of belimumab suggested that this
6 agent was not effective in AA patients,[9, 10] although the numbers of AA patients in
7 these trials were small. In contrast, the results of a pre-specified subgroup analysis
8 suggested that rituximab might be *more* efficacious in AA/Hispanic lupus nephritis
9 patients.[29] However, given the poor recruitment of AA patients into SLE trials,
10 these findings are at best speculative. Recent systematic reviews of potential
11 predictors of response to MMF and rituximab have concluded that the overall quality
12 of evidence supporting differential effects related to ancestry and ethnicity are low,
13 and further confirmatory studies are needed to discern whether such a difference
14 exists.[30, 31] Other factors, including the small size of the trials and socioeconomic
15 status, may have contributed to the result.

16 **Heterogeneity of clinical manifestations**

17 SLE is a heterogeneous disease, involving numerous organ systems. In general, trials
18 have focused either on generalized SLE or lupus nephritis. In trials of generalized
19 SLE, it is common to exclude patients with rapidly progressive kidney or CNS
20 disease.[9, 10] As a result, studies have largely enrolled patients with
21 mucocutaneous and musculoskeletal involvement. This not only limits the
22 heterogeneity of the enrolled population, but excludes patients with less common
23 and more severe disease manifestations. As a result, little information has emerged
24 on the efficacy of agents in these patients.

25 Lupus nephritis trials have typically enrolled patients with biopsy-proven nephritis,
26 although there is considerable variation in the timing of the biopsy relative to trial
27 entry.[32] As a result, the exact nature of kidney involvement at the time of trial
28 enrollment may not be certain, owing to the possible role of hypertensive kidney
29 disease and progressive kidney fibrosis. Moreover, entry has usually been based on
30 glomerular involvement, despite evidence that interstitial inflammation may play a
31 more important role in progression to kidney failure.[33] In addition, the level of
32 proteinuria at baseline might be an important predictor of renal response. For
33 example, in a trial comparing the addition of abatacept or placebo to background

1 MMF in patients with lupus nephritis, those with baseline nephrotic syndrome had a
2 greater response to abatacept as measured by reduction in proteinuria.[34]

3 **Outcome measures**

4 Although numerous outcome measures were used in early SLE trials, the FDA
5 released draft guidelines in 2005 to facilitate their standardization.[35] This included
6 the recommendation of a composite endpoint that could measure clinically
7 meaningful improvements in active organ systems without worsening in others, and
8 detect both early and overall changes in disease activity. The FDA seemed to favour
9 the BILAG;[36] however, the success of the belimumab BLISS trials resulted in
10 widespread adoption of the SLE Responder Index (SRI)-4 as the primary outcome
11 measure. The BILAG-Based Composite Lupus Assessment (BICLA) and the SRI-5
12 were used in unsuccessful phase III trials of epratuzumab and tabalumab,
13 respectively.[37-39] However, the BICLA was employed as an outcome in successful
14 phase II trials of anifrolumab[15] and epratuzumab,[40] and in a post-hoc analysis
15 of an IL-6 receptor antibody,[24] both in generalized SLE.

16 The decision to adopt the SRI-4 was driven from a retrospective analysis of the
17 phase II belimumab data, which found that this instrument distinguished active drug
18 from placebo. This hypothesis was borne out in subsequent trials with both
19 intravenous and subcutaneous belimumab.[41, 42] In addition, the FDA believed it
20 was important to determine whether an agent might be effective in some domains,
21 while at the same time measuring whether deterioration occurs in others. However,
22 subsequent analyses have shown that the overwhelming contributor to the SRI-4 is
23 improvement in SLEDAI alone, with very few patients manifesting improvement in
24 SLEDAI but deterioration in BILAG or Physician's Global Assessment (PGA).[9, 10]
25 Since the majority of patients in the belimumab trials had skin and joint involvement,
26 SLEDAI was sufficient to capture improvement in this case. However, SLEDAI cannot
27 capture some types of organ involvement, and therefore may not be sufficient for
28 assessing the outcomes of less common disease manifestations. In addition, higher
29 baseline SLEDAI scores may improve the ability to detect an SRI-4 response.

30 It is also important to note that while the SRI-4 continues to be used as the
31 preferred primary outcome measure in major SLE clinical trials, it is not used as an
32 assessment in routine clinical practice. This creates a disconnect between clinical trial

1 data and information that is meaningful to a practitioner or patient, and might delay
2 the uptake of newly approved therapies into practice, since physicians are unclear
3 about the expected clinical response and are often inexperienced at using the
4 component instruments (SLEDAI, BILAG and PGA). Nevertheless, there is now a
5 requirement to use BILAG and SLEDAI when assessing patients for treatment with
6 rituximab or belimumab in the NHS in England.[43-45] However, both of these
7 instruments have significant limitations, including low inter-observer correlation and
8 high complexity in the case of the BILAG. Lastly, careful consideration should be
9 given to the use of flare rather than response as an endpoint.[46]

10 Collectively, these considerations suggest that a re-evaluation of outcome measures
11 in clinical trials based on available data might be necessary to develop more clinically
12 meaningful ways to assess the impact of new therapies. Unfortunately, an initial
13 attempt to create a novel SLE response index from the belimumab trial data was not
14 successful.[47] However, a more recent effort based on the BLISS-76 data yielded
15 the Lupus Multivariable Lupus Outcome Score (LuMOS), a robust outcome measure
16 that outperformed the SRI-4 and was validated in the BLISS-52 database.[48] If
17 recapitulated in trials for agents with other mechanisms of actions, LuMOS will be
18 the first evidence-based SLE outcome measure, and may provide a better means to
19 assess treatment response in clinical trials.[48] As new outcome measures are
20 developed, it will be important to perform validation studies examining their
21 association with longer-term outcomes, quality of life, and cost effectiveness.

22 The aforementioned FDA guidelines have since been replaced by a finalized
23 document, which was issued in 2010 and is still operational.[49] This includes
24 guidance for a range of trial design issues, including statistical considerations. At the
25 time of release, the FDA issued separate documents for SLE and lupus nephritis,
26 although the latter was eventually withdrawn and has not yet been replaced. In the
27 absence of specific guidelines for lupus nephritis, the most effective short-term renal
28 response measures remain elusive, with different instruments generating significant
29 variability in the data obtained and the conclusions drawn.[50]

30 Importantly, the process by which new outcome measures might be incorporated
31 into SLE clinical trials has not been clearly articulated by the regulatory agencies.
32 Some outcome measures, such as the Cutaneous Lupus Area and Severity Index
33 (CLASI) to evaluate skin involvement have been developed by the academic

1 community, but not accepted by regulatory authorities as a validated outcome
2 measure in clinical trials. As a result, nearly all SLE trials rely on evidence derived
3 from the standard composite outcome measures described in the 2010 FDA guidance
4 document. Given the recent developments and lessons learned from SLE trials (both
5 successful and unsuccessful), we firmly believe that it is time for the regulatory
6 guidance to be revised through collaboration between a range of stakeholders,
7 including physicians, patients, members of industry, and regulatory agencies who
8 have expertise in this area. In addition, evidence-based guidance for outcomes in
9 lupus nephritis are sorely needed. An even better option would be to propose and
10 adopt new trial designs and outcome measures through an accelerated process that
11 could bypass a traditional guidance document.

12 **The role of serological assessments in entry criteria**

13 The use of serological biomarkers for enrollment in SLE trials is a relatively recent
14 development, having become standard practice within the past decade. This
15 approach was based largely on a post-hoc analysis of phase II belimumab data,[51]
16 which revealed a subset of autoantibody positive patients who responded to
17 belimumab better than their seronegative counterparts. Before this, eligibility was
18 based primarily on the ACR Classification Criteria for SLE (which do not require a
19 serological criterion) and established indices of disease activity, with no stand-alone
20 serological component.[19, 52] While SLEDAI includes measures of anti-DNA and
21 complement levels, antinuclear antibody [ANA] positivity was not always required for
22 trial entry.

23 Although ANA, anti-DNA, low complement C3 and C4, and/or anti-Smith
24 autoantibodies are now commonly used as entry criteria, there is no consensus on
25 the specific autoantibody or serological marker required, nor the method used to
26 measure it. As previously noted, the use of autoantibody positivity to classify patients
27 was based on phase II data from a B-cell directed therapy, providing some rationale
28 for its use in that context.[51] However, the use of serological positivity to subset
29 patients in trials of agents *not* directed toward B cell function may not be appropriate.

30 In reality, this approach has been embraced in an attempt to confirm that patients
31 enrolled in trials actually have SLE. It is thought that a positive ANA test increases
32 that likelihood, and therefore the test has been widely employed as an entry criterion.

1 Of note, the recent SLE classification criteria developed by the American College of
2 Rheumatology and the European League Against Rheumatism require a positive ANA
3 at 1:80 titer.[53] However, given its poor specificity, variability between assays, and
4 the observation that patients with SLE may convert to a negative ANA over time and
5 with immunosuppressive therapy,[54] the use of a positive ANA to classify patients
6 and assess eligibility in clinical trials is problematic. Using more specific tests, such as
7 a positive anti-DNA, imposes additional problems.[55] Restricting trials to anti-DNA
8 positive patients would exclude approximately 40% of SLE patients because of the
9 lesser sensitivity of these assays. Similarly, a requirement for low complement levels
10 would exclude many patients, particularly those in non-renal lupus trials. In short,
11 the utility of specific serologic testing for assessing eligibility in SLE trials has not
12 been carefully examined, and will require thoughtful consideration in the future.

13 **Biomarkers**

14 Apart from the use of autoantibodies, and possibly complement levels, no biomarkers
15 are currently accepted as informative in SLE clinical trials. Recent data have indicated
16 that anifrolumab, a monoclonal antibody to the type 1 interferon receptor, might be
17 effective in generalized SLE based on phase II data.[15] These results also
18 suggested that the treatment was only effective in individuals who had increased
19 expression of certain interferon-responsive gene products. There are phase III trials
20 currently underway with secondary endpoints to assess whether this “interferon
21 signature” might facilitate stratification, and thus serve as a companion diagnostic to
22 identify patients with a greater likelihood of responding to treatment.[56] If
23 successful, this would represent the first biomarker for selecting and monitoring the
24 treatment of patients with SLE.

25 **Background therapy**

26 Most trials in SLE test new agents on the background of standard of care therapy.
27 This stems largely from investigators’ concerns about the development of irreversible
28 organ damage in the placebo group if adequate background medication were not
29 continued. However, there are a number of problems with this approach.

30 First, standard of care can be quite effective in many patients, leaving a narrow
31 window for improvement with the experimental agent, particularly if patients take
32 their medications more reliably in the trial setting.[57] Secondly, there is no

1 consensus on what constitutes 'standard of care', meaning that participants within
2 the same trial may be treated with different background medications. Thirdly, many
3 trials permit variation in the dosing of background medication for a period of time
4 before or during the study, making it even more difficult to discern benefit from the
5 experimental agent. Finally, recent work from the Systemic Lupus International
6 Collaborating Clinics (SLICC) cohort has revealed substantial variation in the dose of
7 steroids used across centers. While patient and disease factors contribute to this
8 variation, differences between centers suggest that physician-related factors also
9 contribute. Such patient-independent heterogeneity in steroid use will contribute to
10 'noise' in multicenter trials and increase the likelihood of type two errors. A period of
11 standardization in steroid use prior to randomization may be necessary to address
12 such variation as was done in the April-SLE atacicept trial.[23, 58]

13 Two recent studies that support the possibility of minimizing background therapy
14 through steroid tapering are the phase II anifrolumab and voclosporin trials,[15, 59]
15 both of which reported low placebo responses. These studies suggest, though do not
16 prove, that lowering standard of care therapy in a safe manner might permit better
17 discernment of the benefit of the experimental agent. This would also be beneficial
18 for the safety of trial participants, by providing clearer criteria for rescue therapy or
19 study withdrawal.

20 **Time and expense**

21 Clinical drug development is very costly and time-consuming. This has frequently
22 prompted pharmaceutical companies to design clinical development programs that
23 save time and utilize the fewest number of patients. Since drug approval requires
24 data in two well-designed clinical trials,[60] the standard phase I through III
25 programs have often been truncated, typically by short-circuiting phase II trials or
26 even treating them as pivotal in order to save time and resources. As a result, phase
27 III trials are often initiated without proper dose-ranging or robust power calculations,
28 and with little information on the optimal regimen and outcome measures. In
29 addition, the potential contribution of ancestry to trial outcomes is frequently
30 neglected (the FDA has requested additional trials of belimumab in patients of
31 African descent). The impact of body composition may also be underestimated. Most
32 trials use fixed-dose drug regimens regardless of body mass index, which does not
33 account for the potential pharmacokinetic variation between patients.

1 While understandable in terms of cost and efficiency, agents such as tabalumab and
2 epratuzumab[61] may ultimately have failed because of these drawbacks. Thus, the
3 effectiveness of phase III trials hinges critically on the data obtained in phase II,
4 highlighting the need to conduct more extensive studies at this stage.

5 **AREAS IN NEED OF COLLABORATION AND CONSENSUS**

6 The authors believe that there are two major areas in which collaboration and
7 consensus would be useful. The first relates to data that are already available from
8 clinical trials in SLE. Over 5,000 patients have participated in these studies, providing
9 a wealth of data that may help us to answer important questions about trial design
10 and conduct. The second area relates to issues that cannot be addressed using the
11 existing trial data alone. Questions falling within each of these areas are listed in
12 **Table 1.**

13 **Table 1.** Aspects of SLE drug development that are in need of collaboration and
14 consensus

Questions that can be addressed using existing clinical trial data

- **Adverse events**
 - What factors influence adverse events in SLE trials?
 - When do adverse events occur?
 - Are adverse events more likely during the first few weeks of the trial when steroid doses tend to be higher?
 - What is the evidence that adverse events are influenced by steroid dose and/or background immunosuppressants?
 - Are adverse events more common in particular geographic regions or certain types of research institution than others?
 - **Outcome measures**
 - Is the SRI the most appropriate outcome measure?
 - Does it matter which version of the SRI is used?
 - Can we simplify this by focusing only on improvement in disease activity, or change in disease activity using a single instrument?
 - Which outcome measures should be used in generalized SLE trials, and which in lupus nephritis trials?
 - Should we consider flare prevention as a primary outcome measure?
 - Which outcome measures have performed best in lupus nephritis trials?
-

Are these endpoints influenced by the duration of renal involvement, time since renal biopsy, the result of renal biopsy and/or a patient's treatment history?

- **Background therapy**
 - Do trial outcomes differ with different background regimens?
 - What is the role of background steroids?
 - Should the target steroid dose depend on the patient's baseline dose or body weight?
 - Should there be a 'run-in' period to standardize steroid use prior to randomization?
- **Regional differences**
 - Are there consistent regional differences in the use of background medications, or the development of adverse events?
 - Should trials require a mandatory number of subjects of different ancestries? How should ancestry be determined? How should mixed ethnicity be dealt with?
- **Others**
 - What are the best biomarkers to judge efficacy? Are they specific to the agent's mechanism of action, or related to disease manifestations?
 - Is autoantibody stratification useful and/or necessary?
 - Will an AUC approach be better than a landmark analysis?

Questions that require expertise and consensus beyond what is available from clinical trial data

- **Trial design**
 - What is the most appropriate length of a trial? Should there be "induction" and "maintenance" trials?
 - What is the most appropriate design of a non-renal SLE trial? Should we enroll active patients and measure improvement in disease activity, or should we be measuring "time to flare" instead after initial treatment of flare?
 - **Patient-reported outcomes**
 - What is the role of PROs, and which is the most appropriate to use?
 - What is the role of PROs in clinical trial design and drug approval? Should drugs be approved based on improvement in PROs? What is the contribution of comorbidities to PROs?
 - **Background therapy**
 - What is "standard of care"? Are standard of care regimens used for clinical
-

or ethical reasons?

- Should there be a mandatory steroid taper versus the commonly used “suggested” steroid taper? Should steroid taper to a certain dose be part of the primary endpoint?

- **Other**

- What does “treat to target” really mean in lupus?
-

1 AUC: area under curve; PRO: patient-reported outcome; SLE: systemic lupus erythematosus; SRI: SLE
2 responder index.

3 **The current landscape**

4 Various initiatives are already taking shape to address the outstanding issues in SLE
5 clinical trials. Among these is the Definitions of Remission In SLE (DORIS) taskforce,
6 an international collaboration between 60 specialists and patient representatives to
7 formulate a universal definition of ‘remission’ in SLE, in line with treat-to-target
8 recommendations.[62] The taskforce recently published a framework for this
9 purpose comprising eight key statements, as well as three principles to guide the
10 refinement of this definition in future.[62] Since remission is rarely a goal in SLE
11 trials, because it is too stringent and hard to achieve,[63] optimal trial design will
12 require the development of alternative endpoints. To this end, one group of
13 investigators is developing the Lupus Low Disease Activity State (LLDAS) for
14 generalized SLE,[64] and another group has developed a low disease activity (LDA)
15 outcome.[65] These new endpoints could initially be incorporated in SLE trials as a
16 secondary endpoint for comparison with existing instruments, and might eventually
17 replace SRI or SLEDAI as the primary outcome measure. For example, LLDAS has
18 been incorporated as a secondary endpoint in the currently enrolling BLISS-BELIEVE
19 trial sponsored by GlaxoSmithKline.[66]

20 Further to these efforts, the Lupus Industry Counsel is working with Outcome
21 Measures in Rheumatology (OMERACT) to develop new instruments by reanalyzing
22 existing trial data,[67] and the Lupus Foundation of America (LFA) is developing a
23 system of tools (dubbed LFA-REAL) for the measurement of both systemic and
24 organ-specific disease activity.[68]

25 Another recent focus of collaboration in SLE is the identification of genetic and/or
26 phenotypic markers for patient stratification. The Innovative Medicines Initiative

1 (IMI) is an EU-based, public-private initiative to improve the drug development
2 process in Europe. Among the projects currently being conducted under this initiative
3 is PRECISESADS, which is bringing together academic, clinical and industry partners
4 to identify biomarkers that will assist with developing a new taxonomy for systemic
5 autoimmune diseases, including SLE.[69] PRECISESADS therefore aims to group
6 patients with a shared pathogenesis, rather than using standard diagnostic and
7 clinical classification criteria.[70]

8 In the UK, the Medical Research Council (MRC) is funding MASTERPLANS
9 (MAximizing Sle ThERapeutic Potential by Application of Novel and Stratified
10 approaches).[71] MASTERPLANS seeks to identify patient-level variables, including
11 genetic and other biomarkers, that define an endotype of response in SLE patients,
12 with an initial focus on mycophenolate and rituximab. The contribution of industry
13 partners to these initiatives is particularly valuable, given their large datasets and
14 extensive libraries of patient samples. Moreover, once new biomarkers are identified,
15 their uptake and use in clinical trials by industry partners will be crucial for their
16 validation.

17 **CONCLUSION**

18 While most recent trials in SLE have failed to meet their primary endpoints, many
19 have offered valuable insights that have shaped the field as we know it today.
20 Nevertheless, meaningful change from this point forward will require community-
21 wide consensus, including academia, industry and patient organizations, in dialogue
22 and partnership with regulators and payers. In short, it is imperative that common
23 goals are identified and that the community speaks with one voice.

24 By forging new collaborations, re-analyzing existing datasets, and pooling data from
25 multiple sources in a 'pre-competitive' way, we will gain new insights to help improve
26 trial design using evidence-based and data-driven approaches. The ability to identify
27 subsets of disease with a common pathogenic mechanism, or patient endotypes
28 more likely to respond to a particular therapeutic agent, will also allow us to offer
29 patients the right drug for their condition in a timely manner, and shorten the time
30 from diagnosis to disease control. Keeping the patient at the forefront of our efforts
31 should spur us to achieve consensus on the way forward, and steer efforts to refine
32 the guidance for trial design and conduct.

1 **AUTHOR CONTRIBUTIONS**

2 Substantial contributions to the development of this publication, or revising it
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27 manufactured or developed by them.

28 SM has a patent portfolio that was licensed and commercialized by Exagen, Inc. She
29 has served as a consultant or member of an advisory board for Exagen, Inc., GSK,
30 UCB Pharma and AstraZeneca. She serves as the Chair, Board of Directors for the
31 Lupus Foundation of America.

- 1 MD, JM and PL have no conflicts of interest to declare.
- 2 The views expressed in this publication are those of the author(s) and not
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