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DOI:
10.1136/annrheumdis-2018-214530

Document Version
Peer reviewed version

Citation for published version (Harvard):
Dall'Era, M, Bruce, IN, Gordon, C, Manzi, S, McCaffrey, J & Lipsky, P 2019, 'Current challenges in the development of new treatments for lupus', *Annals of the Rheumatic Diseases*, vol. 78, no. 6, pp. 729-735. https://doi.org/10.1136/annrheumdis-2018-214530

Current Challenges in the Development of New Treatments for Lupus

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Short title: The Lupus Landscape [TBC]

Funding: UCB Pharma

Key words: Systemic lupus erythematosus, lupus nephritis, autoimmune diseases, autoantibodies

Word count: 4101

Abstract

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

INTRODUCTION

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

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

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

LESSONS LEARNED FROM PREVIOUS CLINICAL TRIALS IN SLE

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

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

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

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

Disease activity as an entry criterion

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

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

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

Geographic location

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

Ancestry/ethnicity

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

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

Heterogeneity of clinical manifestations

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

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

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

Outcome measures

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

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

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

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

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

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

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

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

The role of serological assessments in entry criteria

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

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

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

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

Biomarkers

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

Background therapy

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

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

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

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

Time and expense

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

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

AREAS IN NEED OF COLLABORATION AND CONSENSUS

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

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

Questions that can be addressed using existing clinical trial data

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

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

The current landscape

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

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

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

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

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

CONCLUSION

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

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

AUTHOR CONTRIBUTIONS

Substantial contributions to the development of this publication, or revising it critically for important intellectual content: MD, INB, CG, SM, JM, PL; Final approval of the publication: MD, INB, CG, SM, JM, PL.

ACKNOWLEDGEMENTS AND AFFILIATIONS

The authors conceived of and wrote the manuscript. The authors acknowledge Sam Fraser, PhD (Costello Medical, Cambridge, UK) for medical writing and editorial assistance in preparing an early draft of this manuscript, which was funded by UCB Pharma and based on the authors' input and direction. UCB Pharma was not involved in the development or review of the final version.

COMPETING INTERESTS

IB is a National Institute for Health Research (NIHR) Senior Investigator and is supported by the NIHR Manchester Biomedical Research Centre. He has also received grants from Genzyme Sanofi and GSK, and undertaken consultancies and speakers' bureau for GSK, AstraZeneca, UCB Pharma, Merck Serono, Genzyme Sanofi, Eli Lilly and BMS.

CG has undertaken consultancies and received honoraria from BMS, GSK, EMD Serono, and UCB Pharma, related to clinical trial design and analysis. CG has also been a member of the speakers' bureau for GSK and UCB Pharma. She has received research grant support at Sandwell and West Birmingham Hospitals NHS Trust from UCB Pharma in the past and currently, unrelated to the study of any specific drug and without any personal payments to herself. She has participated in clinical trials sponsored by UCB Pharma in the past and funded by Arthritis Research UK, with drug supplied by GSK currently. She has no financial interests in any of these companies, and does not and will not benefit from the sales of any drugs manufactured or developed by them.

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

MD, JM and PL have no conflicts of interest to declare.

The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

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