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Measurement of haemolytic anaemia in a novel treatment response measure for SLE clinical trials

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ABSTRACT

Objectives To define a clinically meaningful treatment response definition for haemolytic anaemia, that will form part of a novel multidomain outcome measure for SLE clinical trials.

Methods An international working group comprising 12 clinicians and 4 patients completed a multistep consensus process. First, the scope of haemolytic anaemia for the SLE clinical trial context was defined. Candidate response measures were then nominated via an online survey and shortlisted for evaluation via a systematic literature review (SLR) focussing on relevant measurement properties and clinical trial utility. Informed by the SLR results, the working group used nominal group technique (NGT) to reach consensus on a response measure, as well as entry, clinically meaningful response and complete response thresholds.

Results The domain scope was unanimously agreed on as 'immune-mediated haemolytic anaemia attributed to active lupus that impacts the patient and is modifiable by therapy to reduce or control disease activity', including Coombs' positive autoimmune haemolytic anaemia and rarer subtypes. Six laboratory measures to fit this scope were shortlisted for the SLR, which screened 1519 articles, of which 10 were included. Consensus via NGT was reached on haemoglobin (Hb) improvement to measure haemolytic anaemia treatment response. Thresholds were defined for entry (Hb <100 g/L with laboratory confirmation of haemolysis), minimum clinically meaningful response (Hb improvement >20 g/L or Hb normalised with ongoing haemolysis) and complete response (Hb normalised without haemolysis).

Conclusions Hb, with meaningful thresholds for entry and improvement, will be adopted to classify haemolytic anaemia treatment response in a novel multi-domain outcome measure for SLE clinical trials.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ New outcome measures are needed for SLE clinical trials to improve trial interpretability and success.

⇒ Haemolytic anaemia is a serious manifestation of SLE. Consensus was previously achieved on its inclusion within a novel multidomain treatment response measure being developed for SLE clinical trials.

WHAT THIS STUDY ADDS

⇒ Using nominal group technique methods informed by a systematic literature review, an expert working group reached consensus on the use of haemoglobin (Hb) as the most fit-for-purpose response measure for haemolytic anaemia in SLE clinical trials.

⇒ Clinically meaningful thresholds were defined for entry (baseline Hb <100 g/L with evidence of haemolysis), minimum clinically meaningful response (improvement in Hb >20 g/L from baseline or Hb normalised with ongoing haemolysis) and complete response (Hb normalised with no evidence of haemolysis) for use in the trial setting.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Hb, with thresholds defining meaningful improvement, will be adopted to classify haemolytic anaemia response in a novel multidomain outcome measure for SLE clinical trials. This will allow patients with haemolytic anaemia to be included in such trials and new medicines evaluated for their effects on this SLE manifestation.

INTRODUCTION

SLE is a complex, multisystem autoimmune disease. Despite recent progress, therapeutic advances are needed to improve patient outcomes. However, challenges associated with the measurement of treatment response and flawed outcome measures used in SLE randomised controlled trials (RCTs) continue to impede clinical trial success and drug approval.[1]

The Treatment Response Measure for SLE (TRM-SLE) project is an international collaboration aiming to develop a novel clinical outcome assessment for SLE RCTs that measures clinically meaningful treatment effects on disease activity, applicable to both adult and adolescent patients. Led by expert lupus clinicians, people living with lupus and their representatives, industry partners and individuals with methodological and regulatory expertise, achievements of the project to date include establishing a multistage instrument development protocol, determining the high-level measurement goals for the instrument[2] and achieving consensus via formal Delphi methods on the domains of disease activity that will be used to measure SLE improvement.[3] These domains, being rash, alopecia, mucosal ulcers, haemolytic anaemia, thrombocytopenia, arthritis, serositis and nephritis, were included based on their importance to how patients feel, function or survive, appropriateness for the context of an RCT in which immune-mediated manifestations of active disease are the subject of intervention, frequency of representation in populations with active SLE and measurability in an RCT context.[3] Having established the domains of active disease to best measure treatment response in trials, we now aim to define a fit-for-purpose instrument with which to measure each included domain.

This study reports on the methodology and outcomes pertaining to the measurement of the haemolytic anaemia domain in TRM-SLE. Haemolytic anaemia is reported in up to 10–15% of adults and children with SLE[4–8] and is included as a criterion within all the major SLE classification systems.[9–11] It is associated with poorer prognosis, including higher rates of organ damage and reduced survival.[4–6] Despite its importance, haemolytic anaemia in SLE is relatively understudied, including in a clinical trial context. This is in part driven by the SLE Disease Activity Index (SLEDAI) which does not assess for haemolytic anaemia, and the British Isles Lupus Assessment Group (BILAG) index which combines items for haemolytic anaemia with non-haemolytic anaemia, leucopenia and thrombocytopenia under a broader haematology umbrella. As the SLEDAI and BILAG form the basis of both legacy SLE RCT response criteria as well as trial eligibility, it is difficult for patients to qualify for current RCTs on the basis of active haemolytic anaemia alone, and if they are included, data on haemolytic anaemia activity and response cannot be specifically gleaned from the standard reporting of SLE trial endpoints.

The aim of this study was to define clinically meaningful treatment response in SLE-related haemolytic anaemia, suitable for use in a clinical trial context. To achieve this, we first aimed to determine a method of measuring haemolytic anaemia activity. We then aimed to define a threshold at which haemolytic anaemia activity becomes clinically meaningful (ie, when it significantly affects how a patient feels, functions or survives), which will determine whether this domain is appropriate for evaluating treatment response. For patients meeting this activity level, we define thresholds of clinically meaningful improvement to accurately assess treatment efficacy. The result will form part of the TRM-SLE multidomain outcome measure for SLE clinical trials.

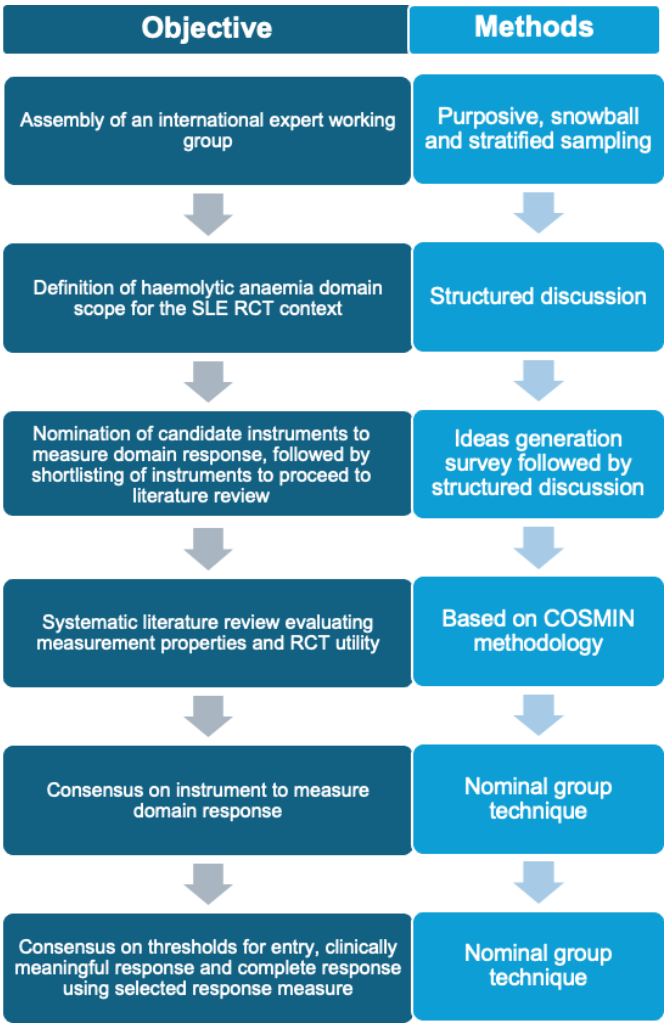


Figure 1 Steps to reach consensus on the response criteria for haemolytic anaemia. COSMIN, COnsensus-based Standards for the selection of health Measurement INstruments; RCT, randomised controlled trial.

METHODS

Consensus on the measure and thresholds defining treatment response for haemolytic anaemia in TRM-SLE was achieved by an expert working group via a multistep consensus process including structured discussion and nominal group technique (NGT), supported by a systematic literature review (SLR). The key phases are outlined in figure 1 and described below and in online supplemental material. All meetings were conducted online using Zoom Video Communications (and recorded for those unable to attend) and surveys were administered online via Qualtrics. Structured discussion was supported by PowerPoint and a virtual whiteboard (MURAL Visual Collaboration).

Haematology working group

An international haematology working group was assembled comprising 12 expert clinicians and 4 patients with lived experience of haematological lupus. The composition, selection criteria and recruitment methods for the working group were approved by the TRM-SLE Steering Committee[2] and achieved via purposive sampling of a wide list of international expert clinicians, with a combination of self-nomination, snowball recruitment and subsequent stratified sampling to ensure a balance of demographics and specific expertise.

Domain definition and scope

The scope of the haemolytic anaemia domain for TRM-SLE was defined across two online meetings via structured discussion. The high-level measurement goal of the overall TRM-SLE instrument[2] was provided as a starting point: 'active immune-mediated disease manifestations that impact on the patient and are modifiable by therapy to reduce or control disease activity'.[2] Impact on the patient in this context specifically refers to a meaningful effect on how a patient 'feels, functions or survives', intended to align with the principles of contemporary patient-focussed drug development,[12–14] while modifiable by therapy relates to the use of treatments targeting SLE activity rather than those that may target haemolysis via other mechanisms. Levels of agreement on elements of the haemolytic anaemia domain definition and scope were evaluated via Zoom polling and recorded as percentage agreement.

Nomination of candidate domain measures

Guided by the domain definition and scope, working group members nominated candidate instruments to measure haemolytic anaemia response via an online survey. These nominations were then grouped, discussed and shortlisted via structured discussion in a dedicated meeting. Participants were provided with criteria to consider when proposing a measure as potentially fit-for-purpose, that is, valid and reliable in the context defined for TRM-SLE[2] (table 1) and based on published regulatory guidance.[12 15]

Systematic literature review

Shortlisted candidate measures were assessed by an SLR to identify and summarise studies that provide evidence of measurement properties (focussing on longitudinal validity and meaningful thresholds of improvement) and/or clinical trial utility relevant to the population of interest. Methods (described in detail in online supplemental material) were developed based on those published by COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN).[16] In brief, we searched MEDLINE, EMBASE and Cochrane Library using a search strategy based on the 'Population, Instrument and Measurement properties' framework.[17] The population included SLE-related haemolytic anaemia, as well as primary autoimmune haemolytic anaemia, given limited literature in SLE-specific haemolytic anaemia. Study type was restricted to trials or longitudinal cohort studies, using a validated search filter.[18] Screening was performed in duplicate using Covidence software and data extracted into template tables. Methodological quality assessments were completed by two reviewers for relevant studies using COSMIN risk of bias checklists and quality criteria.[19] Results were disseminated to working group members via a detailed report.

Table 1 Criteria guiding selection of the response measure and thresholds for the haemolytic anaemia domain in TRM-SLE

Intended outcome	Criteria to consider
Fit-for-purpose response measure	► Abnormalities scored by the measure can be reasonably attributed to active haemolytic anaemia due to SLE (without undue influence from other factors). ► Captures the majority of the target patient population (defined by the domain definition and scope, and including adults and adolescents with SLE). ► Evidence of reliability and validity in the context of use of a SLE clinical trial. ► Can quantify degrees of domain activity and change. ► Feasible for use in a multidomain SLE trial.
Clinically meaningful response and complete response thresholds with acceptable range, sensitivity and specificity	► Entry threshold representing sufficiently severe activity to warrant inclusion in an RCT; representing meaningful impact on how a patient 'feels, functions or survives' with sufficient room to improve and discriminate between treatment arms. ► Clinically meaningful response threshold representing improvement that may impact how a patient 'feels, functions or survives' and discriminate between treatment arms in an RCT. ► Complete response threshold associated with maximum benefit on how a patient 'feels, functions or survives'.

RCT, randomised controlled trial; TRM-SLE, Treatment Response Measure for SLE.

Consensus on domain measure and response thresholds

Two separate formal consensus processes using NGT were undertaken to achieve working group consensus on: (1) the measure(s) to define haemolytic anaemia treatment response in TRM-SLE and (2) the numerical thresholds for entry, clinically meaningful response and complete response using the chosen measure(s). Expert consensus was informed by working group review and discussion of the SLR results. Criteria for including an outcome measure and establishing clinically meaningful thresholds were outlined (table 1), formulated based on published regulatory and instrument development guidance applied to the TRM-SLE context, with a particular focus on anchoring the choice of response measure and thresholds to outcomes directly relevant to patients, that is, how they 'feel, function or survive'.[12–14] Following consensus on the haemolytic anaemia response measure and thresholds, the working group discussed and agreed on any additional elements required in the final response criteria and identified key evidence gaps that will inform a future research agenda to be integrated into prospective validation of the TRM-SLE instrument.

Nominal group technique

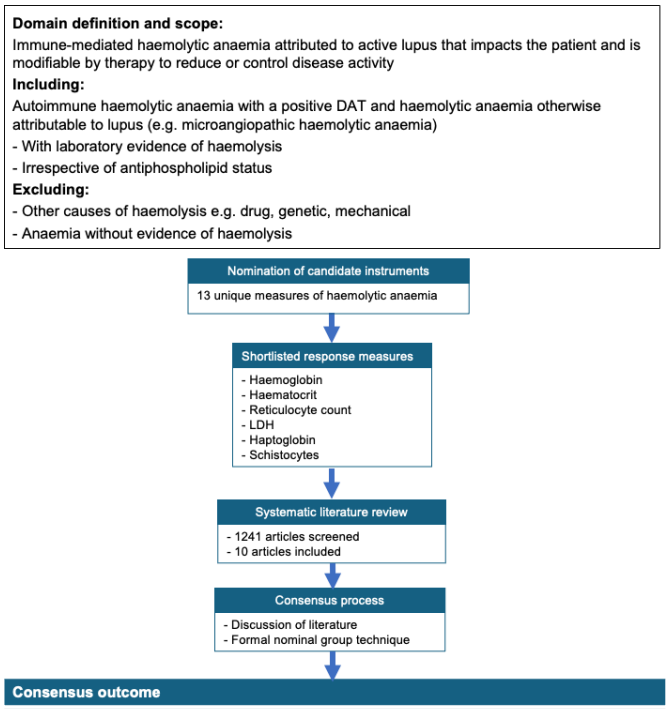
NGT is an established methodology for expert consensus that prioritises ideas via the following steps: introduction and explanation, silent nomination of ideas, central listing of nominations, group discussion and prioritisation via formal ranking.[20 21] NGT was used in our study through a series of online meetings and surveys, limited to working group members who had participated in the online meeting live or asynchronously, using the Qualtrics platform, with a detailed description provided in online supplemental material. The highest ranked outcome of each NGT process was considered the consensus result.

Statistical analyses

Results from each consensus process were summarised descriptively. Qualitative data (from virtual meetings and survey comment fields) were analysed using content analysis and responses were categorised by themes.

Patient and public involvement

The TRM-SLE Taskforce includes a Patient Advisory Panel consisting of 18 people living with SLE, their caregivers and lupus patient organisation representatives,[2] who provide patient-centred input and guidance throughout each stage of instrument development. In this study, patient representatives with lived experience of haematological lupus were included in the haematology working group. The nature of patient involvement in the consensus processes was adopted based on the advice of the Patient Advisory Panel: patient participants were encouraged to provide qualitative commentary on processes and outcomes and had the option to participate in all surveys, voting and ranking at their individual discretion, acknowledging the technical and scientific complexities of the content involved.



Consensus outcome	
Haemoglobin (Hb) chosen as the measure of haemolytic anaemia response	
Entry threshold Additional criteria	Hb <100g/L (<6.2mmol/L) Evidence of active haemolysis: LDH greater than the upper limit of normal AND haptoglobin below the lower limit of normal)
Clinically meaningful response threshold	Improvement in Hb >20g/L (>1.2mmol/L), regardless of ongoing haemolysis OR Hb normalised (above lower limit of reference interval) but ongoing haemolysis
Complete response threshold Additional criteria	Hb normalised (above lower limit of reference interval) AND No evidence of haemolysis (normal bilirubin, LDH, haptoglobin and reticulocytes)

Figure 2 Haemolytic anaemia domain definition and consensus outcome for defining response measure. DAT, direct antiglobulin testing; LDH, lactate dehydrogenase.

RESULTS

Haematology working group

The haematology working group comprised 16 members: 12 expert clinicians (including 1 haematologist and 2 paediatric rheumatologists) and 4 patients with lived experience of haematological lupus (membership listed in online supplemental material). Two clinicians were nominated as co-chairs (MM and GJP-E), and meetings were also facilitated and supported by the core TRM-SLE Research Team (led by EM and KCon).

Domain definition and scope

Haemolytic anaemia was defined for TRM-SLE as "immune-mediated haemolytic anaemia attributed to active lupus that impacts the patient and is modifiable by therapy to reduce or control disease activity" (figure 2) with 14/14 (100%) meeting participants in agreement. The scope of the domain was also agreed on unanimously as including autoimmune haemolytic anaemia with a positive Coombs' (direct antiglobulin) test in addition to other forms of haemolytic anaemia attributable to lupus, such as microangiopathic haemolytic anaemia. Other causes of haemolysis (eg, drug, genetic, mechanical) were listed as specific exclusions, along with anaemia in

the absence of haemolysis (even if attributable to SLE). Key discussion points included the need for laboratory evidence of active haemolysis when classifying patients within the domain scope, and a desire to be inclusive of both classical autoimmune haemolysis as well as rarer causes of haemolytic anaemia seen with active SLE.

Nomination of candidate domain measures

The survey to nominate candidate measures for the haemolytic anaemia domain was completed by 11 working group members, identifying 13 measures. Discussion at the subsequent formal discussion meeting shortlisted six of these measures to proceed to systematic literature review (figure 2): haemoglobin, haematocrit, lactate dehydrogenase (LDH), haptoglobin, reticulocyte count and schistocytes (specifically for microangiopathic haemolytic anaemia).

Systematic literature review

A detailed description of the SLR is provided in online supplemental material. In brief, 1519 studies were identified by the literature search and 1241 screened for relevance following removal of duplicates. 10 studies were ultimately included. Five studies were in SLE-related haemolytic anaemia (all longitudinal cohort studies defining treatment response based on haemoglobin[22–25] or haematocrit[26]). Five studies were in non-SLE autoimmune haemolytic anaemia populations: four RCTs[27–30] and one study evaluating the longitudinal validity of haemoglobin and reticulocyte count.[31] Due to the limited and heterogeneous literature, results were summarised in narrative fashion, and formal grading of the overall quality of evidence for a specific instrument/measurement property was not possible. Table 2 provides a high-level summary of the SLR results for each candidate instrument.

Consensus on domain measure and response thresholds

Two NGT processes were conducted over three meetings and four online surveys, summarised below and described in detail in online supplemental material. The final consensus response criteria are presented in figure 2.

The first NGT process focused on determining the haemolytic anaemia response measure for TRM-SLE. Following discussion of guiding criteria (table 1) and results of the SLR, 12 working group members suggested 13 unique nominations via survey, including individual instruments or a combination. Hb was the most commonly nominated as either a sole response measure or in combination with one or more haemolytic markers. Following presentation and discussion of these nominations, the final NGT ranking survey was completed by nine working group members. Hb was the preferred option as the primary measure of haemolytic anaemia response, ranked first by all survey participants. Key justification for the selection of Hb to measure haemolytic anaemia response included its correlation with important patient-centred outcomes (eg, fatigue), responsiveness, data supporting thresholds of meaningful improvement and feasibility of measurement. The role of haemolytic markers (eg, reticulocytes, haptoglobin, LDH) alongside Hb was debated. Given a lack of data in SLE and primary autoimmune haemolytic anaemia to support any additive value to Hb alone in defining clinically meaningful improvement, including impact on the patient, the working group concluded that haemolytic markers were best placed to determine presence/absence of haemolysis. Thus, these markers are incorporated in the eligibility criteria to ensure accurate attribution of anaemia to haemolytic anaemia and to differentiate compensated haemolysis from a 'complete' response (figure 2).

The second NGT process focused on determining the specific Hb entry threshold, minimum threshold for

Table 2 High-level summary of relevant findings from the systematic literature review investigating evidence of relevant measurement properties and clinical trial utility for each shortlisted instrument to measure haemolytic anaemia response

Candidate measure	Measurement properties summary	RCT summary
Hb	One study in haemolytic anaemia and literature in other forms of anaemia supporting the clinical meaningfulness of Hb response	Core measure used to define severity and response in RCTs of primary autoimmune haemolysis, and in studies of SLE
Haematocrit	Limited use and evidence in haemolytic anaemia; concerns about measurement accuracy and variability	No relevant RCTs identified
Haemolytic markers ► Reticulocyte count ► Haptoglobin ► Lactate dehydrogenase	Responsive alongside Hb improvement in primary autoimmune haemolysis but no established evidence-based thresholds of improvement, or evidence of added value to Hb alone	Included in the response criteria of some RCTs of autoimmune haemolysis to define presence or absence of haemolysis alongside Hb response, or as a secondary endpoint
Schistocytes	No evidence supporting the clinical meaningfulness of improvement, or relevant thresholds to define response	No relevant RCTs identified

Hb, haemoglobin; RCT, randomised controlled trial.

defining clinically meaningful improvement in haemolytic anaemia in TRM-SLE and a complete response threshold. Again, guiding criteria (table 1) and relevant SLR results were presented and discussed, followed by a survey to nominate candidate thresholds. Given the interdependence of entry and response thresholds, nominations were made as a 'set' comprising all three thresholds within each candidate response definition. Eight working group members suggested 17 unique 'sets' of response thresholds, consisting of combinations of 5 different entry thresholds, 7 different minimum response thresholds and 6 different complete response thresholds. These nominations were discussed, followed by a final NGT ranking survey completed by 15 working group members.

Consensus was reached on an Hb entry threshold of <100 g/L, with the requirement for active haemolysis to be demonstrated at entry via elevated LDH and low haptoglobin. The Hb threshold of <100 g/L was the most common inclusion criteria used in studies of both SLE-associated and primary autoimmune haemolytic anaemia identified in the SLR,[24 28 29] and reflects clinically significant anaemia.[32 33] In addition, the combination of abnormal LDH and haptoglobin is highly specific for haemolytic anaemia.[34] This entry criteria will define the conditions for eligibility to have treatment response measured in the haemolytic anaemia domain of TRM-SLE, and thus potential eligibility for trial entry in patients in whom haemolytic anaemia is the only active domain (figure 3).

Consensus was reached on a clinically meaningful response as requiring an improvement in Hb of >20 g/L, or Hb normalisation if there is evidence of ongoing haemolysis (figure 2). Reaching this threshold in response to treatment would result in responder classification within the haemolytic anaemia domain in the TRM-SLE instrument. The choice of Hb increment of >20 g/L was based on data showing an association of Hb improvement >10–20 g/L with improvements in patient-centred outcomes including fatigue and quality of life,[31 32] while accommodating Hb laboratory measurement variability of up to 10 g/L.[35 36] The use of continuous data permits the definition not only of clinically meaningful response but also of complete response. Consensus was reached to define complete response as Hb normalisation (above the lower limit of the reference interval) with normalisation of all haemolytic markers (figure 2). This complete response threshold reflects clinically relevant benefits being observed for Hb levels up to 120 g/L,[32] while accounting for differences in 'normal' Hb across patient populations including lower ranges of normal for those of female sex and ancestral differences, of particular relevance in SLE. Thus, when applying the complete response threshold, the patient-specific Hb reference interval provided by the laboratory should be used.

Although informed by available evidence, the working group acknowledged a number of important knowledge gaps when reaching their consensus decisions, in particular the extrapolation of evidence from primary

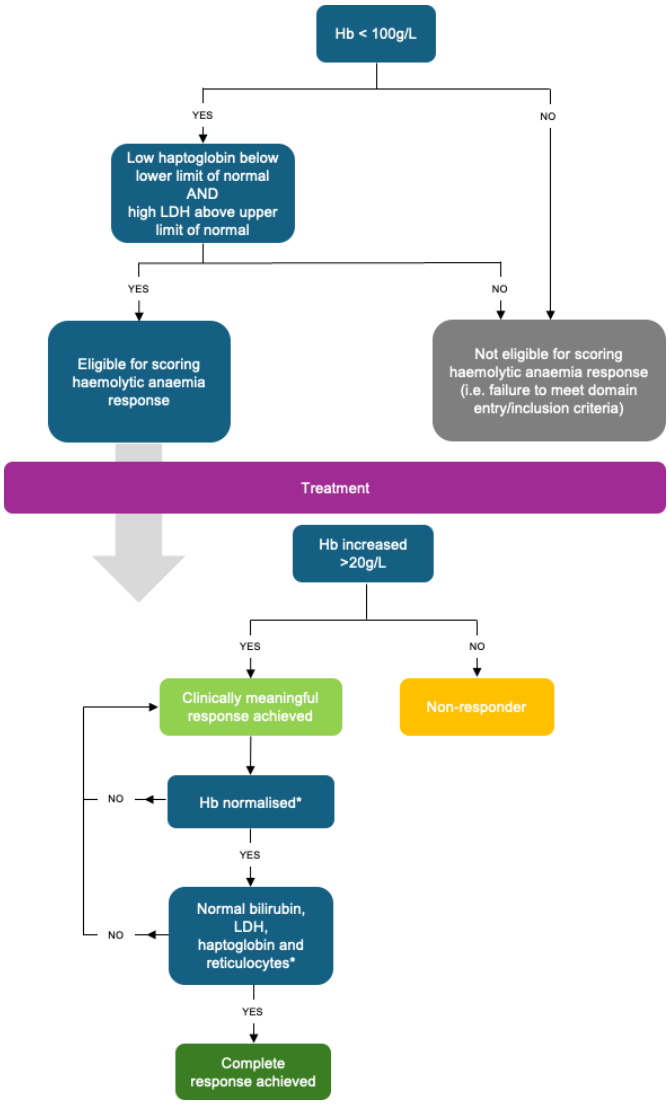


Figure 3 Flow chart for assessment of haemolytic anaemia in TRM-SLE. *Normalisation defined according to the patient-specific laboratory reference interval. Hb, haemoglobin; LDH, lactate dehydrogenase; TRM, Treatment Response Measure.

autoimmune haemolytic anaemia and other causes of anaemia to the specific context of SLE-associated haemolytic anaemia. There were no studies or RCTs specifically retrieved in SLE-associated haemolytic anaemia that aimed to evaluate measurement properties. Therefore, we acknowledge that the consensus threshold recommendation has been made based on best practice and limited empirical data in SLE. Research to address this will be integrated into prospective validation of the TRM-SLE instrument, in both longitudinal cohorts and within future SLE RCTs.

DISCUSSION

New approaches to measuring clinically meaningful treatment effects on disease activity in SLE RCTs are urgently needed to improve trial interpretability and support the regulatory approval of novel therapies. In this study, an international expert working group achieved consensus

on a fit-for-purpose response criteria for haemolytic anaemia, including the measure to be used, thresholds of activity that define eligibility for measurement of response in that domain and thresholds of improvement that will define response. These will contribute to the definition of clinically meaningful improvement within a novel multi-domain treatment response measure for SLE clinical trials (TRM-SLE).

Haemolytic anaemia is an important SLE manifestation that is under-represented in SLE studies including clinical trials, despite being linked to a poorer prognosis.[4–6] While not as frequent as mucocutaneous or musculoskeletal disease activity, haemolytic anaemia is not rare in active SLE[4–8] and can have a marked impact on patients due to the significant health consequences of anaemia and potential for repeated exposure to high dose glucocorticoids.[4–6] In the recent phase 3 trials of the interferon receptor monoclonal antibody anifrolumab, improvements in haematological domains of SLEDAI were reported, without defining if these related to haemolytic anaemia.[37] The importance of measuring haemolytic anaemia in an SLE RCT context was supported by the results of our previous Delphi study[3] where haemolytic anaemia was rated as 'highly important' for inclusion in TRM-SLE by more than 90% of participants, who included patients. Developing a response criterion that defines clinically meaningful haemolytic anaemia activity and response for use in SLE RCTs is therefore an important research priority.

Defining haemolytic anaemia activity and response based primarily on Hb, with thresholds for entry (Hb <100 g/L), clinically meaningful response (improvement by >20 g/L) and complete response (Hb normalisation to above the lower limit of the reference interval), all achieved high levels of consensus, despite limited empirical evidence specifically in SLE. Rather, agreement was based on the SLE-specific expertise of the working group, informed by relevant evidence from studies in patients with haemolytic anaemia without SLE and published consensus response criteria for primary forms of autoimmune haemolytic anaemia,[34] which share similar pathogenesis and symptoms. Importantly, as anaemia can be present in patients with SLE for reasons unrelated to haemolysis, such as anaemia of chronic disease or blood loss, eligibility for measurement of treatment response on the basis of haemolytic anaemia also requires the presence of abnormal results for both LDH and haptoglobin.

It was expected that data relating to clinically meaningful improvement in Hb from non-SLE studies would be applicable in the context of SLE, although the working group acknowledged that Hb kinetics may differ in SLE due to disease-specific characteristics such as the predominance of young females and multifactorial contributions to anaemia, including kidney dysfunction, chronic inflammation and treatment side effects. Notably, the response criteria arising from our consensus process are largely consistent with what has been adopted in previous non-randomised treatment studies of SLE-associated haemolytic anaemia[22–25] as well as having similarities to the BILAG disease activity measure for SLE (developed based on clinician intention-to-treat); the threshold for at least moderate haemolytic anaemia activity in the BILAG mirrors the entry threshold of Hb <100 g/L defined in this study, while improvement from major to moderate haemolytic anaemia activity using the BILAG requires an Hb increment of at least 20 g/L, the same as the clinically meaningful response threshold consensus reached in our study.

Importantly, novel aspects of the response criteria arising from this study have the potential to address significant issues associated with the current approaches to haemolytic anaemia activity and response measurement in SLE RCTs. For over a decade, the SLE Responder Index (SRI)[38] and BILAG-based Combined Lupus Assessment (BICLA)[39] have served as the two endpoint measures most commonly used to determine efficacy in trials of general SLE, where response is primarily defined based on either the change in SLEDAI score (for the SRI) or improved activity across BILAG domains that have major/moderate activity at baseline (for the BICLA). Haemolytic anaemia does not feature as a disease activity item in the SLEDAI, thus even complete resolution cannot contribute towards an SRI response and haemolytic anaemia cannot be a contributor to trial enrolment based on SLEDAI. Using the BICLA, improvement in haemolytic anaemia can contribute towards response if a baseline Hb <100 g/L improves to an Hb ≥100 g/L. However, this binary threshold means potentially insignificant changes in Hb (eg, 99 g/L to 100 g/L) could result in patients being classified as responders in a clinical trial. Furthermore, in BILAG, haemolytic anaemia is grouped with other haematological manifestations (anaemia without haemolysis, leucopenia/neutropenia and thrombocytopenia), meaning the independent contribution of haemolytic anaemia to disease activity and response cannot be easily ascertained. In contrast, the response criteria which achieved consensus in this study separates the measurement and reporting of haemolytic anaemia from unrelated haematological manifestations and uses measurement of Hb change as a continuous variable with response thresholds that avoid the risk of clinically insignificant increments being classified as a response compared with current instruments such as the BICLA. This approach allows a more nuanced understanding of Hb kinetics in response to treatment in patients with baseline active haemolytic anaemia and also ensures that response classification more accurately reflects clinically meaningful improvement.

The proceedings and outcomes reported here represent one of several concurrent consensus processes that address the measurement and response definition for all the domains that will define clinically meaningful treatment response in TRM-SLE. Following the finalisation of outcome measures and response criteria across each domain, the final step of the TRM-SLE instrument development focuses on the integration of these domains to

define overall patient response, mechanisms to capture flare and activity in unmeasured domains, and finalisation of an endpoint assessment ready to be deployed in validation studies and SLE RCTs. Defining response based on a select group of disease activity domains, that are important to patients and suited to measurement in a trial setting, allows these specific manifestations to be evaluated in sufficient detail to understand treatment responses at a more granular level than traditional outcome measures that collapse a spectrum of disease features into limited scoring systems. As illustrated for haemolytic anaemia in this study, response thresholds recommended for each TRM-SLE domain focus on clinically meaningful improvement, as opposed to crossing thresholds that effectively define discrete categories of disease activity, as is the case with the SLEDAI and BILAG. Furthermore, by defining an entry threshold for each domain alongside response thresholds, TRM-SLE can be used to guide trial inclusion based on clinically significant active disease in individual organ systems, rather than relying on composite measures that may exclude patients with important disease activity due to weightings or omission from the relevant indices.[40]

A limitation of this study is the reliance on expert consensus where empirical evidence is lacking. However, we ensured the use of robust consensus methodology with clearly predefined steps and goals that incorporated consideration of contemporary regulatory guidance for RCT endpoints and support from a systematic literature review including evidence from both SLE-associated and primary forms of autoimmune haemolysis. The expert working group contributed a range of relevant expertise, reflected in cross-disciplinary discussion between rheumatology and haematology specialists and benefited from input from patient members throughout. Nevertheless, evidence from both measurement properties studies and RCTs is lacking in patients with SLE-associated haemolytic anaemia, and the extrapolation of evidence from primary autoimmune haemolysis and anaemia more generally to SLE would benefit from further validation and anchor-based analyses. This includes consideration of how the entry and response criteria may be impacted by the multifactorial nature of anaemia in many patients with SLE, such as concurrent anaemia due to chronic inflammation or kidney dysfunction, as well as the potential impact of SLE on LDH and haptoglobin levels when defining haemolysis for inclusion. We intend that these consensus haemolytic anaemia response criteria will be prospectively evaluated, defined as clinically meaningful and/or refined in the specific context of an SLE RCT. This validation process will also investigate considerations relevant to how domain-specific response criteria are implemented and analysed in a trial setting. For example, within the context of a general SLE trial, interpretation of haemolytic anaemia outcomes specifically may be limited by low patient numbers and/or uneven distribution of this feature between treatment arms. Furthermore, the defined scope of the haemolytic anaemia domain is broad, including subtypes that may differ in pathophysiology and/or response trajectories. The role of stratifying by haemolytic anaemia subtype will be considered within validation studies.

In conclusion, we report the definition of a novel response criteria for haemolytic anaemia attributable to active SLE. We anticipate this outcome will standardise and improve the study of haemolytic anaemia and its treatment in SLE, by facilitating recruitment of appropriate patients with this important manifestation to clinical trials, including patients with clinically significant haemolytic anaemia who are currently excluded, and ensure that meaningful improvement contributes to the classification of treatment response. This domain measure will be compiled with the others being developed by the TRM-SLE taskforce into a multidomain instrument which can classify patients with diverse manifestations of disease as responders or non-responders in SLE clinical trials.

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