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Selection of indicators reporting response rate in pharmaceutical trials for systemic lupus erythematosus: preference and relative sensitivity

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ABSTRACT

Objective SLE is a common multisystem autoimmune disease with chronic inflammation. Many efficacy evaluation indicators of randomised clinical trials (RCTs) for SLE have been proposed but the comparability remains unknown. We aim to explore the preference and comparability of indicators reporting response rate and provide basis for primary outcome selection when evaluating the efficacy of SLE pharmaceutical treatment.

Methods We systematically searched three databases and three registries to identify pharmacological intervention-controlled SLE RCTs. Relative discriminations between indicators were assessed by the Bayesian hierarchical linear mixed model.

Results 33 RCTs met our inclusion criteria and we compared eight of the most commonly used indicators reporting response rate. SLE Disease Activity Index 4 (SLEDAI-4) and SLE Responder Index 4 were considered the best recommended indicators reporting response rate to discriminate the pharmacological efficacy. Indicator preference was altered by disease severity, classification of drugs and outcome of trials, but SLEDAI-4 had robust efficacy in discriminating ability for most interventions. Of note, BILAG Index-based Combined Lupus Assessment showed efficacy in trials covering all-severity patients, as well as non-biologics RCTs. The British Isles Lupus Assessment Group response and Physician's Global Assessment response were more cautious in evaluating disease changes. Serious adverse event was often applied to evaluate the safety and tolerability of treatments rather than efficacy.

Conclusions The impressionable efficacy discrimination ability of indicators highlights the importance of flexibility and comprehensiveness when choosing primary outcome(s). As for trials that are only evaluated by SLEDAI-4, attention should be paid to outcome interpretation to avoid the exaggeration of treatment efficacy. Further subgroup analyses are limited by the number of included RCTs.

PROSPERO registration number CRD42022334517.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The comparability between indicators reporting response rate in randomised clinical trials of SLE remains unknown. We innovatively conduct a Bayesian hierarchical linear mixed model and provide advice for the primary endpoint selection.

WHAT THIS STUDY ADDS

⇒ Indicator preference is altered by disease severity, classification of drugs and outcome of trials. SLE Disease Activity Index 4 and SLE Responder Index 4 are considered the best recommended indicators reporting response rate.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings determine the preference and relative sensitivity of indicators reporting response rate under different circumstances, and highlight the importance of evaluating trial validity using a multidimensional criterion.

INTRODUCTION

SLE is an aberrant autoimmune disease with diverse clinical manifestations and antibodies that predominantly affects females.[1 2] The substantial prevalence and chronic disease course of SLE, combined with the adverse effects brought by corticosteroid usage, result in the increased disease burden globally.[3–5] The purpose of SLE management is to achieve the remission of systemic symptoms and organ manifestations, which is considered a desirable outcome for patients with SLE with at the very least the absence of significant symptoms and signs of SLE, but high therapeutic needs are still unmet.[6] For regular treatment, hydroxychloroquine and glucocorticoids are recommended in all patients with lupus, and appropriate initiation of immunosuppressive agents can expedite the discontinuation of glucocorticoids. Additionally, calcineurin inhibitors, belimumab and rituximab should be considered to add in persistently active condition.[7] Recently, many innovative and targeted therapies have been proposed, showing promise in

disease control even in patients with intractable complications.[8 9] Nevertheless, the development and implementation of new SLE therapies have lagged behind that of other autoimmune rheumatic diseases. Due in large part to its heterogeneity with involvement in multiple principal domains, which are inconsistent at different times, the change or improvement in the course of SLE is difficult to measure.[10] Indicators are important tools to monitor the performance of drugs and to identify emerging problems for improvement. To reflect intervention-derived benefits accurately, the ideal efficacy-evaluated indicators are the important basis of the field. In early 1996, the Systemic Lupus International Collaborating Clinics proposed the need to build a comprehensive assessment that includes disease activity, chronic damage and quality of life for patients with SLE.[11] A set of quality indicators for SLE were then published by the European League Against Rheumatism, which covered a number of aspects of patient assessment.[12] The most frequent applied metrics in randomised clinical trials (RCTs) are the British Isles Lupus Assessment Group (BILAG) and the SLE Disease Activity Index (SLEDAI).[13] Currently, composite indices are also used as primary endpoints in clinical trials.

Although many indices are widely used in clinical trials and research, criteria for evaluating efficacy in pharmaceutical clinical trials for SLE have not been unified and recognised yet.[14] The preference (ranking of different indicators based on their weight) and relative sensitivity (ability to detect and reflect variations) of indicators between trials with different design, drug format and baseline characteristics may alter final results, mislead researchers and limit the comparability of trial results.[15 16] The diversity in the usage of scales underscores the fact that no single indicator has been universally accepted so far. Furthermore, the sensitivity and specificity of these indicators remain uncertain. In addition, the failure of many drugs to meet their primary or secondary endpoints has led to the re-examination of the design of SLE trials.[10 17] Accordingly, there is a need to compare indicators within the same population to determine their comparability and preference in different types of RCTs for SLE. Our results determine the relative sensitivity of the indicators reporting response rate under different circumstances and underline the importance of assessing the efficacy of interventions using a multidimensional criterion.

MATERIALS AND METHODS

Study design

This systematic review and meta-analysis was prospectively registered on PROSPERO (ID: CRD42022334517), and reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[18]

Search strategy

Two investigators (JT and DZ) searched published articles and clinical trial registry records, appraised studies on eligibility and extracted data independently. The search for RCTs included published articles from peer-reviewed English-language journals and registered trials in clinical trial registries, from inception to 4 May 2021. Three databases, that is, PubMed, EMBASE and Cochrane Library Central Register of Controlled Trials (CENTRAL), were systematically searched, and search strategies were adjusted to meet the specifications of each database. The search was supplemented by manual review of the reference lists of included publications and relevant reviews. Records of registered RCTs were collected from three publicly available web-based clinical trial registries including the ClinicalTrials.gov of the US National Library of Medicine, the International Standard Randomised Controlled Trial Number Register and the Australian and New Zealand Clinical Trials Registry. The keyword search term “lupus” was entered combined with other specific filtering options in advanced search function for ‘Country’, ‘Study type’, ‘Current status’, etc in searching for eligible RCTs. Only studies that contained two or more specific outcome indices reporting response rate were included. Discrepancies were discussed and agreed by consensus. Detailed search strategies, study selection and screening and data extraction methods were provided in online supplemental appendices 1–4.

Indicators

We studied eight most commonly used SLE disease activity assessment tools reporting response rate, including three indicators based on the SLE Responder Index (SRI), namely SRI-4, SRI-5 and SRI-6; BILAG Index-based Combined Lupus Assessment (BICLA); serious adverse events (SAE); SLEDAI-4 (≥4-point improvement from baseline using SLEDAI); BILAG response (no worsening in BILAG index from baseline); and Physician’s Global Assessment (PGA) response (no worsening in PGA from baseline). Details of the above indicators were shown in online supplemental appendix 5. The outcome of interest was the percentage change between intervention and control groups.

Data analysis

To remove the influence of other factors, the gold standard model for sparse and heterogeneous data[19–21]—a Bayesian hierarchical linear mixed model—was applied to estimate the difference between control group and intervention group to obtain relative sensitivity and preference of outcome indicators in SLE. In hierarchical model, we calculated the percentage change (control group possibility–intervention group possibility) for discrete groups. The statistical analysis was implemented by brms package in R (V.4.0.5) with 8000 iterations and four chains. This package used Hamiltonian Markov chain Monte Carlo method to estimate posterior distribution. The model had three predictor covariates with fixed effects: topical or systemic application, age and disease

severity. The intervention and type of intervention had hierarchical relationship in our model. Although there was variation in the variables, the difference between each index variable was stable in each chain.

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model < − brm(mean | se(sd) ∽ 1 + (1 | index) + (1 | Type_intervention/
Intervensions) + (1 | Severity) + (1 | Topical) + (1 | Age), data = datause,
thin = 10, chains = 4, iter = 8000, cores = 4, control = list(adapt_delta = 0.99,
max _treedepth = 20))
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Subgroup analyses of topical or systemic application, age, disease severity and unsuccessful trials were conducted using the same Bayesian hierarchical linear mixed model to remove preference distortion of SLE outcome indicators brought by different participant situations, intervention application methods and intervention efficacy, which further demonstrated the sensitivity of different SLE outcome indicators. Detailed method and results were listed in online supplemental appendices 6 and 7.

Quality assessment

The risk of bias for individual studies was assessed according to the Cochrane Risk of Bias 2.0 tool[22] for RCTs by two investigators (JT and SK) independently and disagreements were determined by discussion.

Patient and public involvement

No patients were involved in the design, conduct or reporting of this research owing to the nature of the study as a systematic review. Ethics approval was not required for this study.

RESULTS

Overview of indicators in pharmacological intervention-controlled RCTs for SLE

The characteristics of 33 enrolled studies were summarised in online supplemental appendices 8 and 9, and the most used indicator was SRI-4 (81.8%, 27). A total of 97.0% of the included studies were judged as having a low medium risk of bias (online supplemental appendix 10). Network plot of indicator comparisons was presented in figure 1, with nodes representing competing indicators and edges representing RCTs for pairs of indicators. These were divided into three subgroups based on disease severity, type of intervention and outcome of the trials. The majority of trials covered moderate-to-severe patients (84.8%, 28), and only five RCTs (15.2%) included all severity. According to pharmaceutical interventions, 21 RCTs (63.6%) were with antibodies, 10 (30.3%) with small molecules and 2 (6.1%) with non-biologics. Moreover, 17 RCTs (51.5%) concluded the pharmacological interventions were non-effective and 16 RCTs (48.5%) yielded effective results, with similar proportions. No obvious difference was found when assessing indicators among RCTs examined less effective medications, with different intervention types, with different characteristics of participants.

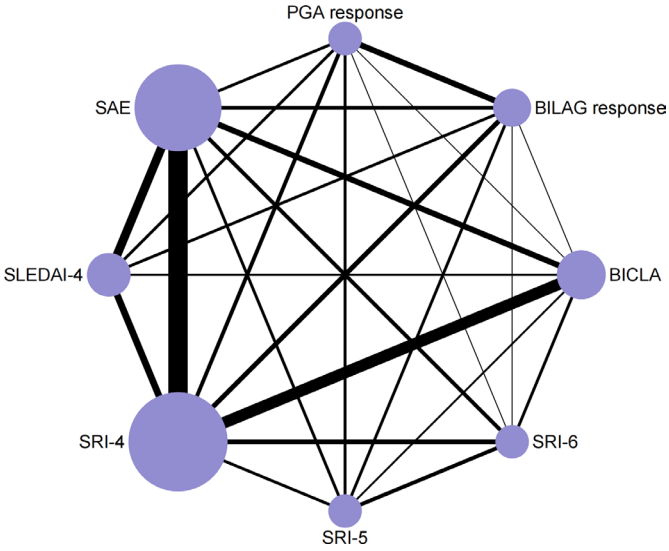

Figure 1 Network of eligible comparisons for efficacy evaluation indicators. The size of the nodes (purple circles) corresponds to the number of trials. Comparisons are linked with a line, the thickness of which corresponds to the number of trials that assessed the comparison. BICLA, BILAG Index-based Combined Lupus Assessment; BILAG, British Isles Lupus Assessment Group; PGA, Physician's Global Assessment; SAE, serious adverse event; SLEDAI, SLE Disease Activity Index; SRI, SLE Responder Index.

Relative sensitivity and preference of indicators reporting response rate in pharmacological intervention-controlled RCTs for SLE

The overall preference of indicators was evaluated by Bayesian model considering the influence of topical or systemic application, age and disease severity (online supplemental appendix 11). Since the estimation of each indicator was calculated by its control group possibility minus intervention group possibility, a larger difference between two indicators represented a relatively better discrimination ability of the first indicator. The results were all presented as the weighted mean differences with corresponding 95% uncertainty intervals. If the null value was not included in the 95% uncertainty intervals, a statistically significant difference was detected. Given that, SLEDAI-4 was the best indicator with significantly higher response rate in intervention groups than in control groups compared with BILAG response, PGA response and SAE, which meant for the same participants, SLEDAI-4 was more likely to uncover the effectiveness of pharmacological interventions than other indicators. SRI-4 was the second preferred indicator, with SRI-6, SRI-5 and BICLA in descending order, which significantly preceded SAE. On the contrary, SAE was shown to perform worst with statistical significance compared with BICLA, SLEDAI-4, SRI-4, SRI-5 and SRI-6, which meant it could barely reflect the

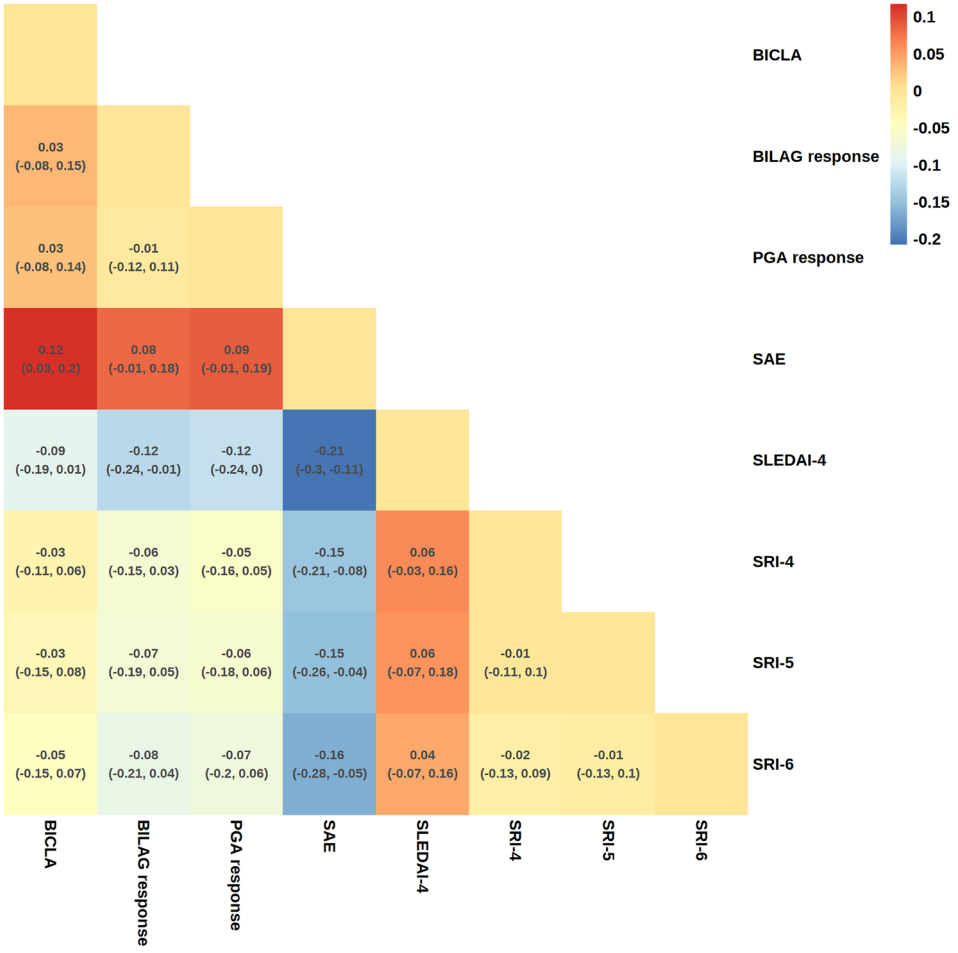

Figure 2 Bayesian hierarchical linear mixed model estimated effectiveness with 95% uncertainty intervals on indicators reporting response rate in pharmacological intervention-controlled randomised clinical trials (RCTs) for SLE. BICLA, BILAG Index-based Combined Lupus Assessment; BILAG, British Isles Lupus Assessment Group; PGA, Physician's Global Assessment; SAE, serious adverse event; SLEDAI, SLE Disease Activity Index; SRI, SLE Responder Index.

discrepancies between pharmacological interventions and controls. Besides, BILAG response was supposed to be the second worst indicator and PGA response was the third, both had significantly lower response rates in intervention groups than in control groups compared with SLEDAI-4 (figures 2 and 3).

Subgroup analyses of relative sensitivity and preference of indicators reporting response rate in pharmacological intervention-controlled RCTs for SLE

The preference for indicators was also implicated when evaluating groups with different disease severity, intervention type or the outcome of trials. The sensitivity of SLEDAI-4 was attenuated in terms of evaluating and comparing the treatment efficacy for participants with moderate-to-severe SLE. SLEDAI-4 was comparable to SRI-4, SRI-5 and SRI-6, being significantly better than SAE, while SAE still showed limited discrimination ability and was significantly worse than other indicators except BILAG response and PGA response. The remaining indicators were not significantly different (online supplemental figure S5). Besides, in patients with all severity, SLEDAI-4 tended to be a more powerful indicator than other indicators even without statistical significance. It was noteworthy that BICLA could become a recommended indicator along with SRI-4, and SAE still lagged behind (online supplemental figure S6).

Moreover, SLEDAI-4 was also the most powerful indicator in the evaluation of antibody pharmacological interventions, being significantly superb than BILAG response and SAE. SRI-4 showed a non-dominant advantage compared with SRI-5 and SRI-6, which tied for same place. In addition, BICLA ranked next, with significant difference from SAE. Still, SAE remained the significantly least effective indicator when comparing it to other indicators except the BILAG response. What's more, BILAG response was the second worst indicator and PGA response the third, which were significantly different from SLEDAI-4 and SAE, respectively (online supplemental figure S7). When assessing small molecules, though all indicators were comparable and no obvious difference was observed, it was supposed that SLEDAI-4 and SRI-4 were preferred (online supplemental figure S8). Within non-biologics interventions, there was also no clear superiority or inferiority among these indicators,

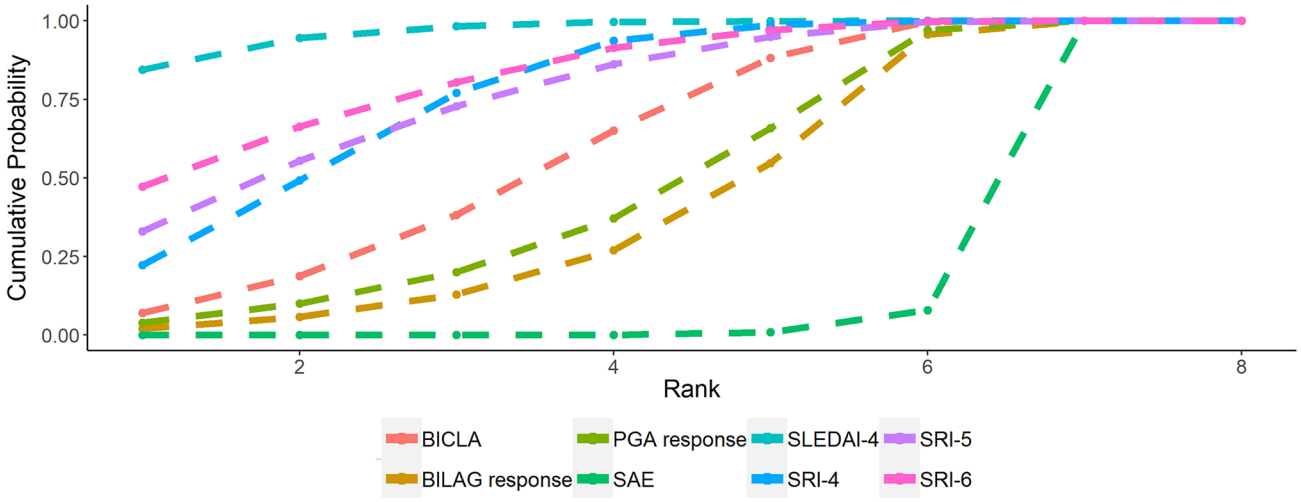

Figure 3 Preference of indicators reporting response rate in pharmacological intervention-controlled randomised clinical trials (RCTs) for SLE. The rank of indicators reporting response rate. The sooner an indicator reaches 1, the stronger the ability to discriminate treatment efficacy. BICLA, BILAG Index-based Combined Lupus Assessment; BILAG, British Isles Lupus Assessment Group; PGA, Physician's Global Assessment; SAE, serious adverse event; SLEDAI, SLE Disease Activity Index; SRI, SLE Responder Index.

but BICLA and SLEDAI-4 were more relatively sensitive (online supplemental figure S9).

When evaluating the efficacy of successful RCTs, SAE performed significantly worst compared with other indicators again, and BILAG response was significantly less preferred for measuring intervention efficacy compared with SAE and SLEDAI-4. In contrast, SLEDAI-4 achieved better significant discrimination ability than SAE and BILAG response, while SRI-4 was another indicator significantly suggested compared with SAE. Both SLEDAI-4 and SRI-4 were comparable in successful SLE trials. Besides, SRI-5 and SRI-6 presented equivalent efficacy revealing ability than SAE. Although with no statistical significance, BICLA and PGA response were also comparable (online supplemental figure S10). Seventeen unsuccessful RCTs were further analysed, and none of the indicators had robust efficacy discriminating ability for interventions that brought minor benefit. However, according to the rank of sensitivity, SLEDAI-4 was still the leading indicator that could reveal minimal benefits for pharmacological interventions. Besides, SRI-4, SRI-5, SRI-6, BICLA, BILAG response and PGA response had comparable tendencies to uncover the intervention effectiveness, although the differences were not significant (online supplemental figure S11).

DISCUSSION

Precision and accuracy in defining SLE disease activity has improved over the past 30 years and optimal indicators need to be cost-effective and robust when discriminating performance that correlate with the outcome of interest.[10 23] For the first time, our study outlines the protocol for a Bayesian hierarchical linear mixed model designed to identify the most suitable indicators for SLE intervention assessment. SLEDAI-4 was the most valid indicator for nearly all types of pharmacological RCTs of SLE, and others were recommended together with it in

Table 1 Recommendations for the selection of response rate indicators as primary outcome of RCTs for SLE

Items	Suggested indicators	Not suggested indicators
Overall	SLEDAI-4 SRI-4	SAE BILAG response PGA response
SLE baseline severity		
Moderate to severe	SLEDAI-4 SRI-4 SRI-5 SRI-6	SAE
All severity	SLEDAI-4 BICLA SRI-4	SAE
Type of intervention		
Antibodies	SLEDAI-4 SRI-4	SAE BILAG response PGA response
Small molecules	SLEDAI-4 SRI-4	SAE
Non-biologics	BICLA SLEDAI-4	–
Outcome of trials		
Successful	SLEDAI-4 SRI-4	SAE BILAG response
Unsuccessful	SLEDAI-4	SAE

BICLA, BILAG Index-based Combined Lupus Assessment; BILAG, British Isles Lupus Assessment Group; PGA, Physician's Global Assessment; RCT, randomised clinical trial; SAE, serious adverse event; SLEDAI, SLE Disease Activity Index; SRI, SLE Responder Index.

different subgroups including different disease severity, intervention type or the outcome of trials, respectively. In contrast, SAE proved to be the least preferred indicator for efficacy discrimination under different circumstances. Our recommendations for the selection of primary outcome indicator(s) in future SLE RCTs are provided in table 1.

Notably, the primary outcome played a dominant role in the statistical determination of intervention efficacy in clinical trials.[24 25] After SRI-related indexes were proposed, they became favoured by numerous RCTs as the preferred primary outcome.[15] Interestingly, the efficacy-reflecting ability of SRI-4 was not superb, while SLEDAI-4 as a component of SRI criteria was found to be the most sensitive indicator in our article. Similarly, in the phase III belimumab trial, it was analysed that the main contributor of SRI-4 was the improvement in SLEDAI alone and it was sufficient to discern improvement in most cases.[26] Approximately one-third of included trials had SLEDAI-4 as a secondary outcome but few took it as a primary outcome, we recommended new trials that focus on revealing drug efficacy could attempt to apply SLEDAI-4 as a primary outcome indicator to avoid false negative.[27] Meanwhile, choosing SLEDAI-4 as the only outcome indicator might lead to overestimates of treatment benefits, thus a cautious interpretation was needed.[28] Furthermore, reduction of background therapy (especially glucocorticoids) and rigorous requirements for the trial sites would contribute to maximising the possibility of developing successful therapies.[17]

SRI-5 and SRI-6 were comparable most of the time, so one of them was advised to be selected as an outcome indicator to avoid redundancy in experimental design. PGA response and BILAG response were less preferred, representing that they were more cautious in evaluating disease changes. Owing to their low efficacy of assessment and the complexity of the criteria, both were not suggested as routine except as a supplement for SLEDAI-4 to obtain SRI-4. Though most trials demonstrated that the two composite response indices—SRI-4 and BICLA—were synergistic in terms of efficacy identification,[29–31] a prior study noted that SRI-4 was more sensitive in patients with moderate-to-severe SLE.[32] Similarly, based on our analysis, we recommended SRI-4 in patients with moderate-to-severe SLE instead of BICLA, while for patients with all severity, these two indicators were comparable.

Further detailed subgroup analysis was limited by the insufficient number of trials and the results need careful interpretation owing to the limitations of this study. As the most sensitive indicator was accompanied by increased false positives, a balanced indicator selection was always necessary. Immunological and clinical biomarkers also played an essential role in improving diagnosis, assessment and control of SLE; combining those indices could provide a more comprehensive assessment of the disease status in patients with SLE.[33] Current indicators struggle to distinguish between responders and non-responders in SLE. Despite efforts in clinical trials like the Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER), Belimumab International Systemic Lupus Erythematosus (BLISS)-52 and BLISS-76, results have been inconsistent.[34] In response, there's a shift towards alternative measures. 'Treat to target' endpoints focusing on low disease activity and remission were introduced.[35] The Treatment Response Measure for SLE Taskforce is formed to create a multidomain clinical outcome measure for SLE trials. This can cover organ-specific manifestations like lupus nephritis, symptoms such as rashes and findings from laboratory tests.[36] Additionally, the Lupus Foundation of America Rapid Evaluation of Activity in Lupus provides comprehensive lupus activity evaluations from both patient and clinician viewpoints.[37] Moreover, SLE encompassed multidimensional issues such as physical, psychological and socioeconomical burden. Treatments of SLE were directed at prolonging patients' survival, preventing organ damage and flares and optimising health-related quality of life (HRQoL). Therefore, HRQoL should be highlighted, offering the patients' perspective on the disease and the impact of treatment on daily life. HRQoL was measured by Lupus Patient-Reported Outcome, Lupus Quality of Life, EuroQol-5D, Short Form 36 Health Survey, etc.[10 38] Additionally, the evaluation ability of indices reporting score change could be explored further.

In summary, given the problems encountered in previous unsuccessful clinical trials, it is imperative to evaluate and demonstrate the therapeutic advantages of pharmacological interventions. Our results present evidence for the determination of indicators reporting response rate as primary outcome(s) in SLE RCTs and will help to propose and adopt better trial designs. SLEDAI-4 with the relatively highest sensitivity is the most objective indicator for this complex condition, and SRI-4 should be considered either. Comprehensive assessments together with other types of indicators are also essential. As for trials that are only evaluated by SLEDAI-4, attention should be paid to the interpretation of outcomes to avoid the exaggeration of treatment efficacy.

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Contributors QL and JT conceived the study. JT and QL developed the protocol. JT and DZ did the literature search. SK and JT appraised the study quality and extracted and analysed the data. DZ was in charge of computation and coding. JT, SK, DZ, MZ, XY and QL interpreted the data. JT and SK wrote the first draft of the article. XY and YH revised the first draft of the article. QL reviewed and critically evaluated the draft paper. QL is responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Ethics approval was not applicable, since patients were not involved in the design of this protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Smith PP, Gordon C. Systemic lupus erythematosus: clinical presentations. *Autoimmun Rev* 2010;10:43–5.
2 Yaniv G, Twig G, Shor DB-A, *et al*. A volcanic explosion of Autoantibodies in systemic lupus erythematosus: a diversity of 180 different antibodies found in SLE patients. *Autoimmun Rev* 2015;14:75–9.
3 Yen EY, Singh RR. Brief report: lupus-an unrecognized leading cause of death in young females: A population-based study using nationwide death certificates, 2000-2015. *Arthritis Rheumatol* 2018;70:1251–5.
4 Durcan L, O'Dwyer T, Petri M. Management strategies and future directions for systemic lupus erythematosus in adults. *Lancet* 2019;393:2332–43.
5 Tian J, Zhang D, Yao X, *et al*. Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and Modelling study. *Ann Rheum Dis* 2023;82:351–6.
6 van Vollenhoven R, Voskuyl A, Bertsias G, *et al*. A framework for remission in SLE: consensus findings from a large International task force on definitions of remission in SLE (DORIS). *Ann Rheum Dis* 2017;76:554–61.
7 Fanouriakis A, Kostopoulou M, Alunno A, *et al*. Update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:736–45.
8 Gatto M, Zen M, Iaccarino L, *et al*. New therapeutic strategies in systemic lupus erythematosus management. *Nat Rev Rheumatol* 2019;15:30–48.
9 Parra Sánchez AR, Voskuyl AE, van Vollenhoven RF. Treat-to-target in systemic lupus erythematosus: advancing towards its implementation. *Nat Rev Rheumatol* 2022;18:146–57.
10 Wallace DJ. The evolution of drug discovery in systemic lupus erythematosus. *Nat Rev Rheumatol* 2015;11:616–20.
11 Gladman D, Urowitz M, Fortin P, *et al*. Systemic lupus International collaborating clinics conference on assessment of lupus flare and quality of life measures in SLE. systemic lupus International collaborating clinics group. *J Rheumatol* 1996;23:1953–5.
12 Mosca M, Tani C, Aringer M, *et al*. European League against rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. *Ann Rheum Dis* 2010;69:1269–74.
13 Ceccarelli F, Perricone C, Massaro L, *et al*. Assessment of disease activity in systemic lupus erythematosus: lights and shadows. *Autoimmun Rev* 2015;14:601–8.
14 Wollaston SJ, Farewell VT, Isenberg DA, *et al*. Defining response in systemic lupus erythematosus: a study by the systemic lupus International collaborating clinics group. *J Rheumatol* 2004;31:2390–4.
15 Luijten KMAC, Tekstra J, Bijlsma JWJ, *et al*. The systemic lupus erythematosus Responder index (SRI); a new SLE disease activity assessment. *Autoimmun Rev* 2012;11:326–9.
16 Hay E, Gordon C, Emery P. Assessment of lupus: where are we now *Ann Rheum Dis* 1993;52:169–72.
17 Murphy G, Isenberg DA. Author correction: new therapies for systemic lupus erythematosus - past imperfect, future tense. *Nat Rev Rheumatol* 2019;15:509.
18 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
19 Finucane MM, Paciorek CJ, Danaei G, *et al*. n.d. Bayesian estimation of population-level trends in measures of health status. *Statist Sci*;29.
20 Joseph L, Gyorkos TW, Coupal L. Bayesian estimation of disease prevalence and the parameters of diagnostic tests in the absence of a gold standard. *Am J Epidemiol* 1995;141:263–72.
21 Flor M, Weiß M, Selhorst T, *et al*. Comparison of Bayesian and Frequentist methods for prevalence estimation under Misclassification. *BMC Public Health* 2020;20:1135.
22 Sterne JAC, Savović J, Page MJ, *et al*. n.d. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*:l4898.
23 Coiera E, Choong MK, Tsafnat G, *et al*. Linking quality indicators to clinical trials: an automated approach. *Int J Qual Health Care* 2017;29:571–8.
24 Andrade C. The primary outcome measure and its importance in clinical trials. *J Clin Psychiatry* 2015;76:e1320–3.
25 Drazen JM, Harrington DP, McMurray JJV, *et al*. The primary outcome is positive - is that good enough *N Engl J Med* 2016;375:971–9.
26 Dall'Era M, Bruce IN, Gordon C, *et al*. Current challenges in the development of new treatments for lupus. *Ann Rheum Dis* 2019;78:729–35.
27 Burness CB, McCormack PL. Belimumab: in systemic lupus erythematosus. *Drugs* 2011;71:2435–44.
28 Singh JA, Shah NP, Mudano AS. Belimumab for systemic lupus erythematosus. *Cochrane Database Syst Rev* 2021;2:CD010668.
29 Furie R, Khamashta M, Merrill JT, *et al*. Anifrolumab, an anti-interferon-A receptor Monoclonal antibody. *Arthritis & Rheumatology* 2017;69:376–86.
30 Kim M, Merrill JT, Kalunian K, *et al*. Evaluating duration of response to treatment in systemic lupus erythematosus clinical trials. *Lupus Sci Med* 2018;5:e000266.
31 Furie RA, Bruce IN, Dörner T, *et al*. Phase 2, randomized, placebo-controlled trial of Dapirolizumab Pegol in patients with moderate-to-severe active systemic lupus erythematosus. *Rheumatology* 2021;60:5397–407.
32 Chia YL, Zhang J, Tummala R, *et al*. Relationship of Anifrolumab pharmacokinetics with efficacy and safety in patients with systemic lupus erythematosus. *Rheumatology* 2022;61:1900–10.
33 Yu H, Nagafuchi Y, Fujio K. Clinical and immunological biomarkers for systemic lupus erythematosus. *Biomolecules* 2021;11:928.
34 Ohmura K. Which is the best SLE activity index for clinical trials *Mod Rheumatol* 2021;31:20–8.
35 Golder V, Tsang-A-Sjoe MWP. Treatment targets in SLE: remission and low disease activity state. *Rheumatology* 2020;59(Supplement_5):v19–28.
36 Connelly K, Eades LE, Koelmeyer R, *et al*. Towards a novel clinical outcome assessment for systemic lupus erythematosus: first outcomes of an international Taskforce. *Nat Rev Rheumatol* 2023;19:592–602.
37 Askanase AD, Daly RP, Okado M, *et al*. Development and content validity of the lupus foundation of America rapid evaluation of activity in lupus (LFA-REAL™): a patient-reported outcome measure for lupus disease activity. *Health Qual Life Outcomes* 2019;17:99.
38 Shi Y, Li M, Liu L, *et al*. Relationship between disease activity, organ damage and health-related quality of life in patients with systemic lupus erythematosus: A systemic review and meta-analysis. *Autoimmun Rev* 2021;20:102691.

SUPPLEMENTARY MATERIAL

Selection of indicators reporting response rate in pharmaceutical trials for systemic lupus erythematosus: preference and relative sensitivity

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Appendices index

Appendix 1. Detailed methods

a. Search strategy

Two investigators (JR.T and DY.Z) searched published articles and clinical trial registry records, and appraised studies on eligibility, and extracted data independently. Discrepancies were discussed and agreed by consensus.

The search for RCTs included published articles from peer-reviewed English-language journals and registered trials in clinical trials registries, both up to May 4, 2021 and without start date restriction. The published articles were searched in literature databases including the PubMed, EMBASE, and Cochrane Library Central Register of Controlled Trials (CENTRAL). The MeSH and keyword search terms associated with systemic lupus erythematosus were used in each database. In order not to miss out on potentially useful articles, references cited in relevant reviews were also searched manually. RCTs published in Chinese medical journals were also included.

Records of registered RCTs were collected from 3 publicly available web-based clinical trials registries, including the ClinicalTrials.gov of the US National Library of Medicine, the International Standard Randomised Controlled Trial Number Register (ISRCTN), and the Australian and New Zealand Clinical Trials Registry (ANZCTR). The keyword search term “lupus” was entered combined with other specific filtering options in advanced search function for ‘Country’, ‘Study type’, and ‘Current status’ et al. in searching for eligible RCTs.

b. Study selection

We evaluated published articles at the title or abstract level, with divergences resolved after consensus by two independent investigators. If potentially relevant, we evaluated them as complete reports according to prespecified selection criteria. For both published articles and registered records, trials were included if they enrolled subjects with SLE patients, and randomly assigned patients to different intervention groups. We excluded studies which are: 1) non-human studies; 2) observational studies; 3) studies without randomization or intervention groups; 4) studies not conducted in patients with SLE; 5) studies without ethics committee approval. In addition, published articles which are: 1) not in the English language or not in Chinese

full text; 2) without full text (i.e. abstracts and conference proceedings) or not reporting original studies (i.e. narrative reviews, meta-analyses, editorials, commentaries, protocols, guidelines, or perspectives); or 3) duplicate reports and registration were also excluded. The search processes of literature from published articles and records from clinical trial registries are shown below.

c. Data extraction

Two investigators independently extracted information on characteristics of each included study, including general information (author, publication year, registration ID, year of start, domestic or multinational, single- or multi-center, affiliations of primary investigators), participant characteristics (subject type, number of participants, loss to follow-up), study intervention (measures of intervention or control, duration, blinding), and primary outcomes. Some information of participant characteristics was not available for multinational trials because they did not provide information separately for participants in individual countries. Extracted data from published articles and records from clinical trials registries were entered separately into two piloted spreadsheets, and then combined together matched by the registration ID or other information if the registration ID was unavailable. For studies with data available from both sources, data from published articles were used. Potential duplicate registry entries were searched for by matching on important trial characteristics including year of start, affiliation of primary investigator, subject category, number of participants, interventions, and primary outcome. Published trials which did not include a trial registration ID was considered not registered.

The following information will be extracted from each included trial.

1 General information

1.1 Data source: ‘clinical trial registry’, or ‘published articles’.

1.2 Author, year of publication: the first author and publication year of the trial from published articles. For trials in the registries, name of the registers including ‘ClinicalTrials.gov’, ‘International Standard Randomised Controlled Trial Number Register’, and Australian New Zealand Clinical Trials Registry’ will be used.

1.3 Registration ID: the registered number of the trial. For trials without registration ID, 'not available' will be used.

2 Trial information

2.1 Year of start: the start year of the trial if it is available, otherwise 'not mentioned' will be used.

2.2 Multinational study: 'Yes' if the trial is a multinational study, or 'No' if the trial was conducted entirely in one country.

2.3 Affiliation of primary investigator: The affiliation of the primary investigator can be found in registries. For published articles, the affiliation of the corresponding author will be used. The last corresponding author will be chosen if there are multiple corresponding authors.

2.4 Single or Multicenter: 'Single center' if it is a single-center study, 'Multicenter' if the trial is conducted at ≥2 centers, or 'Not mentioned' if it is not recorded.

2.5 Primary outcome: the primary outcome identified in the included trial. For trials which list several outcomes without identification of the primary outcome, all the reported outcomes will be extracted and 'primary outcome not identified' will be noted.

3 Participant characteristics

3.1 Subjects: 'SLE' if subjects are patients with systemic lupus erythematosus; 'JSLE' if subjects are patients with juvenile-onset systemic lupus erythematosus; 'SCLE' if subjects are patients with subacute cutaneous lupus erythematosus; 'LN' if subjects are patients with lupus nephritis; 'MLN' if subjects are patients with membranous lupus nephritis; 'DPSLE' if subjects are patients with diffuse proliferative lupus nephritis; 'NPSLE' if subjects are patients with neuropsychiatric Lupus Erythematosus.

3.2 Number of participants: the number of randomized subjects in published articles, or the number of estimated enrollments for ongoing trials and the number of actual enrollments for completed trials in the registries.

3.3 Number of participants loss to follow-up: the number of participants who did not complete the follow-up. 'not available' will be used for registered

ongoing trials.

3.4 Percentage of loss-to-follow-up (%): calculated by 'Number of participants loss to follow-up' divided by 'Number of participants'. 'not available' will be used for registered ongoing trials.

3.5 Age duration (years): the age duration in years of participants. 'Not mentioned' if it is not recorded or only has average age.

3.6 Country and area: the country and area where the clinical trial is located. For trials which are multinational studies, all the reported locations will be extracted. 'Not mentioned' if it is not recorded.

4 Study intervention

4.1 Intervention categories: including 'Pharmacological treatment'.

4.2 Intervention; control: intervention and control measures used in the included trial.

4.3 Intervention duration (months): the intervention duration in months for completed trials. 'not available' will be used for ongoing registered trials or if information is not provided.

4.4 Blinding: including 'Single-blind', 'Double-blind', 'Open-label', or other types of blinding (triple-blind or quadruple-blind) if it is available. 'Not mentioned' if information on blinding is not provided.

5 Reference: the reference for published articles and URL for registered trials.

d. Study categorization

We included RCTs conducted in subjects with lupus, lupus with complications, lupus with comorbidities, and mixture of lupus with and without complications. Under each subject category, we further classified included RCTs according to interventions.

We used classifications adapted from the ClinicalTrials.gov registry, which has 7 categories of intervention including pharmacological treatment, behavioral intervention, dietary supplement, biological therapy, procedure, device, and others. We only included RCTs examined pharmacological treatments, and the following table S1 listed the detail information.

Table S1. The classification of intervention categories

Categories	Interventions
Pharmacological treatment	
Chemical drugs and biologicals	This includes trials which evaluate the effects of monotherapy of glucocorticoids, vitamin D, immunosuppressants, biologicals, combination therapy of glucocorticoids and/or antimalarial drugs and other immunosuppressants and/or biologicals, and other chemical drugs such as docosahexaenoic acid, sublingual immunotherapy, etc.
Traditional Chinese medicine	This includes trials which evaluate the effects of herbal compound formula and herbal concentrate-granules.
Antibodies	This includes trials which evaluate the effects of humanized monoclonal antibody against different targets.
Vaccines	This includes trials which evaluate the effects or safety of vaccines, such as herpes zoster vaccine, etc.

Appendix 2. Search strategies

Table S2. The search strategy in PubMed (Medline)

#	Terms	Quotes
4	#1 AND #2 AND #3	**2.367**
3	(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh])	**1.343.564**
2	("Therapeutics" [Mesh] OR "therapy" [Subheading] OR "prevention and control" [Subheading] OR Intervention OR prevention)	**15.006.631**
1	(((((("Lupus Erythematosus, Systemic"[Mesh] OR Systemic Lupus Erythematosus OR Lupus Erythematosus Disseminatus OR Libman-Sacks Disease OR Disease, Libman-Sacks OR Libman Sacks Disease) OR ("Lupus Nephritis"[Mesh] OR Lupus Glomerulonephritis OR Nephritis, Lupus OR Lupus Nephritides OR Nephritides, Lupus OR Glomerulonephritis, Lupus OR Glomerulonephritides, Lupus OR Lupus Glomerulonephritides)) OR ("Lupus Vasculitis, Central Nervous System"[Mesh] OR Central Nervous System Lupus Vasculitis OR Systemic Lupus Erythematosis, Central Nervous System OR Central Nervous System Lupus OR central nervous system systemic lupus erythematosus OR Neuropsychiatric Systemic Lupus Erythematosus OR Lupus Meningoencephalitis OR Lupus Meningoencephalitides OR Meningoencephalitides, Lupus OR Meningoencephalitis, Lupus)) OR (systemic lupus erythematosus)) OR (lupus erythematosus)) OR (systemic lupus)) OR (Lupus Erythematosus, Discoid[MeSH Terms])) OR (Lupus Erythematosus, Cutaneous[MeSH Terms])	**83.756**

Table S3. The search strategy in Embase

#	Terms	Quotes
9	#6 AND #7 AND #8 AND ([chinese]/lim OR [english]/lim) AND [humans]/lim	**1.645**
8	('randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled trial' OR 'randomized controlled trials' OR 'randomized controlled trials as topic' OR 'trial, randomized controlled' AND [embase]/lim) OR ('randomization'/exp OR 'random allocation' OR 'randomisation' AND [embase]/lim) OR ('double blind procedure'/exp OR 'double-blind method' OR 'double blind clinical trial' OR 'double blind comparison' OR 'double blind studies' OR 'double blind study' OR 'double blind test' OR 'double blind trial' AND [embase]/lim)	**687.328**
7	'therapy'/exp OR 'prevention'/exp OR 'intervention':ti,ab,kw OR 'treatment':ti,ab,kw OR 'prevention':ti,ab,kw	**13.421.869**
6	#1 OR #2 OR #3 OR #4 OR #5	**115.502**
5	('lupus erythematosus nephritis'/exp OR 'glomerulonephritis lupoid' OR 'lupoid nephritis' OR 'lupus erythematosus nephritis' OR 'lupus glomerulonephritis' OR 'lupus kidney' OR 'lupus nephritis' OR 'lupus nephropathy' OR 'nephritis lupus erythematosus' OR 'nephritis systemic lupus erythematosus' OR 'systemic lupus erythematosis, nephritis') AND [embase]/lim	**17.968**
4	('systemic lupus erythematosus'/exp OR 'dermatovisceritism malignant' OR 'disseminated lupus' OR 'disseminated lupus erythematodes' OR 'disseminated lupus erythematosis' OR 'disseminated lupus erythematosus' OR 'erythematodes visceralis' OR lupovisceritis OR 'lupus erythematodes disseminatus' OR 'lupus erythematosus disseminatus' OR 'lupus	**99.836**

	erythematosus visceralis' OR 'lupus erythematosus systemic' OR 'osler libman sacks disease' OR 's.l.e.' OR 'sle' OR 'systemic lupus erythematodes' OR 'systemic lupus erythematosis' OR 'systemic lupus erythematous') AND [embase]/lim	
3	'brain vasculitis'/exp OR 'angiitis brain' OR 'arteritis brain' OR 'brain angiitis' OR 'brain arteritis' OR 'cerebral arteritis' OR 'cerebral vasculitis' OR 'lupus vasculitis central nervous system' OR 'vasculitis brain' OR 'vasculitis central nervous system' AND [embase]/lim	**3.364**
2	'lupus'/exp OR 'discoid lupus erythematosus' OR 'cutaneous lupus erythematosus' AND [embase]/lim	**7.793**
1	('systemic lupus erythematosus'/exp OR 'dermatovisceritism malignant' OR 'disseminated lupus' OR 'disseminated lupus erythematodes' OR 'disseminated lupus erythematosis' OR 'disseminated lupus erythematosus' OR 'erythematodes visceralis' OR lupovisceritis OR 'lupus erythematodes disseminatus' OR 'lupus erythematosus disseminatus' OR 'lupus erythematosus visceralis' OR 'lupus erythematosus systemic' OR 'osler libman sacks disease' OR 'sle' OR 'systemic lupus erythematodes' OR 'systemic lupus erythematosis' OR 'systemic lupus erythematous') AND [embase]/lim	**99.638**

Table S4. The search strategy in Cochrane Library

#	Terms	Quotes
1	(therapy):ti,ab,kw	**704.834**
2	MeSH descriptor Therapeutics explode all trees	**143**
3	(intervention):ti,ab,kw	**379.140**
4	(treatment):ti,ab,kw	**782.201**
5	(prevention):ti,ab,kw	**182.665**
6	MeSH descriptor Treatment Outcome explode all trees	**3.459**
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)	**1.219.409**
8	MeSH descriptor Lupus Erythematosus, Systemic explode all trees	**48**
9	MeSH descriptor Lupus Nephritis explode all trees	**11**
10	MeSH descriptor Lupus Vasculitis, Central Nervous System explode all trees	**2**
11	MeSH descriptor Lupus Erythematosus, Cutaneou explode all trees	**0**
12	(Lupus Erythematosus, Systemic):ti,ab,kw	**2.267**
13	"Lupus":ti,ab,kw	**3.298**
14	(#8 OR #9 OR #10 OR #11 OR #12 OR #13)	**3.342**
15	(#7 AND #14)	**2.773**
16	pubmed:an OR embase:an	**1.078.710**
17	(#15 NOT #16)	**967**

Table S5. The search terms and specific filtering options used in the clinical trials registries

#	Terms	Quotes
Using "lupus" as search criteria		
1	**Filtering options set in advanced search function in ClinicalTrials.gov** Study type: "Intervention"; Current status: "Recruiting" OR "Active, not recruiting" OR "Completed" OR "Enrolling by invitation" OR "Not yet recruiting"	**480**
2	**Filtering options set in advanced search function in International Standard Randomised Controlled Trial Number Register (ISRCTN)** Trial status: "Completed" OR "On going" Recruitment status: "Recruiting" OR "No longer recruiting"	**183**

3	**Filtering options set in advanced search function in Australian and New Zealand Clinical Trials Registry (ACTR)** Study type: “Intervention”; Registry: ANZCTR Allocation to intervention: “Randomised”; Current status: “Recruiting” OR “Active, not recruiting” OR “Completed” OR “Not yet recruiting”	**12**

Appendix 3. Literature search and selection

Figure S1. Literature search and selection from published articles

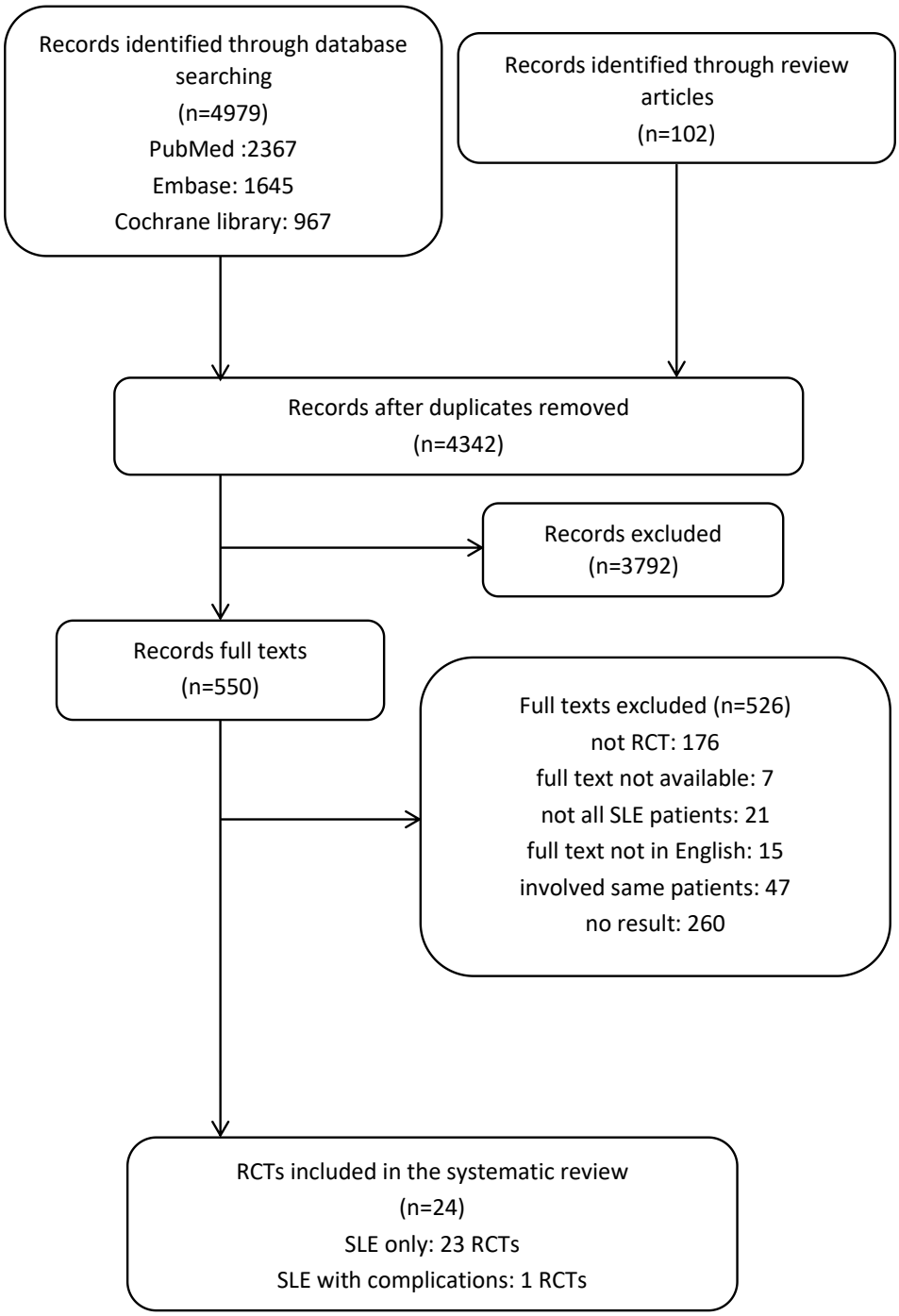
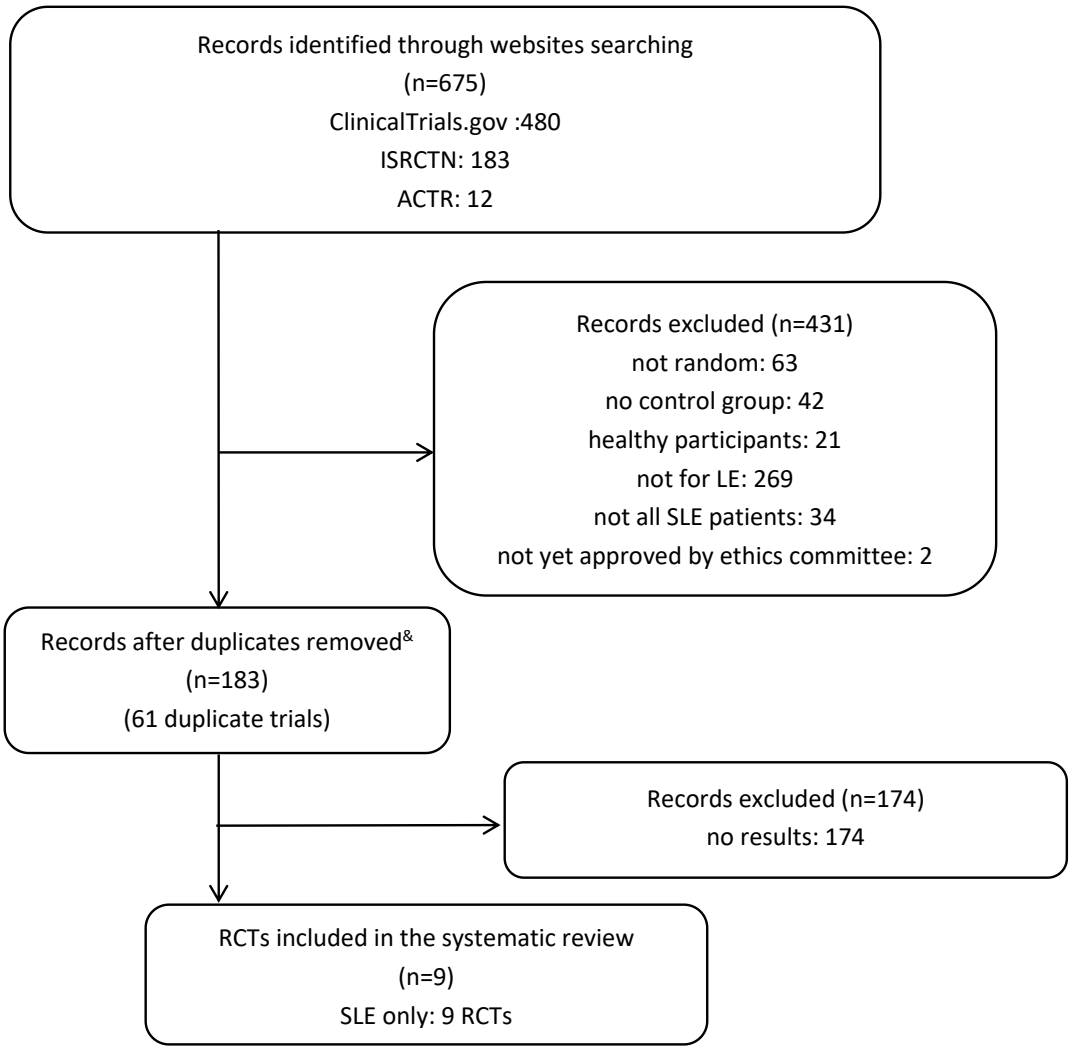


Figure S2. Record search and selection from clinical trials registries



The searching term "lupus" was used in each clinical trial registries.

& Records from clinical trials registries and published articles were matched using registration ID or other information if registration ID was unavailable. 61 trials were duplicated in published articles with registry entries.

Appendix 4. Data abstraction form

Table S6. Data abstraction form

No.	Data Source	Author, year of publication	Registration ID	Year of start	Multinational study	Affiliation of primary investigator	Single or Multicenter	Subject categories	Number of participants

Continued table S6. Data abstraction form

Number of participants loss to follow-up	Percentage of loss-to-follow-up (%)	Intervention categories	Interventions	Intervention duration (month)	Age duration (years)	Blinding	Primary outcome	References	Country or area

Appendix 5. Definition of the 8 included indicators

Indicators	Interpretation
SRI-4	[1] Greater than or equal to 4-point reduction in SLEDAI-2K, modified SLEDAI-2K or SELENA-SLEDAI total score; [2] No new BILAG A and no more than 1 new BILAG B domain scores; [3] No worsening (< 0.30 points or 10%) from baseline in PGA.
SIR-5	[1] Greater than or equal to 5-point reduction in SLEDAI-2K, modified SLEDAI-2K or SELENA-SLEDAI total score; [2] No new BILAG A and no more than 1 new BILAG B domain scores; [3] No worsening (< 0.30 points or 10%) from baseline in PGA.
SRI-6	[1] Greater than or equal to 6-point reduction in SLEDAI-2K, modified SLEDAI-2K or SELENA-SLEDAI total score; [2] No new BILAG A and no more than 1 new BILAG B domain scores; [3] No worsening (< 0.30 points or 10%) from baseline in PGA.
BICLA	[1] At least 1 gradation of improvement in baseline BILAG scores in all body systems with moderate or severe disease activity at entry (e.g., all A (severe disease) scores falling to B (moderate), C (mild), or D (no activity) and all B scores falling to C or D); [2] No new BILAG A or more than 1 new BILAG B scores; [3] No worsening of total SLEDAI score from baseline; [4] No significant deterioration in physician's global assessment; [5] No treatment failure (initiation of non-protocol treatment).
SAE	Any adverse event that leads to death, is life threatening (NIH criteria Grade 4), causes or prolongs hospitalization, results in a congenital anomaly, or any other important medical event not described above.
SLEDAI-4	Greater than or equal 4-point improvement in SLEDAI total score (SLEDAI-2K, modified SLEDAI-2K or SELENA-SLEDAI), e.g., the SLEDAI-2K score measures disease activity through assessment of 24 lupus manifestations using a weighted score of 1 to 8 points.
BILAG response	No worsening in BILAG is defined as no new BILAG A and no more than 1 new BILAG B domain score compared to baseline. The BILAG 2004 Index is a composite index and assesses the changing severity of clinical manifestations of SLE using an ordinal scale scoring system that contain 9 systems (constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal and hematological). Activity in each organ system is scored as: A=most active disease; B=intermediate activity; C=mild, stable disease; D=previous involvement, currently inactive; E=no previous activity.
PGA response	No worsening in PGA is defined as an increase of < 0.30 points or 10% from baseline. PGA is a single-item clinician rated assessment of the patient's current level of disease activity measured on a continuous 100 millimeter (mm) visual analytic scale with benchmarks of 0, 1, 2, and 3 from left to right corresponding to no, mild, moderate, and severe SLE disease activity. Scores are presented from 0 to 100.

SRI: Systemic Lupus Erythematosus Responder Index;
SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment;
SLEDAI: Systemic Lupus Erythematosus Disease Activity Index;
BICLA: British Isles Lupus Assessment Group Index-based Combined Lupus Assessment;
SAE: Serious adverse events;
NIH: National Institutes of Health;
BILAG: British Isles Lupus Assessment Group;
SLE: Systemic Lupus Erythematosus;
PGA: Physician's Global Assessment.

Appendix 6. Statistical methods for indicator preference calculation

The model fitted by a Bayesian hierarchical linear mixed model. In hierarchical model, the effectiveness of an intervention was estimated based on study data both from the same intervention and from other interventions in the same type of Interventions.

The model applied binomial family, and log-transformation was used to transform effectiveness to a linear response variable. The statistical was implemented by brms package in R (version 4.0.5). This package is based on Stan and will estimate posterior distribution by Hamiltonian Markov Chain Monte Carlo method. Four chains were used, and the warmup number and iteration number are both 4000. Besides interventions, we have set another three predictor variables with fixed effects. The four fixed variables are indicator type, severity of the disease, whether the intervention is topical, and age of the patients.

Additionally, the model used a student_t(3, 0, 2.5) prior for the intercept. We reported the effectiveness estimate with 95% uncertainty intervals. Finally, we also assessed the models in total, the fit of each model was assessed by effective sample size, autocorrelation, and trace plots. Please contact Dingyao Zhang for the code of model estimation.

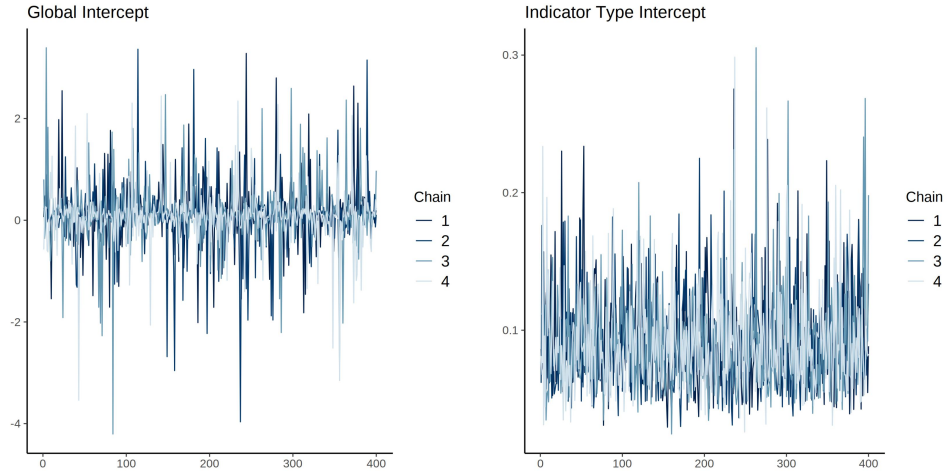
For discrete model:

```
model <- brm(mean | se(sd, sigma = TRUE) ~ 1 + (1 | index) + (1 | Type_intervention/Interventions) + (1 | Severity) + (1 | Topical) + (1 | Age), data = datause, thin = 10, chains = 4, iter = 8000, cores = 4, control = list(adapt_delta = 0.9995, max_treedepth=20))
```

Appendix 7. Trace plots for covariates in the Bayesian multilevel model

Figure S3. Trace plots for covariates in the Bayesian multilevel model showing 400 posterior draws total across 4 parallel chains.

For the discrete model:



Note: Global intercept is for fixed effect; Indicator type is for the variable of indicator type.

Appendix 8. List of included RCTs

Table S7. List of included RCTs.

No.	Study	Year of start	References
1	Askanase et al., 2020	2016	Askanase AD, Zhao E, Zhu J, Bilyk R, Furie RA. Repository Corticotropin Injection for Persistently Active Systemic Lupus Erythematosus: Results from a Phase 4, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Rheumatol Ther. 2020 Dec;7(4):893-908.
2	Brunner et al., 2020	2012	Brunner HI, Abud-Mendoza C, Viola DO, Calvo Penades I, Levy D, Anton J, Calderon JE, Chasnyk VG, Ferrandiz MA, Keltsev V, Paz Gastanaga ME, Shishov M, Boteanu AL, Henrickson M, Bass D, Clark K, Hammer A, Ji BN, Nino A, Roth DA, Struemper H, Wang ML, Martini A, Lovell D, Ruperto N; Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG). Safety and efficacy of intravenous belimumab in children with systemic lupus erythematosus: results from a randomised, placebo-controlled trial. Ann Rheum Dis. 2020 Oct;79(10):1340-1348.
3	Chamberlain et al., 2017	2013	Chamberlain C, Colman PJ, Ranger AM, Burkly LC, Johnston GI, Otoul C, Stach C, Zamacona M, Dörner T, Urowitz M, Hiepe F. Repeated administration of dapirolizumab pegol in a randomised phase I study is well tolerated and accompanied by improvements in several composite measures of systemic lupus erythematosus disease activity and changes in whole blood transcriptomic profiles. Ann Rheum Dis. 2017 Nov;76(11):1837-1844.
4	Cheng et al.,2018	2012	Cheng LE, Amoura Z, Cheah B, Hiepe F, Sullivan BA, Zhou L, Arnold GE, Tsuji WH, Merrill JT, Chung JB. Brief Report: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multiple-Dose Study to Evaluate AMG 557 in Patients With Systemic Lupus Erythematosus and Active Lupus Arthritis. Arthritis Rheumatol. 2018 Jul;70(7):1071-1076.
5	Clowse et al., 2017	2010	Clowse ME, Wallace DJ, Furie RA, Petri MA, Pike MC, Leszczyński P, Neuwelt CM, Hobbs K, Keiserman M, Duca L, Kalunian KC, Galateanu C, Bongardt S, Stach C, Beaudot C, Kilgallen B, Gordon C; EMBODY Investigator Group. Efficacy and Safety of Epratuzumab in Moderately to Severely Active Systemic Lupus Erythematosus: Results From Two Phase III Randomized, Double-Blind, Placebo-Controlled Trials. Arthritis Rheumatol. 2017 Feb;69(2):362-375.
6	Furie et al., 2011	2006	Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, Sanchez-Guerrero J, Schwarting A, Merrill JT, Chatham WW, Stohl W, Ginzler EM, Hough DR, Zhong ZJ, Freimuth W, van Vollenhoven RF; BLISS-76 Study Group. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011 Dec;63(12):3918-30.
7	Furie et al., 2015	2010	Furie RA, Leon G, Thomas M, Petri MA, Chu AD, Hislop C, Martin RS, Scheinberg MA; PEARL-SC Study. A phase 2, randomised, placebo-controlled clinical trial of blisibimod, an inhibitor of B cell activating factor, in patients with moderate-to-severe systemic lupus erythematosus, the PEARL-SC study. Ann Rheum Dis. 2015 Sep;74(9):1667-75.
8	Furie et al., 2017	2011	Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, Illei GG, Drappa J, Wang L, Yoo S; CD1013 Study Investigators. Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. Arthritis Rheumatol. 2017 Feb;69(2):376-386.
9	Furie et al., 2019	2015	Furie R, Morand E, Bruce I, Manzi S, Kalunian K, Vital E, Ford T, Gupta R, Hiepe F, Santiago M, Brohawn P, Berglind A, Tummala R. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. The Lancet Rheumatology. 2019 Dec;1(4):e208-e219.

10	Houssiau et al., 2020	2016	Houssiau FA, Thanou A, Mazur M, Ramiterre E, Gomez Mora DA, Misterska-Skora M, Perich-Campos RA, Smakotina SA, Cerpa Cruz S, Louzir B, Croughs T, Tee ML. IFN-α kinoid in systemic lupus erythematosus: results from a phase IIb, randomised, placebo-controlled study. Ann Rheum Dis. 2020 Mar;79(3):347-355.
11	Isenberg et al., 2016	2010	Isenberg DA, Petri M, Kalunian K, Tanaka Y, Urowitz MB, Hoffman RW, Morgan-Cox M, Iikuni N, Silk M, Wallace DJ. Efficacy and safety of subcutaneous tabalumab in patients with systemic lupus erythematosus: results from ILLUMINATE-1, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2016 Feb;75(2):323-31.
12	Ishii et al., 2018	2013	Ishii T, Tanaka Y, Kawakami A, Saito K, Ichinose K, Fujii H, Shirota Y, Shirai T, Fujita Y, Watanabe R, Chiu SW, Yamaguchi T, Harigae H. Multicenter double-blind randomized controlled trial to evaluate the effectiveness and safety of bortezomib as a treatment for refractory systemic lupus erythematosus. Mod Rheumatol. 2018 Nov;28(6):986-992.
13	Kahl et al., 2016	2013	Kahl L, Patel J, Layton M, Binks M, Hicks K, Leon G, Hachulla E, Machado D, Staumont-Sallé D, Dickson M, Condreay L, Schifano L, Zamuner S, van Vollenhoven RF; JAK115919 Study Team. Safety, tolerability, efficacy and pharmacodynamics of the selective JAK1 inhibitor GSK2586184 in patients with systemic lupus erythematosus. Lupus. 2016 Nov;25(13):1420-1430.
14	Kalunian et al., 2016	2009	Kalunian KC, Merrill JT, Maciuca R, McBride JM, Townsend MJ, Wei X, Davis JC Jr, Kennedy WP. A Phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon-α) in patients with systemic lupus erythematosus (ROSE). Ann Rheum Dis. 2016 Jan;75(1):196-202.
15	Khamashta et al., 2016	2011	Khamashta M, Merrill JT, Werth VP, Furie R, Kalunian K, Illei GG, Drappa J, Wang L, Greth W; CD1067 study investigators. Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2016 Nov;75(11):1909-1916.
16	Manzi et al., 2012	Not available	Manzi S, Sánchez-Guerrero J, Merrill JT, Furie R, Gladman D, Navarra SV, Ginzler EM, D'Cruz DP, Doria A, Cooper S, Zhong ZJ, Hough D, Freimuth W, Petri MA; BLISS-52 and BLISS-76 Study Groups. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis. 2012 Nov;71(11):1833-8.
17	Merrill et al., 2016	2011	Merrill JT, van Vollenhoven RF, Buyon JP, Furie RA, Stohl W, Morgan-Cox M, Dickson C, Anderson PW, Lee C, Berclaz PY, Dörner T. Efficacy and safety of subcutaneous tabalumab, a monoclonal antibody to B-cell activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2016 Feb;75(2):332-40.
18	Merrill et al., 2018	2013	Merrill JT, Wallace DJ, Wax S, Kao A, Fraser PA, Chang P, Isenberg D; ADDRESS II Investigators. Efficacy and Safety of Atacicept in Patients With Systemic Lupus Erythematosus: Results of a Twenty-Four-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm, Phase IIb Study. Arthritis Rheumatol. 2018 Feb;70(2):266-276.
19	Merrill et al., 2018	2013	Merrill JT, Shanahan WR, Scheinberg M, Kalunian KC, Wofsy D, Martin RS. Phase III trial results with blisibimod, a selective inhibitor of B-cell activating factor, in subjects with systemic lupus erythematosus (SLE): results from a randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2018 Jun;77(6):883-889.
20	Navarra et al., 2011	2007	Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, Li EK, Thomas M, Kim HY, León MG, Tanasescu C, Nasonov E, Lan JL, Pineda L, Zhong ZJ, Freimuth W, Petri MA; BLISS-52 Study Group. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011 Feb 26;377(9767):721-31.

21	Stohl et al., 2017	2011	Stohl W, Schwarting A, Okada M, Scheinberg M, Doria A, Hammer AE, Kleoudis C, Groark J, Bass D, Fox NL, Roth D, Gordon D. Efficacy and Safety of Subcutaneous Belimumab in Systemic Lupus Erythematosus: A Fifty-Two-Week Randomized, Double-Blind, Placebo-Controlled Study. Arthritis Rheumatol. 2017 May;69(5):1016-1027.
22	Tanaka et al., 2016	Not available	Tanaka Y, Takeuchi T, Akashi N, Takita Y, Kovacs B, Kariyasu S. Efficacy and safety of tabalumab plus standard of care in Japanese patients with active systemic lupus erythematosus: Subgroup analyses of the ILLUMINATE-1 study. Mod Rheumatol. 2017 Mar;27(2):284-291.
23	Wallace et al., 2016	2011	Wallace DJ, Strand V, Merrill JT, Popa S, Spindler AJ, Eimon A, Petri M, Smolen JS, Wajdula J, Christensen J, Li C, Diehl A, Vincent MS, Beebe J, Healey P, Sridharan S. Efficacy and safety of an interleukin 6 monoclonal antibody for the treatment of systemic lupus erythematosus: a phase II dose-ranging randomised controlled trial. Ann Rheum Dis. 2017 Mar;76(3):534-542.
24	Zhang et al., 2018	2011	Zhang F, Bae SC, Bass D, Chu M, Egginton S, Gordon D, Roth DA, Zheng J, Tanaka Y. A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea. Ann Rheum Dis. 2018 Mar;77(3):355-363.
25	ClinicalTrials.gov	2014	https://ClinicalTrials.gov/show/NCT02270957
26	ClinicalTrials.gov	2014	https://ClinicalTrials.gov/show/NCT02185040
27	ClinicalTrials.gov	2015	https://ClinicalTrials.gov/show/NCT02349061
28	ClinicalTrials.gov	2016	https://ClinicalTrials.gov/show/NCT02660944
29	ClinicalTrials.gov	2017	https://ClinicalTrials.gov/show/NCT03161483
30	ClinicalTrials.gov	2017	https://ClinicalTrials.gov/show/NCT02908100
31	ClinicalTrials.gov	2015	https://ClinicalTrials.gov/show/NCT02437890
32	ClinicalTrials.gov	2014	https://ClinicalTrials.gov/show/NCT02265744
33	ClinicalTrials.gov	2013	https://ClinicalTrials.gov/show/NCT01632241

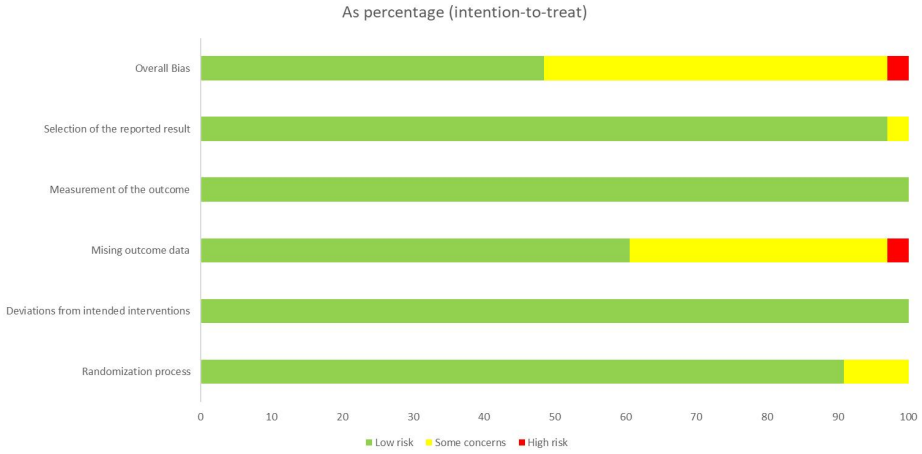
Appendix 9. Characteristics of included RCTs

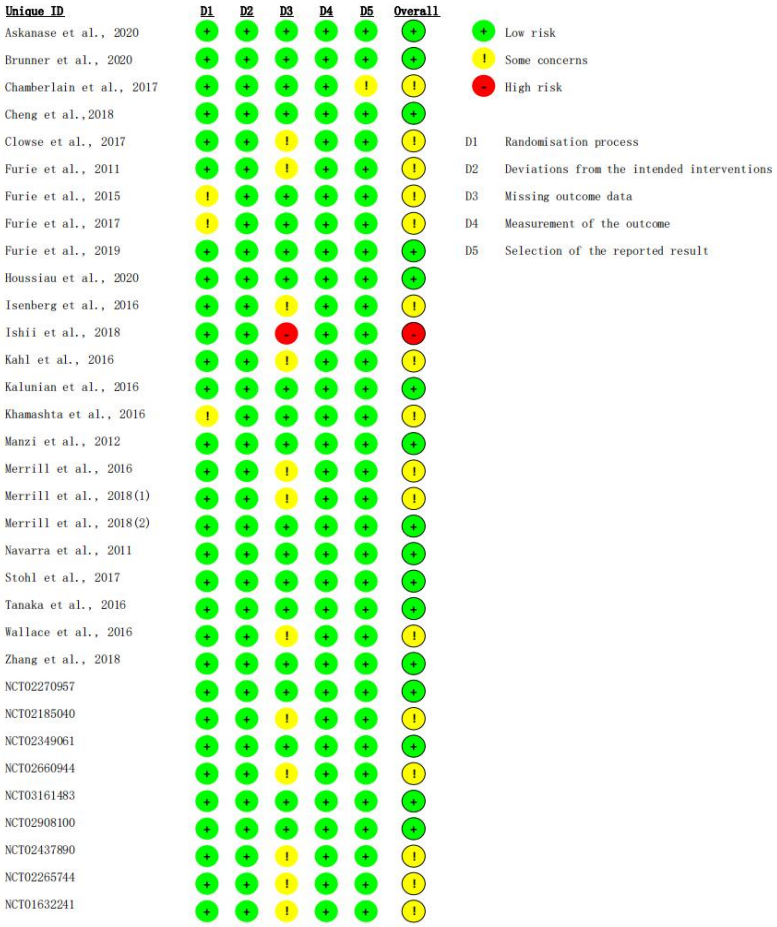
Table S8. Characteristics of included RCTs of SLE

Categories	No (%)
Data source	
Published articles	24 (72.7%)
Clinical trials registries	9 (27.3%)
Center	
Single center	2 (6.1%)
Multiple centers	31 (93.9%)
Year of start	
Before 2010	3 (9.1%)
2010-2015	23 (69.7%)
2016-2021	5 (15.2%)
Not available	2 (6.1%)
No. of participants	
<50	5 (15.2%)
50-99	4 (12.1%)
100-199	4 (12.1%)
≥200	20 (60.6%)
Age	
<18	1 (3.0%)
≥18	31 (93.9%)
Not available	1 (3.0%)
Subjects	
SLE only	32 (97.0%)
SLE with comorbidities	1 (3.0%)
Blinding	
Double blind	22 (66.7%)
Quadruple blind	10 (30.3%)
Not mentioned	1 (3.0%)
Intervention duration (months)	
1-5.9	5 (15.2%)
6-8.9	5 (15.2%)
⩾9	23 (69.6%)
Primary outcome identification	
Yes	33 (100%)
No	0 (0%)
Trial registration	
Yes	30 (90.9%)
No	3 (9.1%)

Appendix 10. Risk of bias assessments

Figure S4. Risk of bias summary graph: review authors' judgements (Low, Some concerns, and High) for each risk of bias item shown as percentages across all included studies

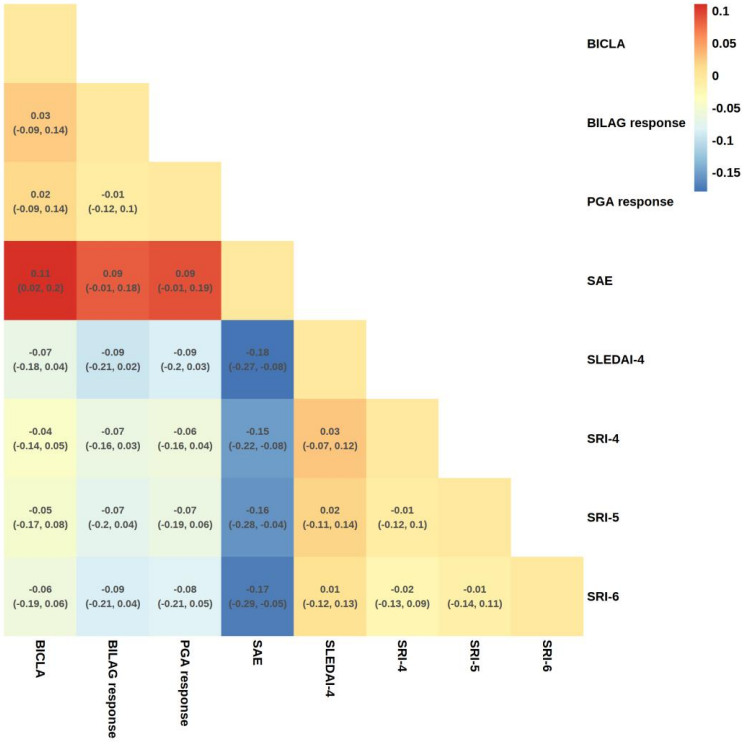




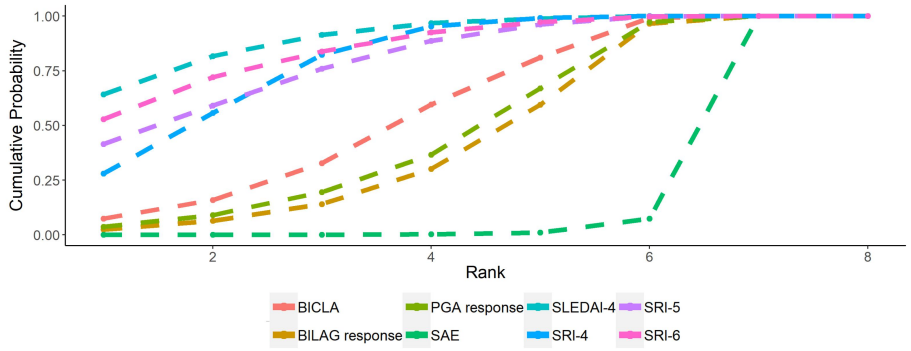
Appendix 11. Subgroup analyses of preference of indicators reporting response rate in pharmacological intervention-controlled RCTs

Figure S5. Preference of indicators reporting response rate in pharmacological intervention-controlled RCTs for moderate-to-severe SLE.

A



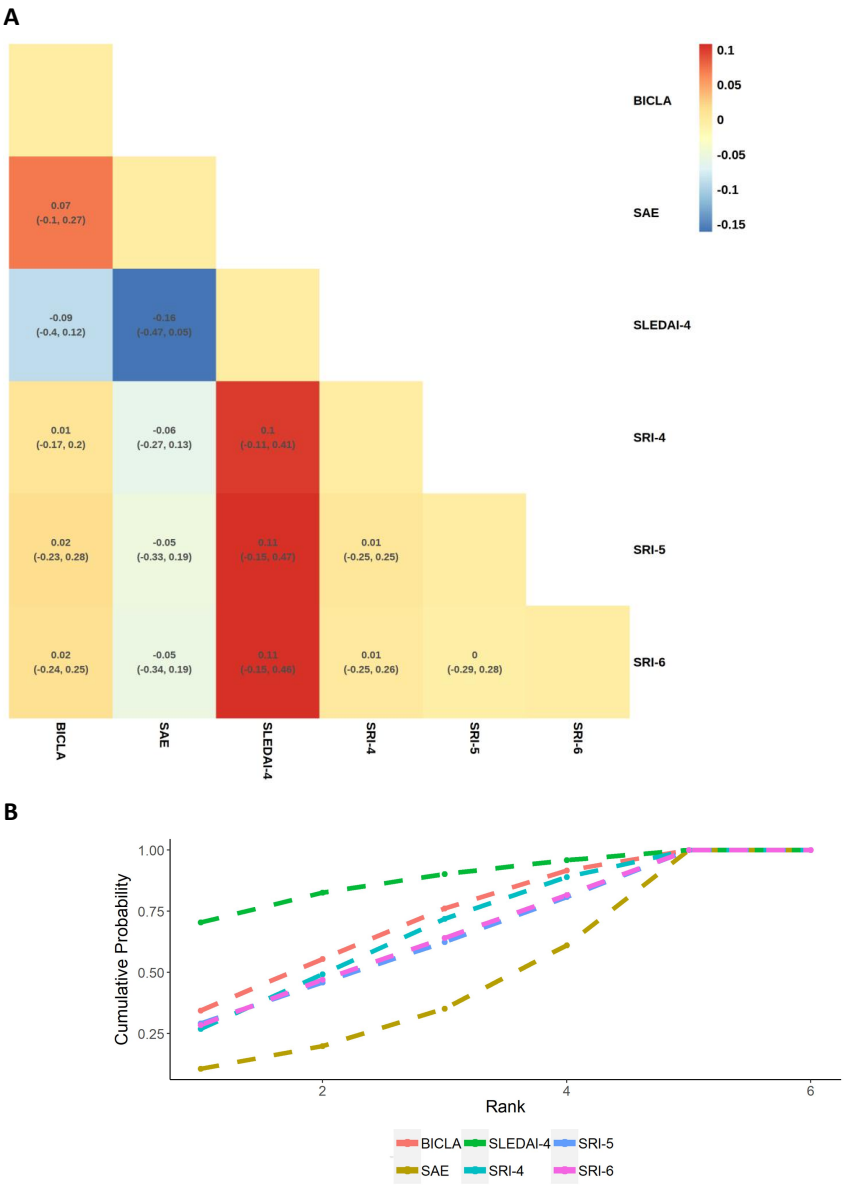
B



(A) *Bayesian hierarchical linear mixed model estimated effectiveness with 95% uncertainty intervals on indicators reporting response rate in pharmacological intervention-controlled RCTs for moderate-to-severe SLE.*

(B) *The rank of indicators reporting response rate. The sooner an indicator reaches 1, the stronger ability to discriminate treatment efficacy.*

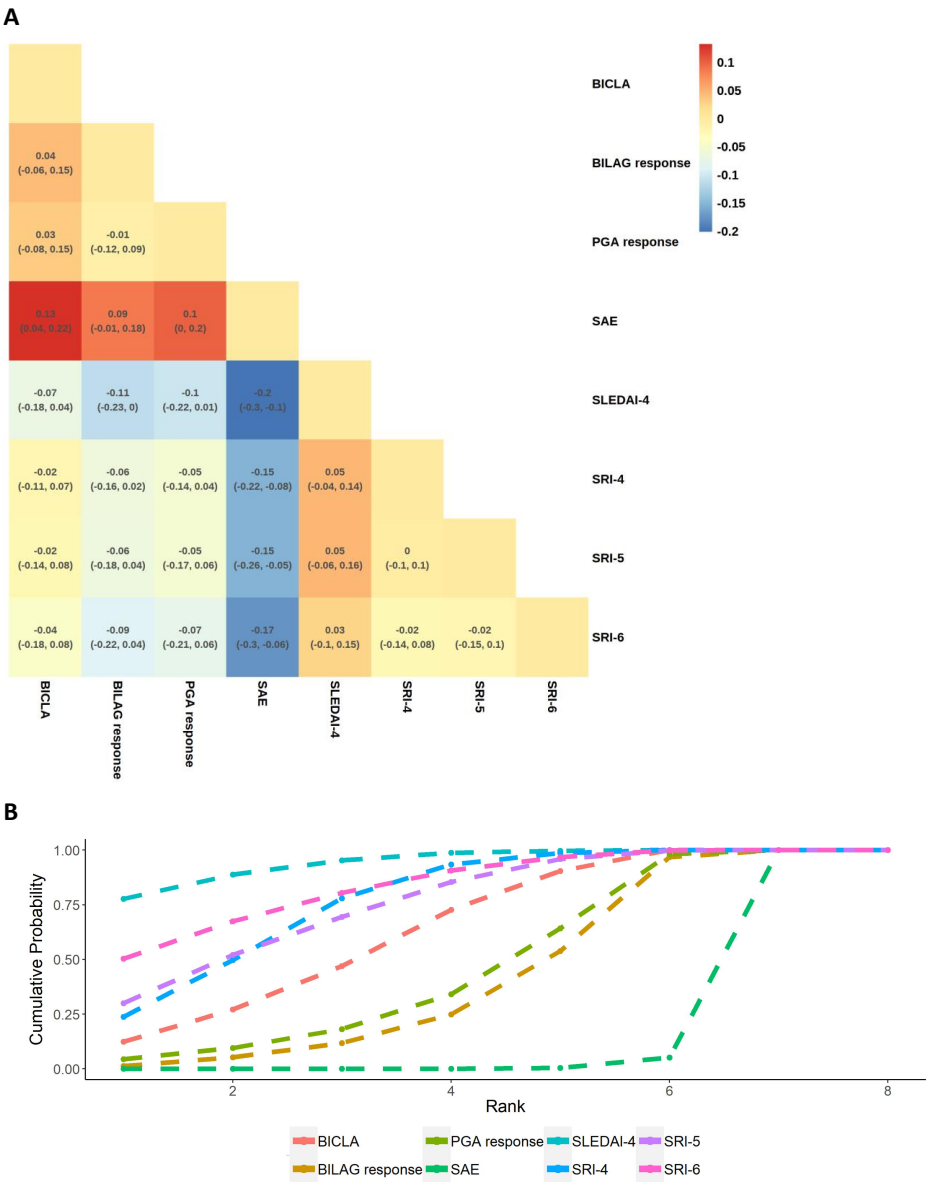
Figure S6. Preference of indicators reporting response rate in pharmacological intervention-controlled RCTs for all-severity SLE.



(A) *Bayesian hierarchical linear mixed model estimated effectiveness with 95% uncertainty intervals on indicators reporting response rate in pharmacological intervention-controlled RCTs for all-severity SLE.*

(B) *The rank of indicators reporting response rate. The sooner an indicator reaches 1, the stronger ability to discriminate treatment efficacy.*

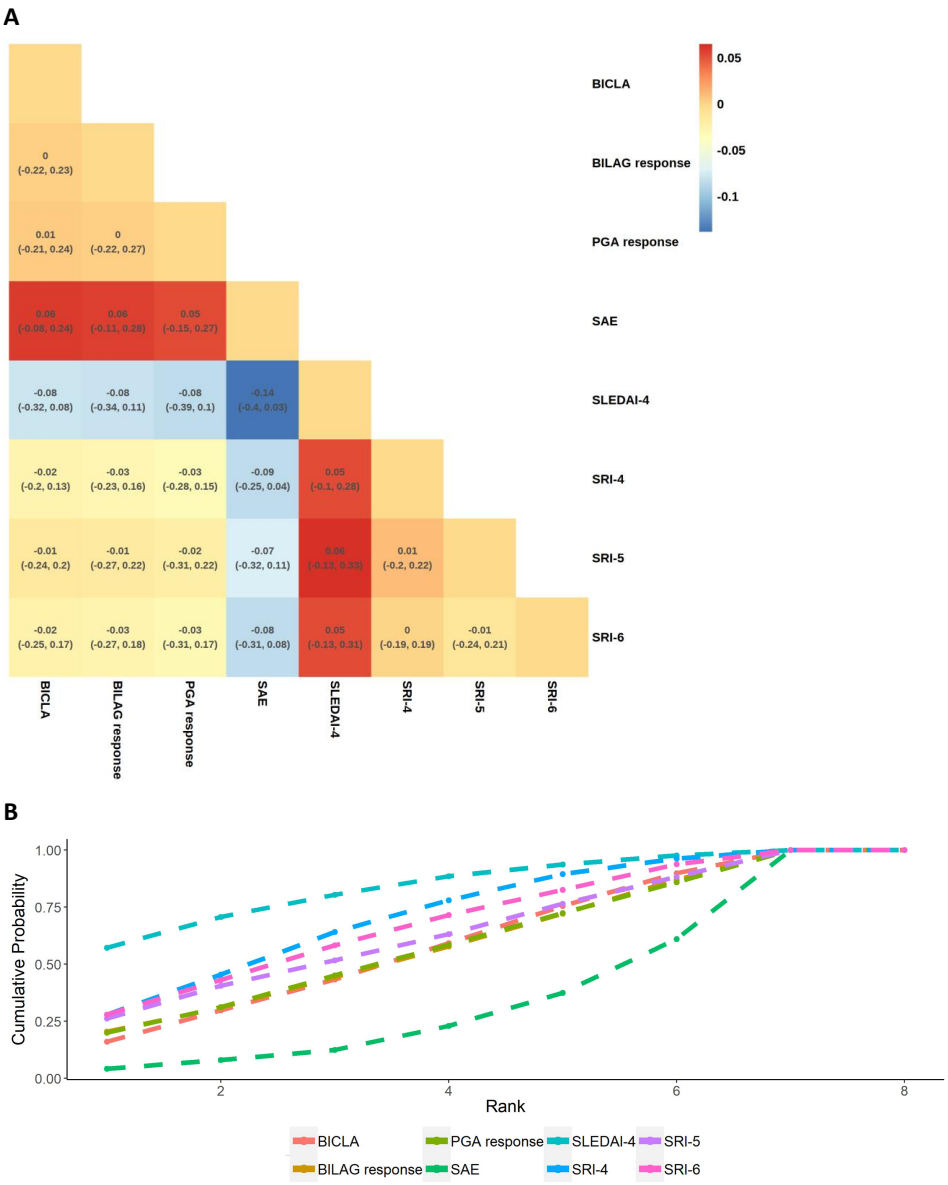
Figure S7. Preference of indicators reporting response rate in antibody pharmacological intervention-controlled RCTs for SLE.



(A) *Bayesian hierarchical linear mixed model estimated effectiveness with 95% uncertainty intervals on indicators reporting response rate in antibody pharmacological intervention-controlled RCTs for SLE.*

(B) *The rank of indicators reporting response rate. The sooner an indicator reaches 1, the stronger ability to discriminate treatment efficacy.*

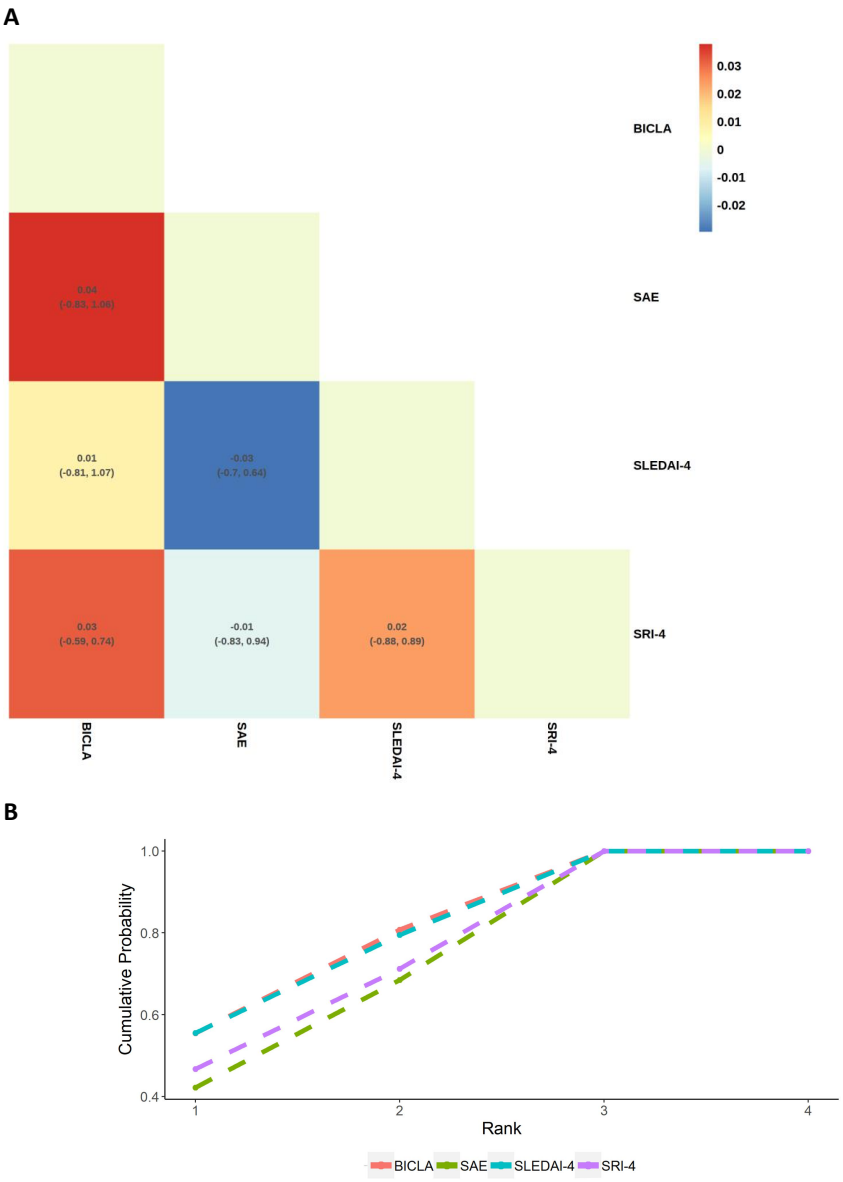
Figure S8. Preference of indicators reporting response rate in small molecule pharmacological intervention-controlled RCTs for SLE.



(A) *Bayesian hierarchical linear mixed model estimated effectiveness with 95% uncertainty intervals on indicators reporting response rate in small molecule pharmacological intervention-controlled RCTs for SLE.*

(B) *The rank of indicators reporting response rate. The sooner an indicator reaches 1, the stronger ability to discriminate treatment efficacy.*

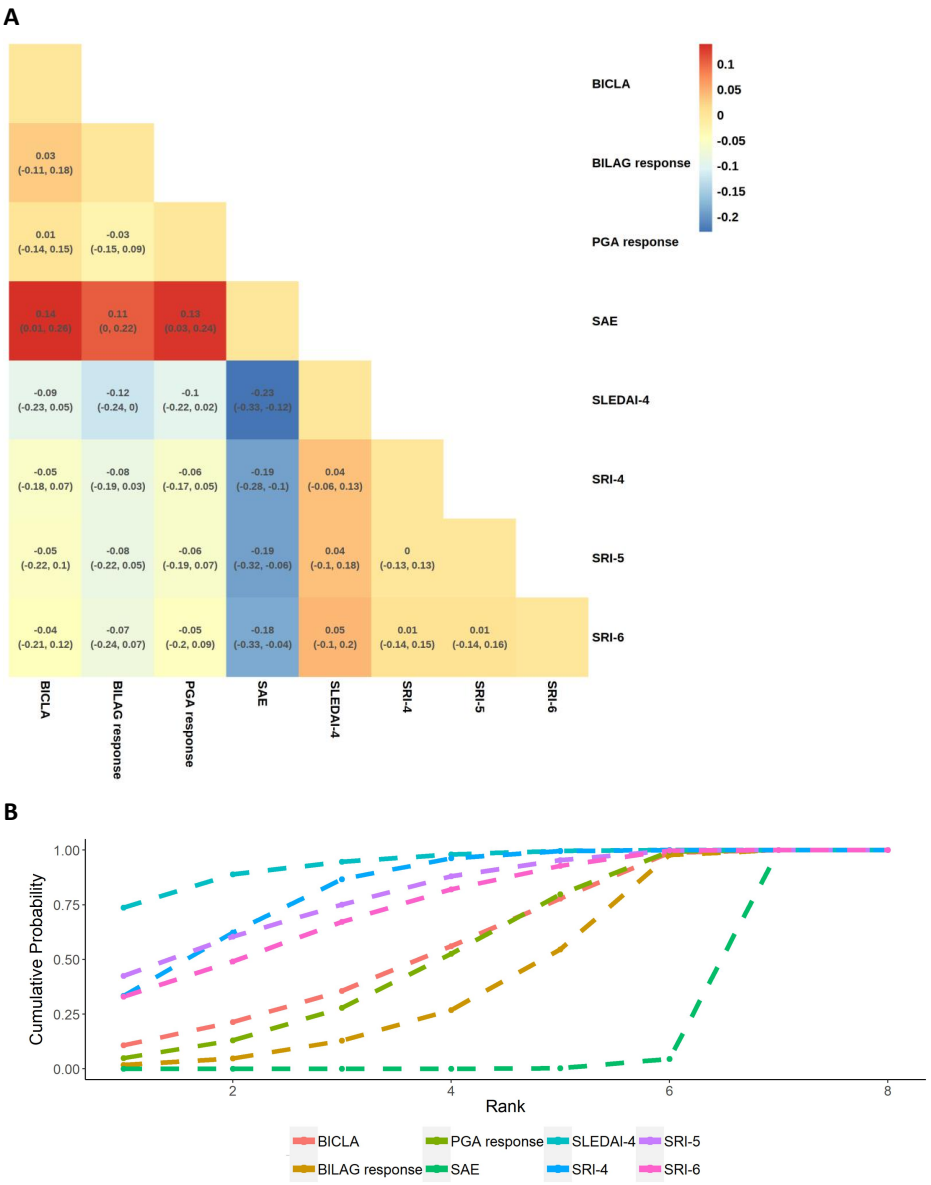
Figure S9. Preference of indicators reporting response rate in non-biologics pharmacological intervention-controlled RCTs for SLE.



(A) *Bayesian hierarchical linear mixed model estimated effectiveness with 95% uncertainty intervals on indicators reporting response rate in non-biologics pharmacological intervention-controlled RCTs for SLE.*

(B) *The rank of indicators reporting response rate. The sooner an indicator reaches 1, the stronger ability to discriminate treatment efficacy.*

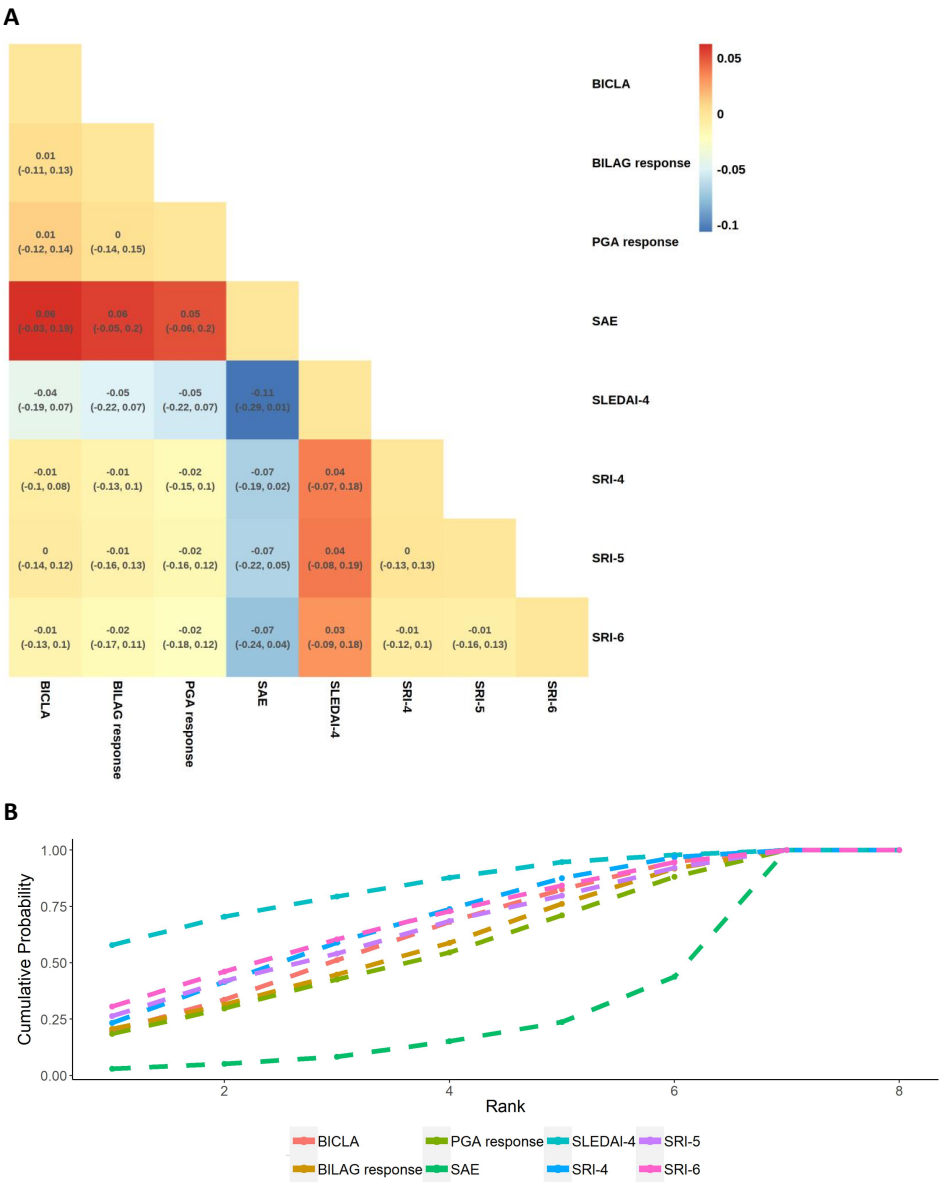
Figure S10. Preference of indicators reporting response rate in successful pharmacological intervention-controlled RCTs for SLE.



(A) *Bayesian hierarchical linear mixed model estimated effectiveness with 95% uncertainty intervals on indicators reporting response rate in successful pharmacological intervention-controlled RCTs for SLE.*

(B) *The rank of indicators reporting response rate. The sooner an indicator reaches 1, the stronger ability to discriminate treatment efficacy.*

Figure S11. Preference of indicators reporting response rate in unsuccessful pharmacological intervention-controlled RCTs for SLE.



(A) *Bayesian hierarchical linear mixed model estimated effectiveness with 95% uncertainty intervals on indicators reporting response rate in unsuccessful pharmacological intervention-controlled RCTs for SLE.*

(B) *The rank of indicators reporting response rate. The sooner an indicator reaches 1, the stronger ability to discriminate treatment efficacy.*