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

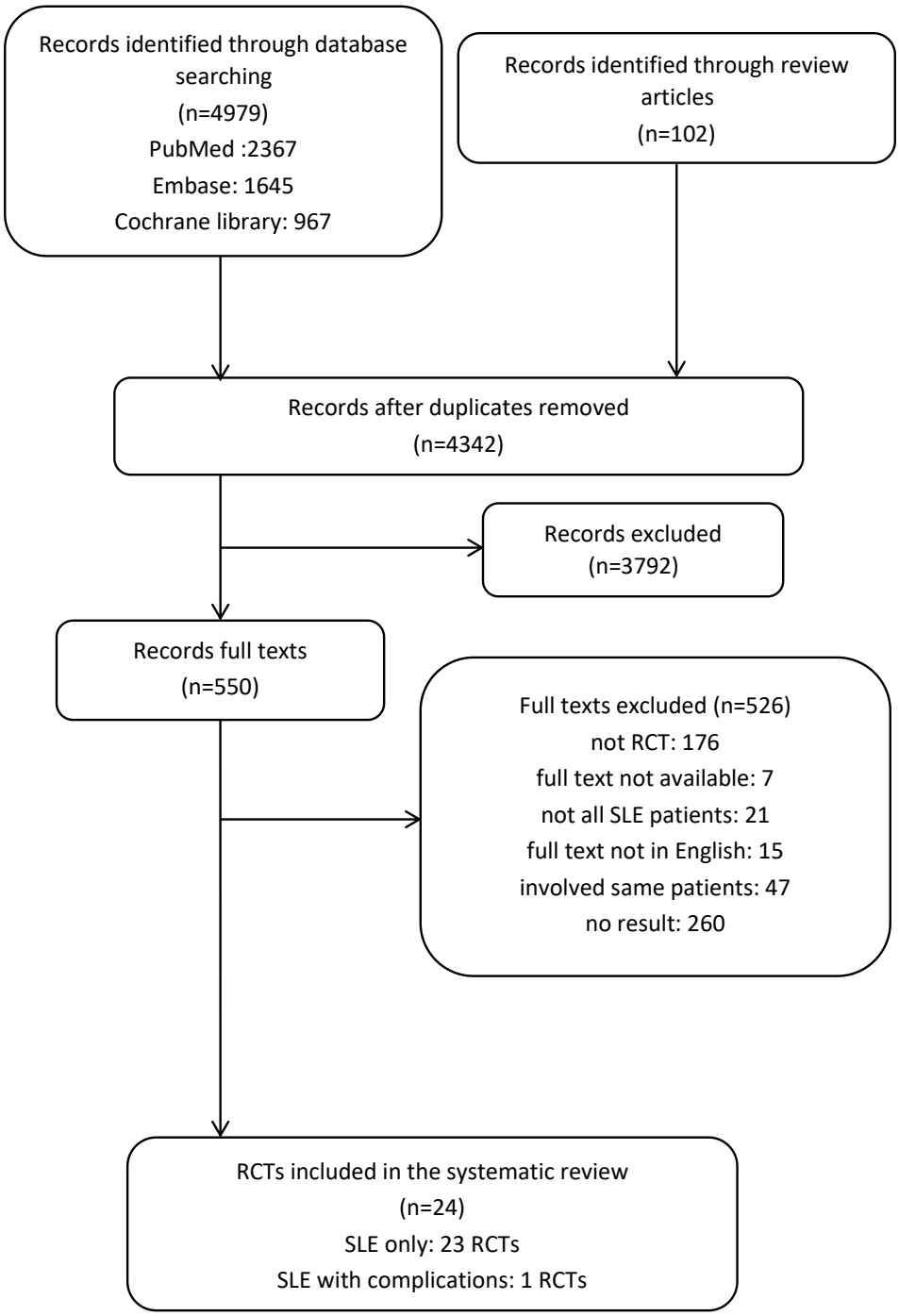
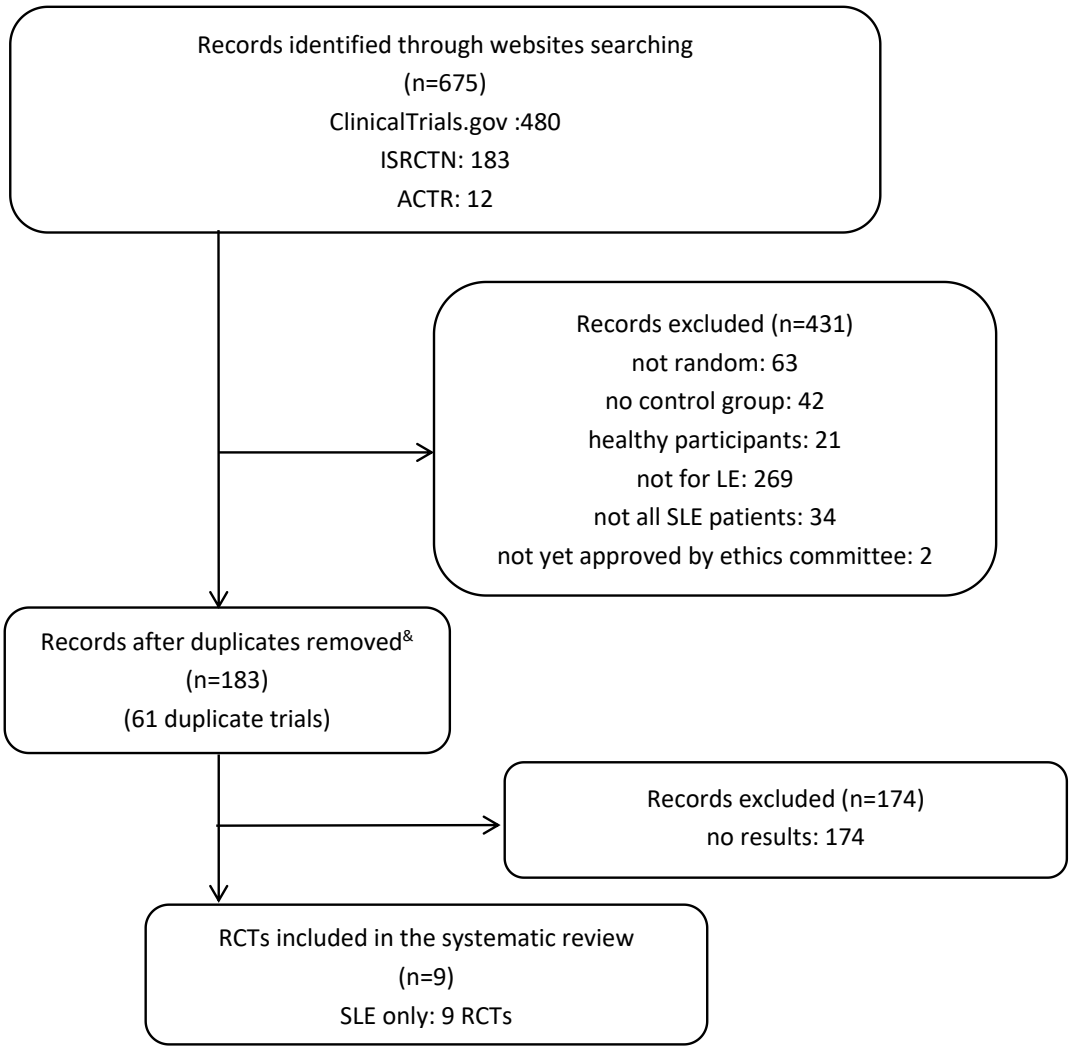


Figure S2. Record search and selection from clinical trials registries



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.

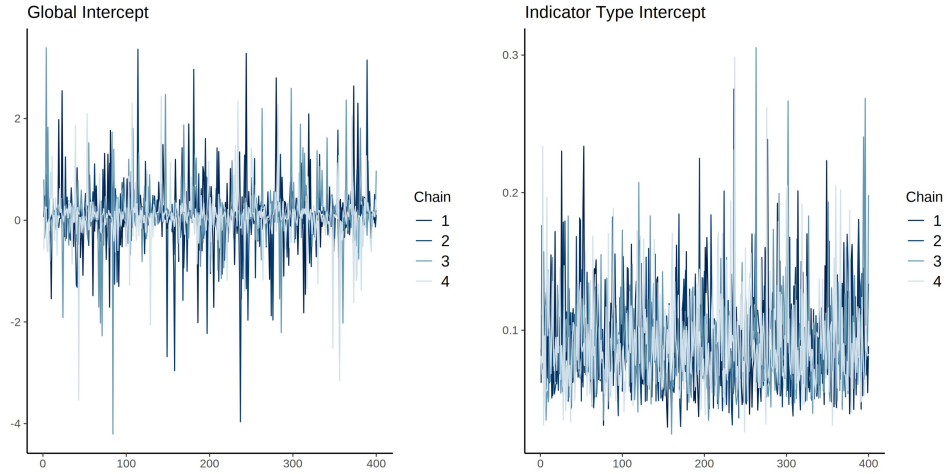
For discrete model:

```
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

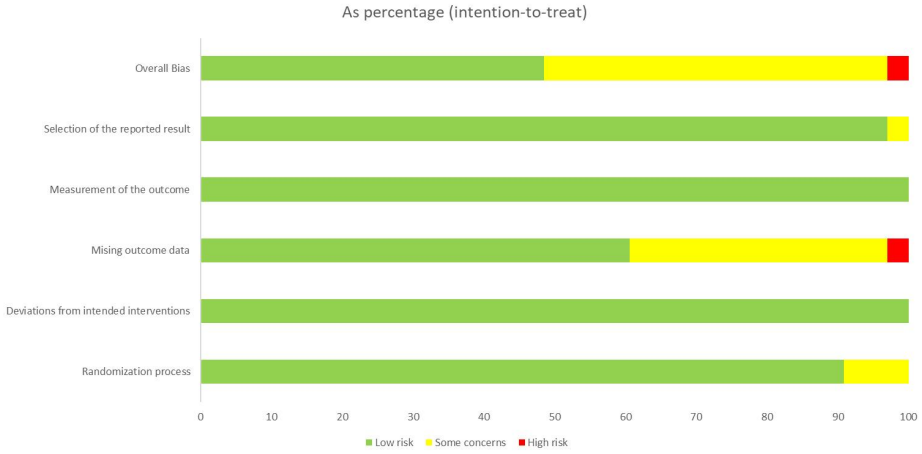
Appendix 9. Characteristics of included RCTs

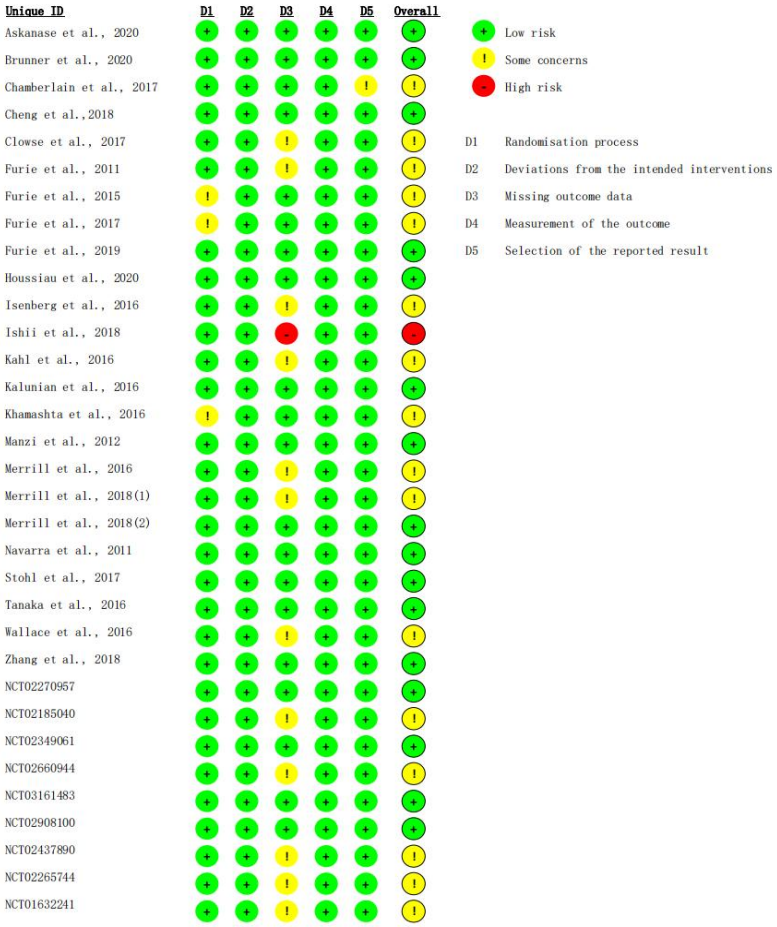
Table S8. Characteristics of included RCTs of SLE

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

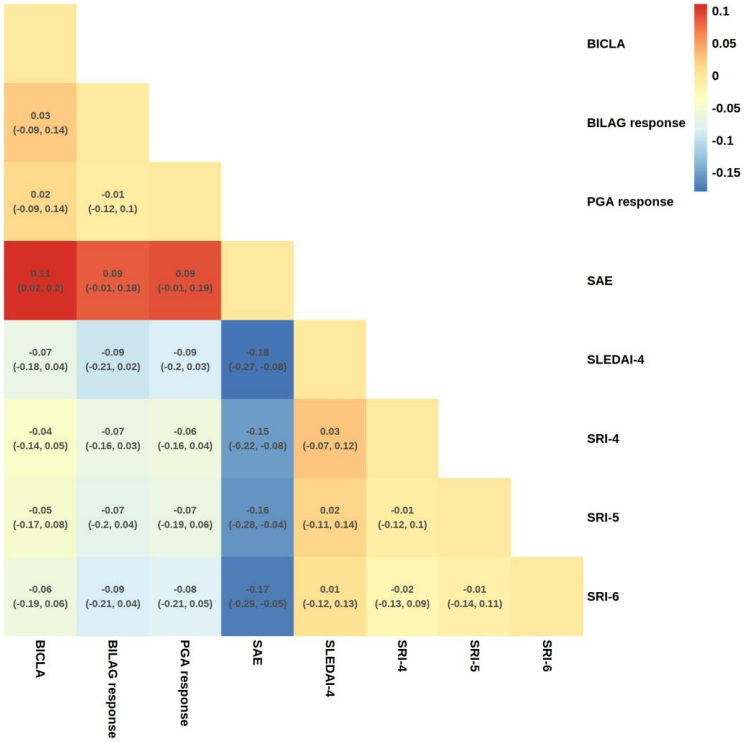




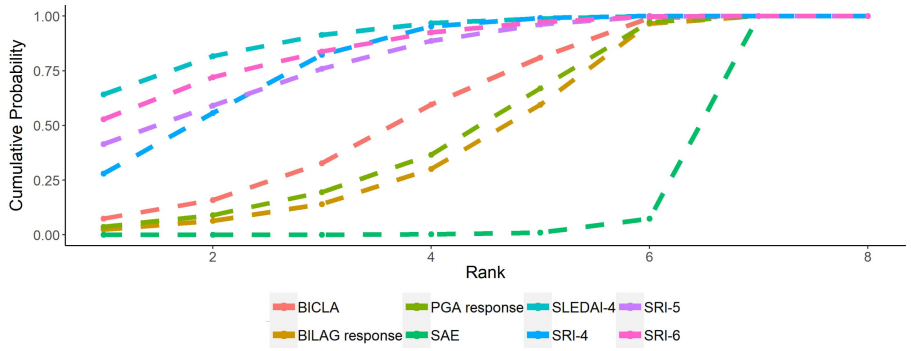
Appendix 11. Subgroup analyses of preference of indicators reporting response rate in pharmacological intervention-controlled RCTs

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

A



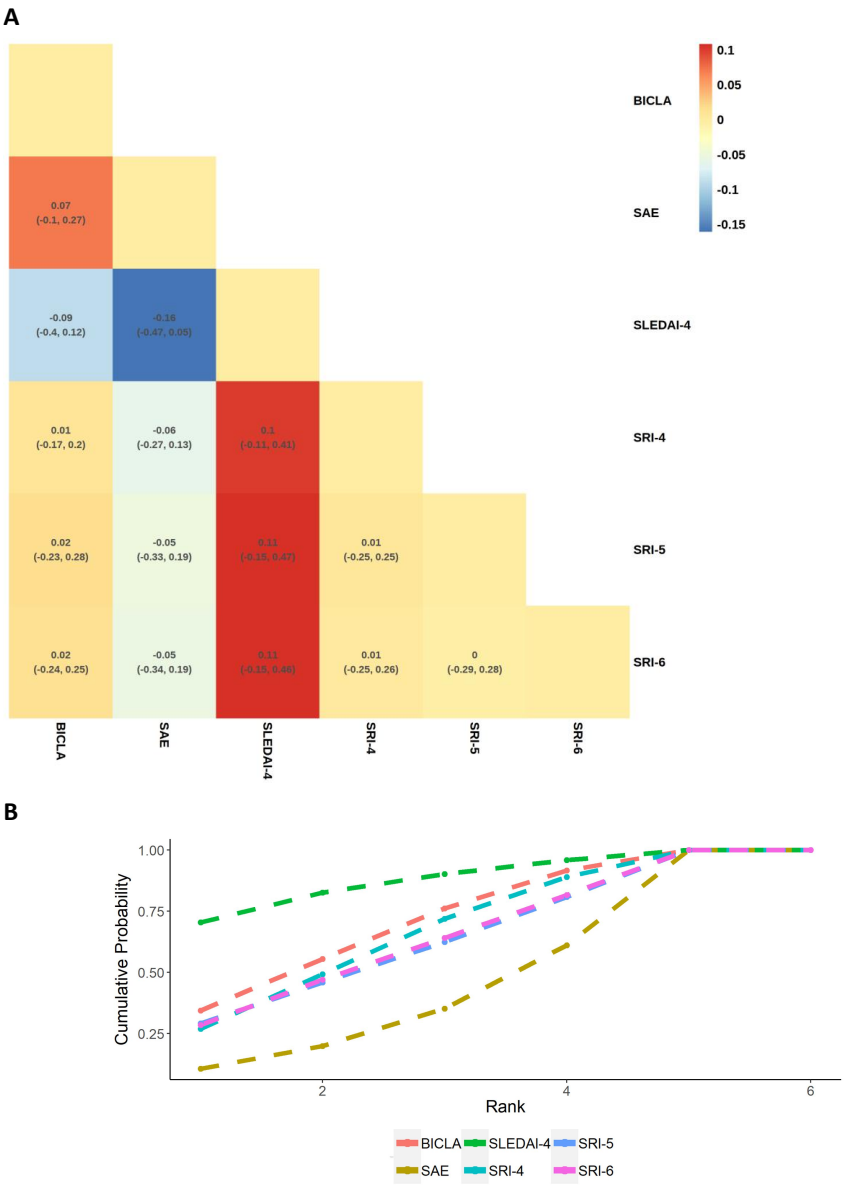
B



(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.*

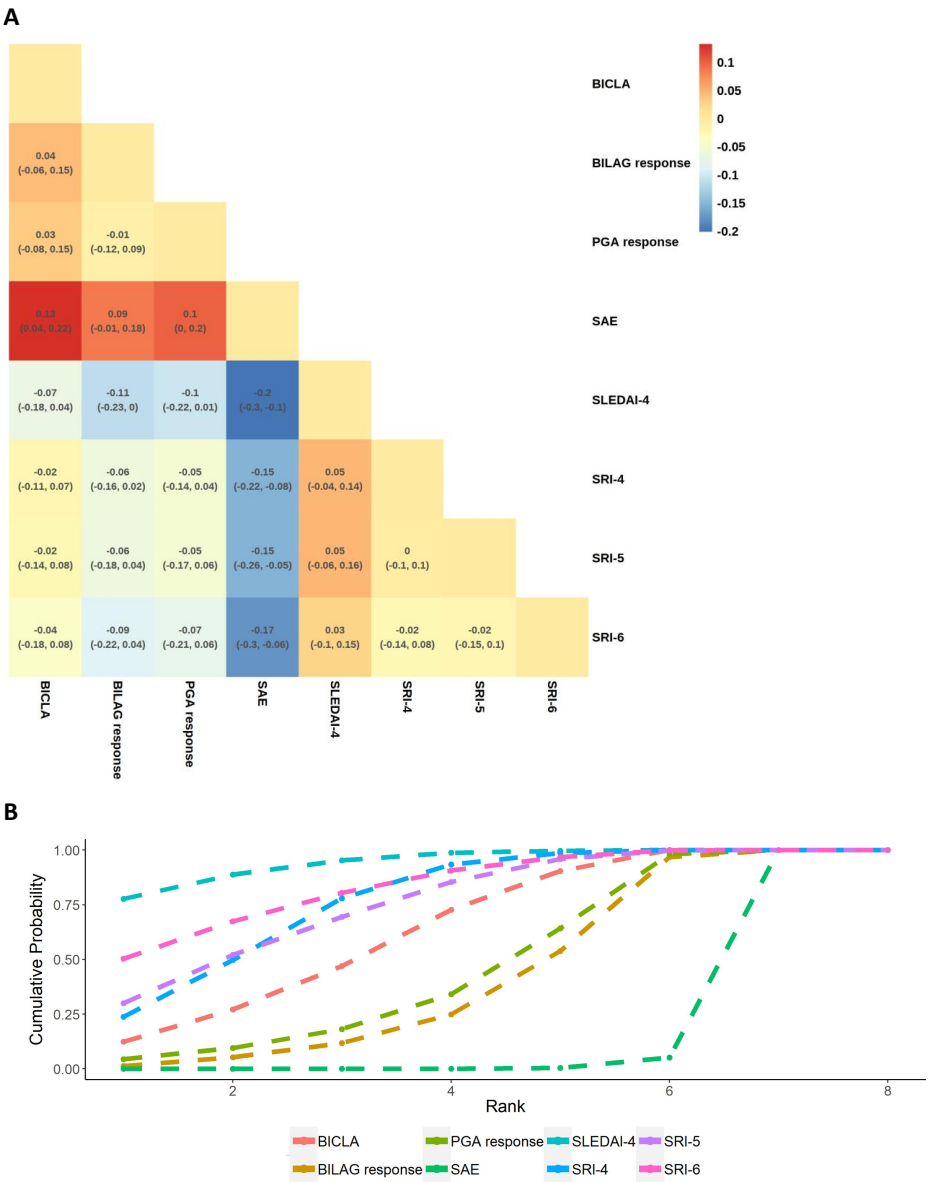
Figure S6. Preference of indicators reporting response rate in pharmacological intervention-controlled RCTs for all-severity SLE.



(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.*

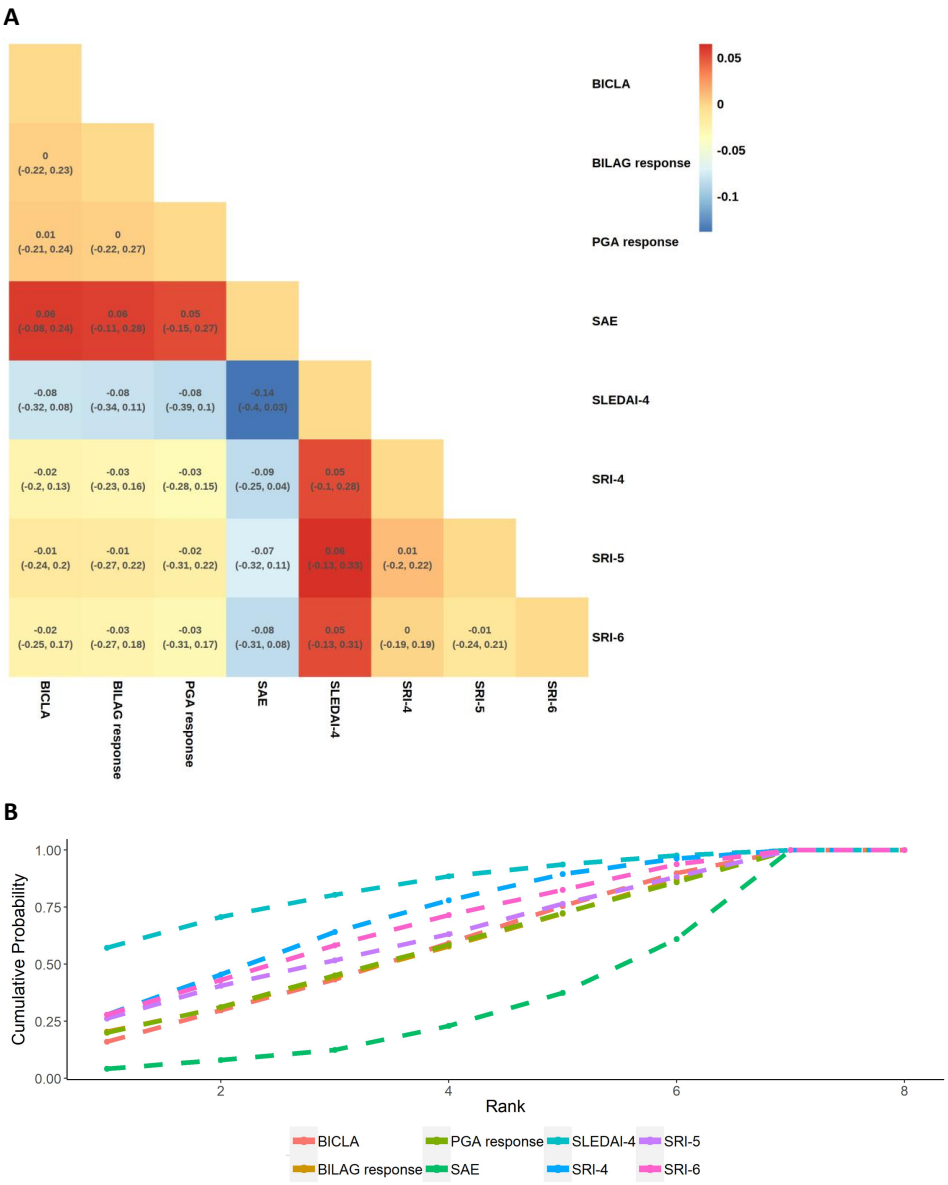
Figure S7. Preference of indicators reporting response rate in antibody pharmacological intervention-controlled RCTs for SLE.



(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.*

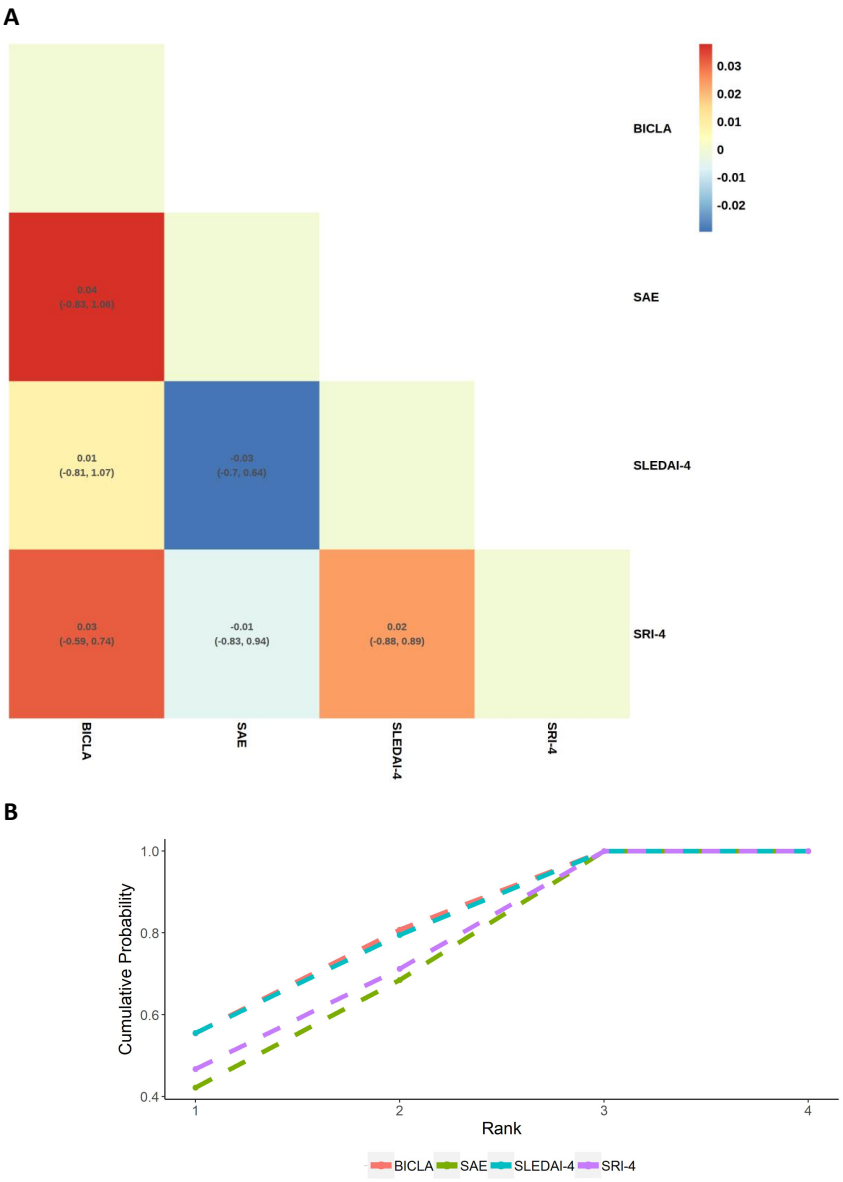
Figure S8. Preference of indicators reporting response rate in small molecule pharmacological intervention-controlled RCTs for SLE.



(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.*

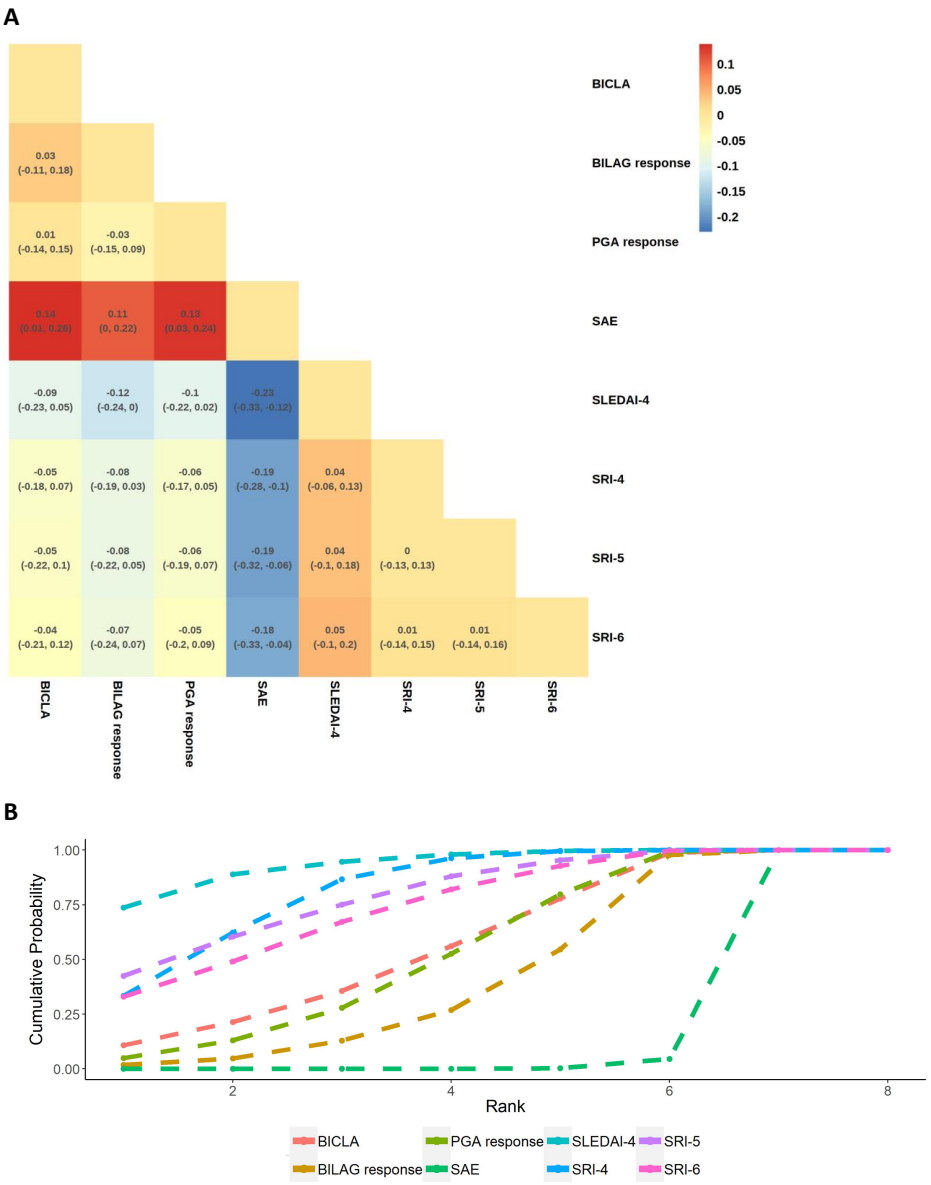
Figure S9. Preference of indicators reporting response rate in non-biologics pharmacological intervention-controlled RCTs for SLE.



(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.*

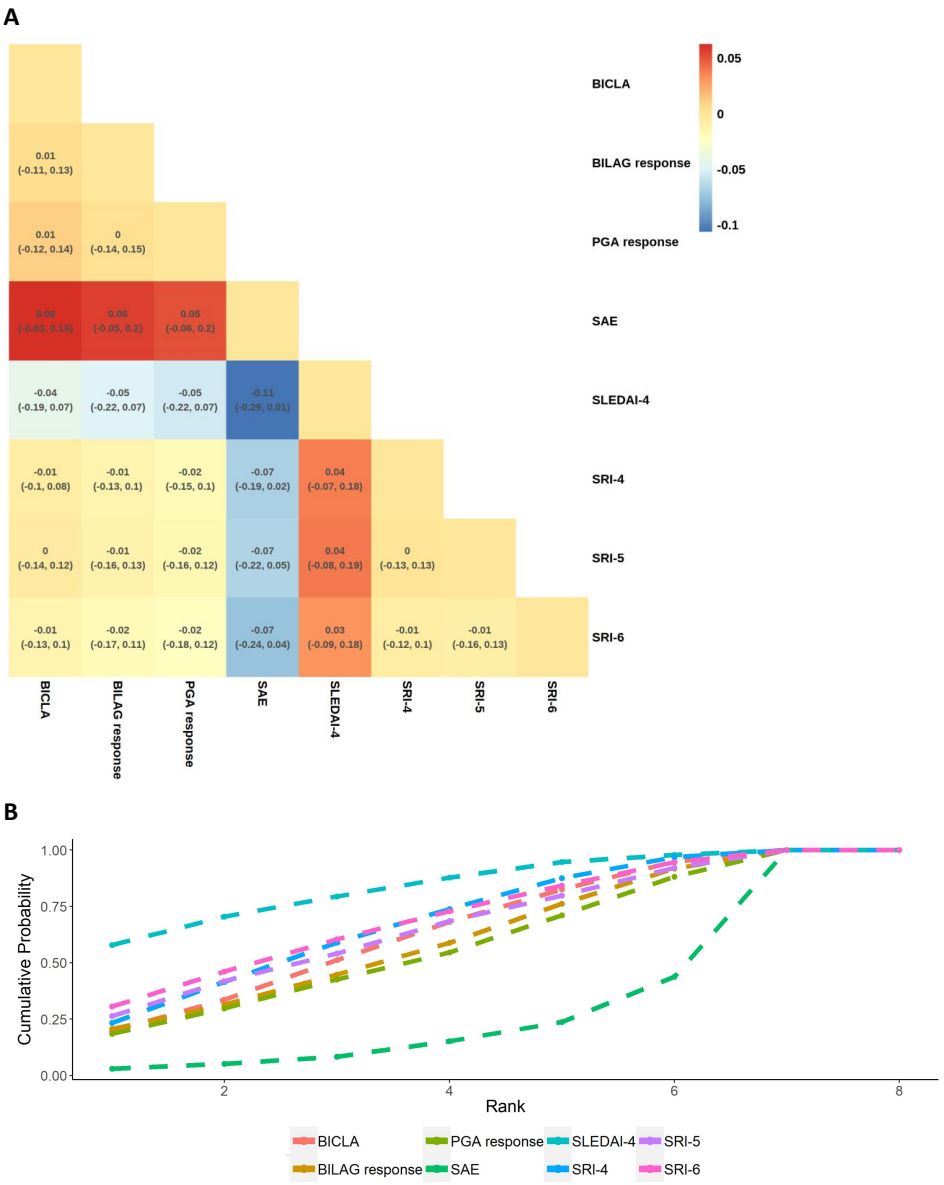
Figure S10. Preference of indicators reporting response rate in successful pharmacological intervention-controlled RCTs for SLE.



(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.*