

BMJ Open Efficacy and safety of pharmacological interventions for managing sickle cell disease in children and adolescents: protocol for a systematic review with network meta-analysis

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ABSTRACT

Introduction Sickle cell disease (SCD), an inherited haemoglobinopathy, has important impact on morbidity and mortality, especially in paediatrics. Previous systematic reviews are limited to adult patients or focused only on few therapies. We aim to synthesise the evidence on efficacy and safety of pharmacological interventions for managing SCD in children and adolescents.

Methods and analysis This systematic review protocol is available at Open Science Framework (doi:10.17605/OSF.IO/CWAE9). We will follow international recommendations on conduction and report of systematic reviews and meta-analyses. Searches will be conducted in PubMed, Scopus and Web of Science (no language nor time restrictions) (first pilot searches performed in May 2022). We will include randomised controlled trials comparing the effects of disease-modifying agents in patients with SCD under 18 years old. Outcomes of interest will include: vaso-occlusive crisis, haemoglobin levels, chest syndrome, stroke, overall survival and adverse events. We will provide a narrative synthesis of the findings, and whenever possible, results will be pooled by means of pairwise or Bayesian network meta-analyses with surface under the cumulative ranking curve analyses. Different statistical methods and models will be tested. Dichotomous outcomes will be reported as OR, risk ratio or HR, while continuous data will be reported as standard mean differences, both with 95% CI/credibility interval. The methodological quality of the trials will be evaluated using the Risk of Bias 2.0 tool, and the certainty of the evidence will be assessed with the Grading of Recommendations Assessment, Development and Evaluation approach.

Ethics and dissemination This study refers to a systematic review, so no ethics approval is necessary. We intent to publish our findings in international, peer-reviewed journal. Data will also be presented to peers in scientific events. Additionally, the results obtained in this study may contribute towards the update of therapeutic guidelines and for the development of health policies for SCD.

PROSPERO registration number CRD42022328471.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A systematic review following international recommendations for conduction and reporting will be performed.
- ⇒ Whenever possible, pairwise and network meta-analyses will be conducted.
- ⇒ Evidence on the effects of pharmacological interventions for managing sickle cell disease in children and adolescents will be balanced.
- ⇒ The certainty of the evidence will be assessed using Grading of Recommendations Assessment, Development and Evaluation.

INTRODUCTION

Sickle cell disease (SCD), a group of inherited blood disorders characterised by mutations in the beta-globin chain of haemoglobin that led to chronic haemolytic anaemia, affects over 3 million people worldwide, with an estimated 300 000 children born with SCD annually—of which 80% are in sub-Saharan Africa.^{1 2} This disorder is currently recognised as a global public health concern, being the leading cause of paediatric stroke (around 11% of unscreened and untreated children and adolescents with SCD will have at least one stroke by the age of 17 years). Other common permanent sequelae of SCD that significantly impair patients' educational attainment, employment status and quality of life include vaso-occlusive crises (VOCs), severe acute and chronic pain, silent cerebral infarcts (silent strokes), increased susceptibility to infections, cognitive morbidity and end-organ damage that occur across lifespan.^{3 4} SCD is also associated with premature death (median age 43 years; IQR 31.5–55),⁵ with an estimated under-5 mortality from the disease of over 50% in sub-Saharan Africa.⁶



Treatment of SCD is complex and requires early diagnosis, prevention of complications and management of end-organ damage.⁷ Therapeutic options are still limited in the market especially for the paediatric population. Although recent pipelines in the context of clinical trials demonstrated promising results with gene therapies towards the cure of SCD, bone marrow or stem cell transplantations are the only available curative approaches for these patients. Other non-pharmacological treatments as chronic blood transfusions can also be used to reduce symptoms; yet, these procedures are associated with several barriers including patients' eligibility, access, costs and related complications (eg, abnormally high levels of iron in the blood, reactions due to a mismatch between donors and recipients).^{8,9}

According to Tambor *et al*, some pharmacological interventions, collectively termed as disease-modifying therapies,⁹ intended to prevent or reduce the occurrence of SCD-related symptoms and complications and improve long-term outcomes, are available worldwide. Hydroxyurea, the most common drug used in this scenario, was first introduced in 1998 for treating adults with SCD. Although studies showed significant reductions of acute complications associated with the disease, this drug does not appear to protect against long-term cardiopulmonary disorders.⁷ More recently, between 2017 and 2020, other agents such as L-glutamine, voxelotor and crizanlizumab were approved by some regulatory agencies aiming at providing further options to manage the complications of SCD. In addition, several novel disease-modifying therapies are under evaluation in clinical trials.^{10,11}

With this overdue increase in the pipeline for SCD therapies, it is important to ensure a robust body of evidence on the efficacy and safety of these interventions, aiming at supporting more assertive decision-making process, both at an individual and society levels. However, updated comparative evidence on the effects of disease-modifying therapies for SCD comes primarily from systematic reviews with meta-analyses limited to adult patients^{12,13} or focused only on some selected therapies, curative approaches or prophylactic measures.¹⁴⁻¹⁷

Thus, given these important literature gaps, we aim to synthesise and critically appraise the current evidence on the effects of the available pharmacological interventions for managing SCD complications in children and adolescents by means of a broad systematic review with meta-analyses.

METHODS AND ANALYSIS

This protocol followed the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) reporting guideline¹⁸ (online supplemental material 1).

The systematic review will be performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, Network Meta-analysis extension (PRISMA-NMA) guidelines and

Cochrane Collaboration recommendations.¹⁹⁻²¹ Two authors will conduct, independently, all steps of studies' selection (title/abstract screening and study's eligibility) and data extraction. A third author will be consulted in case of discrepancies. This systematic review has been registered in the International Prospective Register of Systematic Reviews—PROSPERO (CRD42022328471) and is available at Open Science Framework at DOI: 10.17605/OSF.IO/CWAE9. Any modifications in the protocol during the systematic review will be reported (study has started: May 2022; anticipated completion date: September 2022; the project is ongoing).

Search strategy and eligibility criteria

The following electronic databases will be searched for references of clinical trials: MEDLINE (PubMed), Scopus and Web of Science. Search will not be limited by any filter tool, nor by year of publication, language or country. Search will be performed in each database from inception dates to date of the search (pilot searches performed in May 2022). Trial registration databases (ClinicalTrials.gov) and the reference lists included in the studies will also be searched as part of manual searching process. A comprehensive search strategy was developed using descriptors related to the drug names/classes, the clinical condition under investigation (SCD) and study design (randomised clinical trials), combined with Boolean operators AND and OR. The search strategies adapted for each database are available in online supplemental material 2.

Primary studies meeting all the following eligibility criteria (PICOS acronym) will be included for analyses:

- ▶ Population: children or adolescents (<18 years old) diagnosed with SCD, previously treated or untreated (newly diagnosed).
- ▶ Interventions: any pharmacological intervention (ie, drugs) intended to prevent or reduce the occurrence of SCD-related symptoms and complications used alone or in combination with other therapies, in any regimen or schedule. According to Tambor *et al*,⁹ these interventions can be broadly referred as 'disease-modifying therapies', as they seek to improve long-term outcomes.
 - The most common drugs in the field that are used in SCD include (ie, not restricted to): (1) interventions targeting haemoglobin S polymerisation through the induction of fetal haemoglobin (eg, hydroxyurea, hydroxycarbamide, decitabine, dimethyl butyrate, panobinostat, pomalidomide, lysine-specific demethylase); (2) interventions targeting haemoglobin S polymerisation through sickle red blood cell hydration (eg, dipyridamole, efaroxir, senicapoc, magnesium/sulfates); (3) other sickling inhibitors (eg, carboxyhaemoglobin, 5-hydroxymethyl-2-furfural, dimethyl adipimidate, cetiedil, deferiprone, desferrioxamine, voxelotor); (4) interventions targeting intracellular sickle red blood cell oxidative changes (eg, L-glutamine, endari, N-acetylcysteine, poloxamer);

- (5) interventions targeting abnormal cellular adhesion or vascular dysfunction (eg, immunoglobulins, rivapansel, crizanlizumab).¹¹
- ▶ **Comparator:** any pharmacological intervention or placebo/usual care.
 - ▶ **Outcomes:** we will focus on a minimum core outcome set for SCD adapted from Tambor *et al*,⁹ which includes the measurement: VOC (acute sickle cell pain frequency, duration, intensity), haemoglobin levels, chest syndrome, stroke or cerebrovascular accident, neurocognitive function, frequency of hospitalisation, emergency department/acute care visit, need for blood transfusion, cause-specific survival/mortality, event-free survival, health-related quality of life, safety (adverse events, tolerability/adherence). All evidence relevant to these outcomes of interest will be captured, without timing or effect measure limitations, in any clinical context.
 - ▶ **Study design:** randomised controlled trials (RCTs) presenting an international register number and with results partially or completely published in peer-reviewed journals.

Studies on curative approaches (ie, transplantation, gene therapy), non-pharmacological treatments (ie, blood transfusions, supplements), supportive care with analgesics or complementary medicine; studies on prophylaxis, parasite reduction ratio or malaria incidence/prevalence; other study designs (observational studies, reviews, pharmacokinetic trials, non-randomised trials); articles assessing only economic outcomes, incomplete or not published peer-reviewed evidence; or articles in non-Roman characters (ie, Arabic, Chinese, Cyrillic, Greek, Hebrew, Japanese, Korean, Tamil and Thai script) will be excluded from this systematic review.

Study selection

Records retrieved from the databases will be exported to a reference management program (EndNote, Clarivate, London) where further duplicates will be removed by one author. Thereafter, the references will be exported to an Excel file where management of references (ie, both phases of screening (title/abstract reading) and study's eligibility (full-text appraisal)) and data extraction will be done using different Excel sheets (Microsoft, Redmond, Washington, USA). In the first step, titles and abstracts of the studies will be independently screened by two review authors to identify those that potentially meet the inclusion criteria (ie, screening phase). Any disagreements will be resolved by discussion with a third reviewer arbitrating in the circumstance of unresolved discrepancies. Then, the full text of the potentially eligible studies will be retrieved and independently assessed for eligibility by two review members (ie, second phase). To ensure transparency, the process of selection will be summarised using a PRISMA flow chart.

Data extraction and methodological quality assessment

A standardised form in Excel sheets will be used by two reviewers who will independently extract information

on: articles' general data (authors' name, year of publication, country, sample size); participants and their characteristics (age, diagnosis (including SCD genotypes), comorbidities (if any), previous treatments); details of the intervention or exposition and controls (drugs, regimen); study design; clinical outcome results and times of measurement. If necessary, we will collect indirect data from figures and charts, adapting their interpretation from two different authors by a consensus and authors of original articles will also be contacted for further information and data.

The methodological quality of the included studies will be evaluated using the Cochrane's tool for assessing the risk of bias in randomised trials of interventions (RoB 2.0).¹⁹ This tool is structured into a fixed set of domains of bias focusing on different aspects of trial design, conduct and reporting. It incorporates the evaluation of the following sources of bias for each outcome of interest (ie, aiming at linking risk of bias to the effect estimates): selection, performance, detection, attrition, reporting bias. These domains are finally judged as having 'low risk of bias', 'some concerns' or 'high risk of bias'.¹⁹ Results of the RoB 2.0 will be reported in tables and diagrams.

Statistical analyses

We will provide a narrative synthesis of the findings from the included studies, structured around the type of intervention, target population characteristics and type of outcome. Whenever possible, we will pool the results in pairwise meta-analyses or network meta-analyses (NMAs).

For the pairwise meta-analyses, different statistical methods (eg, Mantel-Haenszel, inverse of variance using DerSimonian and Laird) and models (random or fixed-effects) will be tested according to the available raw data. Dichotomous outcomes will be reported as OR, risk ratio or HR, while continuous data will be reported as standard mean differences, both with a 95% CI. P values of <0.05 (two tailed) will indicate a statistically significant difference between groups of treatments (intervention vs control).^{19 21} Between-trials heterogeneity will be estimated using the inconsistency relative index I^2 ($I^2 >50\%$ indicates high heterogeneity). Tau and tau² measures will be used to estimate the distribution of the true effect sizes and to compute the prediction intervals (PIs) for all meta-analyses presenting a high and significant heterogeneity ($I^2 >50\%$; $p < 0.05$). The calculation of PI will be done in preformatted Excel sheets considering the number of studies, the mean effect (random-effect weights), the upper effect of mean effect and tau² in log units (normal approximation).^{22 23} We additionally propose calculating the number needed to treat (NNT) defined as the average number of patients who need to be treated to obtain the outcome under analysis in one additional person (NNT with 95% CI will be calculated according to Altman and Deeks).^{24 25}

NMA, also called multiple or mixed treatment meta-analysis, is a technique recommended by the International Society for Pharmacoeconomics and Outcome Research to simultaneously compare the effects (eg, safety, efficacy)



among different treatments,²⁶ including both direct (ie, based on existing comparative studies in the literature) and indirect (ie, based on common comparators) evidence.²⁷ To obtain pooled effect sizes, a random-effect model based on the Markov Chain Monte Carlo simulation method will be used. To be consistent with the treatment arms provided by the included trials and to avoid the occurrence of potential biases, the geometry of the treatment network will follow the complexity level of the reports of the primary studies (ie, arm-level entry data). For the inclusion of multiple-arm studies, correlations for the likelihood between arms will be considered. A common heterogeneity parameter will be assumed for all comparisons. A consistency model will be built for each outcome of interest, and the treatments' relative effect sizes will be calculated as OR or mean difference (depending on the type of outcome) and reported with their 95% credibility intervals. We will use a conservative analysis of non-informative priors. Effect models will be selected according to the lowest deviance information criteria. Convergence will be attained based on visual inspection of Brooks-Gelman-Rubin plots and potential scale reduction factor (PSRF) ($1 < \text{PSRF} \leq 1.05$). To increase the estimate precision of the relative effect sizes of comparisons and to properly account for correlations between multiarm trials, rank probabilities involving all therapies will be built for each outcome of interest. These rank probabilities are based on the location, spread and overlap of the posterior distribution of the relative treatment effects and, together with effect sizes, enabled conclusions to be drawn. To better represent the rank results, surface under the cumulative ranking curve analysis will be calculated.^{28 29} To estimate the robustness of the networks, inconsistency, defined as the difference between the pooled direct and indirect evidence for a particular comparison, will be assessed using node-splitting analysis. In this analysis, the evidence on a specific node (the split node) is tested (p values of < 0.05 reveal significant inconsistencies in the network that should be further investigated). The geometry of the networks will be assessed according to Tonin *et al.*³⁰ Analyses will be performed in the software Comprehensive Meta-analysis V.2.0, Addis V.1.16.6 (Aggregate Data Drug Information System; <http://drugis.org/index>) and R/RStudio.

Whenever possible, additional subgroup analyses will be performed, but not limited to subgroups defined by age, sickle cell genotype and country. We also plan to perform sensitivity analysis to evaluate the impact of the individual studies on the meta-analyses (ie, between-trials heterogeneity).

Grading of Recommendations Assessment, Development and Evaluation

The certainty (ie, 'quality') of the evidence at the outcome level will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.³¹ Outcomes for a given comparison will initially be rated as high quality (+4) and then downgraded into moderate (+3), low (+2) or very low (+1) quality based on five main criteria

(risk of bias, imprecision, indirectness, heterogeneity, publication bias). 'High level' of evidence means that we are very confident that the true effect of an intervention lies close to that of the estimate effect (ie, is unlikely that new published data change these conclusions); this can lead to strong clinical recommendations on a given topic. Conversely, 'very low' evidence is associated with uncertainty about the effects of an intervention (ie, new data are likely to change the conclusions). The results of GRADE will be presented in tables and diagrams.

Patient and public involvement

No patient involved.

Ethics and dissemination

No ethical approval is required for this project as we will collect and assess data from published literature (ie, not linked to specific individuals).

The growing dissemination in the scientific literature on the efficacy and safety of the new developed therapies to manage SCD requires further critical analyses to ground more assertive health decisions and support the development of practical recommendations. As far as we are aware, this systematic review will allow, for the first time, to synthesise the findings from RCTs (primary studies considered as gold standard for the straightforward comparison of interventions) addressing the effects of disease-modifying agents in children and adolescents with SCD. Further reviews including other study designs (eg, observational studies), SCD interventions and populations may be conducted in the future grounded on our results. Our systematic review will follow international recommendations on conduction and report, with steps being performed by two reviewers, independently. Three electronic databases (PubMed, Scopus, Web of Science) covering most of the biomedical sciences content will be searched using broad search strategies adapted to the features of each database. Whenever possible, results of outcomes of interest will be quantitatively synthesised by means of meta-analyses around a given comparison (pairwise meta-analyses or NMAs). The certainty of the body of evidence will be critically evaluated using GRADE. We, thus, believe that our findings may directly contribute towards the update of therapeutic guidelines and for the development of health policies for SCD in children and adolescents. As dissemination strategy, we intent to write and submit a scientific paper grounded on the results obtained from the systematic review and meta-analyses to an international, peer-reviewed, leading journal in the field. Additionally, data will be presented to peers in scientific events (congress, conferences) as oral or poster communications.

Contributors FST—conceptualisation, methodology, writing (original draft). CG—writing (review and editing). FF-L—conceptualisation, supervision, writing (review and editing). JAGF—writing (review and editing). MD—writing (review and editing). MB—conceptualisation, supervision, writing (review and editing).

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Disclaimer Funders have no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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 required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplemental Material

1. PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* **2015** 4:1

Section/topic	#	Checklist item	Pa		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X		Pg. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		X	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		Pg. 2
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		Pg. 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		Pg. 9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		X	Not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	X		Pg. 9
Sponsor	5b	Provide name for the review funder and/or sponsor	X		Pg. 9
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X		Pg. 9
INTRODUCTION					

Section/topic	#	Checklist item	Pa		Page number(s)
			Yes	No	
Rationale	6	Describe the rationale for the review in the context of what is already known	X		Pg. 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		Pg. 4-5
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X		Pg. 5
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X		Pg. 5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X		Pg. 5 and suppl material
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		Pg 5-6
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X		Pg 5-6
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X		Pg 5-6
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X		Pg 5-6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		Pg 5-6

Section/topic	#	Checklist item	Pa		Page number(s)
			Yes	No	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X		Pg 6
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		Pg 6-7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	X		Pg 6-7
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		Pg 6-7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		Pg 6-7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		Pg 6-7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		Pg 7

2. Search strategies

Database	Strategy
<p>PubMed</p>	<p>#1 drug[TIAB] OR “pharmacological treatment”[TIAB] OR “pharmacological intervention”[TIAB] OR “drug therapy”[MH] OR “disease modifying”[TIAB] OR antisickling[TIAB] OR desickling[TIAB] OR “sickling inhibitor”[TIAB] OR hydroxycarbamide[TIAB] OR hydroxyurea[TIAB] OR hydroxyurea[MH] OR carboxyhemoglobin[TIAB] OR carboxyhemoglobin[MH] OR decitabine[TIAB] OR decitabine[MH] OR “dimethyl butyrate”[TIAB] OR HQK-1001[TIAB] OR panobinostat[TIAB] OR panobinostat[MH] OR pomalidomide[TIAB] OR pomalidomide[NM] OR “lysine-specific demethylase”[TIAB] OR LSD1[TIAB] OR dipyridamole[TIAB] OR dipyridamole[MH] OR senicapoc[TIAB] OR senicapoc[NM] OR voxelotor[TIAB] OR voxelotor[NM] OR GBT440[TIAB] OR AES-103[TIAB] OR “5-hydroxymethyl-2-furfural”[TIAB] OR 5-HMF[TIAB] OR glutamine[TIAB] OR glutamine[MH] OR endari[TIAB] OR acetylcysteine[TIAB] OR acetylcysteine[MH] OR crizanlizumab[TIAB] OR crizanlizumab[NM] OR rivapansel[TIAB] OR rivapansel[NM] OR immunoglobulins[TIAB] OR poloxamer[TIAB] OR poloxamer[MH] OR adipimidate[TIAB] OR “dimethyl adipimidate”[MH] OR efaproxiral[TIAB] OR efaproxiral[NM] OR cetiedil[TIAB] OR cetiedil[NM] OR velaresol[TIAB] OR BW12C[TIAB] OR BW12C79[TIAB] OR “5-(2-formyl-3-hydroxyphenoxy)pentanoic acid”[TIAB] OR deferiprone[TIAB] OR deferiprone[MH] OR desferrioxamine[TIAB] OR deferoxamine[MH] OR deferasirox[TIAB] OR deferasirox[MH] OR prasugrel[TIAB] OR “prasugrel hydrochloride”[MH] OR ticagrelor[TIAB] OR ticagrelor[MH] OR warfarin[TIAB] OR warfarin[MH] OR heparin[TIAB] OR heparin[MH] OR rivaroxaban[TIAB] OR rivaroxaban[MH] OR apixaban[TIAB] OR apixaban[NM] OR edoxaban[TIAB] OR edoxaban[NM] OR dabigatran[TIAB] OR dabigatran[MH] OR sevuparin[TIAB] OR sevuparin[NM] OR tinzaparin[TIAB] OR tinzaparin[MH] OR tucaresol[TIAB] OR tucaresol[NM] OR niprisan[TIAB] OR niprisan[NM] OR montelukast[TIAB] OR montelukast[NM] OR canakinumab[TIAB] OR canakinumab[NM]</p> <p>#2 “Anemia, Sickle Cell”[MH] OR sickle[TIAB] OR sickling[TIAB] OR “hemoglobin S disease”[TIAB]</p> <p>#3 children[TIAB] OR child[TIAB] OR child[MH] OR infant*[TIAB] OR infant[MH] OR pediatric[TIAB] OR kid[TIAB] OR adolescent*[TIAB] OR adolescent[MH] OR young[TIAB] OR toddler*[TIAB] OR teenager*[TIAB]</p> <p>#4 (clinical[TIAB] AND trial[TIAB]) OR “clinical study”[TIAB] OR controlled[TIAB] OR “clinical trial”[PT] OR random*[TIAB] OR “random allocation”[MH]</p> <p>#1 AND #2 AND #3 AND #4</p>
<p>Scopus</p>	<p>#1 TITLE-ABS(“pharmacological treatment” OR “pharmacological intervention” OR “disease modifying” OR antisickling OR desickling OR “sickling inhibitor” OR hydroxycarbamide OR hydroxyurea OR carboxyhemoglobin OR decitabine OR “dimethyl butyrate” OR HQK-1001 OR panobinosta OR pomalidomide OR “lysine-specific demethylase” OR LSD1 OR dipyridamole OR senicapoc OR voxelotor OR GBT440 OR AES-103 OR “5-hydroxymethyl-2-furfural” OR 5-HMF OR glutamine OR endari OR acetylcysteine OR crizanlizumab OR rivapansel OR immunoglobulins OR poloxamer OR adipimidate OR efaproxiral OR cetiedil OR velaresol OR BW12C OR “5-(2-formyl-3-hydroxyphenoxy)pentanoic acid” OR deferiprone OR desferrioxamine</p>

	<p>OR deferasirox OR prasugrel OR ticagrelor OR warfarin OR heparin OR rivaroxaban OR apixaban OR edoxaban OR dabigatran OR sevuparin OR tinzaparin OR tucaresol OR niprisan OR montelukast OR canakinumab)</p> <p>#2 TITLE-ABS-KEY(sickle OR sickling OR “hemoglobin S disease”)</p> <p>#3 TITLE-ABS-KEY(children OR child OR infant* OR pediatric OR kid OR adolescent* OR young OR toddler* OR teenager*)</p> <p>#4 TITLE-ABS(“clinical trial” OR “clinical study” OR controlled OR random*)</p> <p>#1 AND #2 AND #3 AND #4</p>
Web of Science	<p>#1 TS=(“pharmacological treatment” OR “pharmacological intervention” OR “disease modifying” OR antisickling OR desickling OR “sickling inhibitor” OR hydroxycarbamide OR hydroxyurea OR carboxyhemoglobin OR decitabine OR “dimethyl butyrate” OR HQK-1001 OR panobinosta OR pomalidomide OR “lysine-specific demethylase” OR LSD1 OR dipyridamole OR senicapoc OR voxelotor OR GBT440 OR AES-103 OR “5-hydroxymethyl-2-furfural” OR 5-HMF OR glutamine OR endari OR acetylcysteine OR crizanlizumab OR rivipansel OR immunoglobulins OR poloxamer OR adipimidate OR efaproxiral OR cetiedil OR velaresol OR BW12C OR “5-(2-formyl-3-hydroxyphenoxy)pentanoic acid” OR deferiprone OR desferrioxamine OR deferasirox OR prasugrel OR ticagrelor OR warfarin OR heparin OR rivaroxaban OR apixaban OR edoxaban OR dabigatran OR sevuparin OR tinzaparin OR tucaresol OR niprisan OR montelukast OR canakinumab)</p> <p>#2 TS=(sickle OR sickling OR “hemoglobin S disease”)</p> <p>#3 TS=(children OR child OR infant* OR pediatric OR kid OR adolescent* OR young OR toddler* OR teenager*)</p> <p>#4 TS=(“clinical trial” OR “clinical study” OR controlled OR random*)</p> <p>#1 AND #2 AND #3 AND #4</p>