

## Appendix D. Systematic literature review protocol for transfusions.

### Search protocol

#### Objective

This search protocol aims to supplement new evidence on the treatment effects of transfusion used for preventing crises in sickle cell disease (SCD) patients in adults and adolescents for previous systematic literature review (led by Thomas Statistical Consultants). The search strategy and concept are modified from a recent systematic review by Sins et al.<sup>1</sup> and Fortin et al.<sup>2</sup>. The strategy has been developed to fulfil updated eligibility criteria (Table 1) and retrieve single-arm trials.

Table 1. Eligibility criteria

Criteria	Description
<b>Population</b>	Trials that included SCD patients aged 16 and above
<b>Interventions</b>	<ul style="list-style-type: none"> <li>• Red blood cell transfusions</li> <li>• Other types of transfusions</li> </ul>
<b>Comparators</b>	<ul style="list-style-type: none"> <li>• Placebo or best medical care</li> <li>• Interventions included in previous systematic review</li> </ul>
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Pain, crisis and VOC (frequency, intensity and duration in one event)</li> <li>• Hospital admission, including emergency department (ED) and nurse visits</li> <li>• SCD complications, including acute chest syndromes</li> <li>• Analgesic use</li> <li>• Adverse events*</li> </ul>
<b>Study design</b>	<ul style="list-style-type: none"> <li>• Randomized controlled trials (RCTs)</li> <li>• Single-arm studies</li> </ul>
<b>Language</b>	<ul style="list-style-type: none"> <li>• Only studies published in English</li> </ul>

\*In addition to efficacy outcomes, adverse events are of interest for the review, but will not be used as study selection criteria

#### Resources

##### *Electronic databases*

Studies will be identified by searching the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- Medical Literature Analysis and Retrieval System Online (MEDLINE)
- Excerpta Medica database (Embase)

##### *Hand-searches*

<sup>1</sup> Sins JWR, Mager DJ, Davis S, Biemond BJ, Fijnvandraat K: **Pharmacotherapeutical strategies in the prevention of acute, vaso-occlusive pain in sickle cell disease: a systematic review**. *Blood advances* 2017, 1(19):1598-1616.

<sup>2</sup> Fortin PM, Hopewell S, Estcourt LJ. **Red blood cell transfusion to treat or prevent complications in sickle cell disease: an overview of Cochrane reviews**. *Cochrane Database of Systematic Reviews* 2018, Issue 8. Art. No.: CD012082. DOI: 10.1002/14651858.CD012082.pub2.

- ClinicalTrial.gov

### Search strategy

Search strategies have been developed individually for CENTRAL, MEDLINE, Embase and ClinicalTrial.gov and their results are listed in Appendix 1-4. The concept of a search strategy is elaborated using MEDLINE as an example (Table 2). The search strategy was constructed according to the criteria (e.g. outcomes, population, intervention and study design) using MeSH or Emtree terms (thesaurus terms, headings and subheadings) and text words to retrieve potential references.

Table 2. Search strings and concepts

No	Searches	Results	
1	anemia, sickle cell/	19329	Population
2	hemoglobin, sickle/	3011	
3	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	27120	
4	1 or 2 or 3	27602	
5	Blood Transfusion/	48056	Intervention
6	Erythrocyte Transfusion/	8033	
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	90906	
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	47785	
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	35184	
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	26829	
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1217	
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	24060	
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	183648	
14	Blood Component Transfusion/	3477	
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	16726	

16	14 not 15	3229	
17	ERYTHROCYTES/	128578	
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	216650	
19	17 or 18	258199	
20	16 and 19	834	
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	13177	
22	((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	3326	
23	13 or 20 or 21 or 22	188025	
24	exp pain/	362648	
25	(pain or painfull).tw.	547392	
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	66169	Outcome
27	exp length of stay/	77857	
28	(hospital adj3 (admission or stay)).tw.	104873	
29	(patient adj3 (admission or stay)).tw.	6507	
30	or/24-29	901074	
31	4 and 23 and 30	848	
32	clinical trial/	512148	
33	(clinic adj5 trial*).ti,ab,sh.	1010	
34	single blind method/	25632	
35	double blind method/	147368	
36	random allocation/	95709	
37	placebos/	34063	
38	(placebo or random*).ti,ab,sh.	1263924	
39	randomized controlled trial/	467730	
40	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	786522	
41	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	145215	
42	randomi?ed control trial*.tw.	6481	
43	or/32-42	1565168	

44	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	2187051	Single-arm studies filter
45	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	1071161	
46	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	615678	
47	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	340559	
48	Clinical Trial, Phase I.pt.	18409	
49	Clinical Trial, Phase II.pt.	29604	
50	Clinical Trial, Phase III.pt.	14110	
51	(registry or registries).ti,ab,kf,hw.	139501	
52	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	53439	
53	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	114108	
54	(nonrandom* or non-random*).ti,ab,kf.	34084	
55	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	2644	
56	(all adj3 received).ab.	41192	
57	or/44-56	3114626	
58	31 and 43	120	
59	31 and 57	278	

## Search results

The numbers of references retrieved by search strategies from three databases are listed below. The search date was from the earliest date to 29<sup>th</sup> Aug 2018 in all databases. In total, there were 1,631 references retrieved.

### CENTRAL

- Number of references related to controlled trials: 332

### MEDLINE

- Number of references related to randomised controlled trials: 120
- Number of references related to single-arm studies: 279

#### Embase

- Number of references related to randomised controlled trials: 245
- Number of references related to single-arm studies: 599

#### ClinicalTrial.gov

- Number of references: 56

#### Deduplication

Duplicates were identified firstly by 'find duplicates' function in Endnote X8 and then double-checked manually by sorting author, title, volume and issue. After that, all references were de-duplicate against references retrieved from previous systematic review. This left 825 references from the electronic databases to be screened.

In terms of references from ClinicalTrial.gov, there were only 16 references left to be screened after deduplication.

In total, there are 841 references to go through during the title and abstract screening stage.

## Appendix 1. Search strategy and results for CENTRAL database

Search Strategy:

#	Searches	Results
#1	MeSH descriptor: [Anemia, Sickle Cell] this term only	583
#2	MeSH descriptor: [Hemoglobin, Sickle] this term only	19
#3	(sickle cell or sickle h*emoglobin or drepanocyt* or drepanotic or drepanocytemia or h*emoglobin-s or Hb-S or sickle an*emia or meniscocytosis):ti,ab,kw	4790
#4	#1 or #2 or #3	4790
#5	MeSH descriptor: [Blood Transfusion] this term only	1766
#6	MeSH descriptor: [Erythrocyte Transfusion] explode all trees	564
#7	((blood or erythrocyte* or "red cell*" or "red blood cell*" or RBC*) near/5 (transfus* or infus* or unit*))	14775
#8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) near/5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program* or therapy)):ab	30189
#9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)):ti	3612
#10	("allogeneic blood" or (unit* near/2 blood) or "allogenic blood" or (blood near/2 exposure) or "donor blood" or "blood product*" or "blood component*" or "blood support")	3365
#11	hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*	107
#12	(red cell* or erythrocyte* or blood or RBC*) and transfus*:ti	2434
#13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	41927
#14	MeSH descriptor: [Blood Component Transfusion] this term only	115
#15	MeSH descriptor: [Erythrocytes] this term only	1478
#16	(red cell* or red blood cell* or erythrocyte* or RBC*)	12756
#17	#14 and (#15 or #16)	39
#18	#13 or #17	41927
#19	MeSH descriptor: [Pain] explode all trees	42323
#20	(pain or painfull):ti,ab,kw	124349

#21	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises):ti,ab,kw	4404
#22	MeSH descriptor: [Length of Stay] explode all trees	6488
#23	(hospital near/3 (admission or stay)):ti,ab,kw	20854
#24	(patient near/3 (admission or stay)):ti,ab,kw	1779
#25	#19 or #20 or #21 or #22 or #23 or #24	153780
#26	#4 and #18 and #25	332

Of 332 results:

- Cochrane reviews: 35
- Cochrane Protocol: 1
- Trials: 296
- Editorials: 0
- Special collections: 0
- Clinical Answers: 0

## Appendix 2. Search strategy and results for MEDLINE

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to August 29, 2018

Search Strategy:

#	Searches	Results
1	anemia, sickle cell/	19329
2	hemoglobin, sickle/	3011
3	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	27120
4	1 or 2 or 3	27602
5	Blood Transfusion/	48056
6	Erythrocyte Transfusion/	8033
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti.ab.	90906
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	47785
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	35184
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti.ab.	26829
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1217
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	24060
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	183648
14	Blood Component Transfusion/	3477
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	16726
16	14 not 15	3229
17	ERYTHROCYTES/	128578
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	216650



19	17 or 18	258199
20	16 and 19	834
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	13177
22	((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	3326
23	13 or 20 or 21 or 22	188025
24	exp pain/	362648
25	(pain or painfull).tw.	547392
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	66169
27	exp length of stay/	77857
28	(hospital adj3 (admission or stay)).tw.	104873
29	(patient adj3 (admission or stay)).tw.	6507
30	or/24-29	901074
31	4 and 23 and 30	848
32	clinical trial/	512148
33	(clinic adj5 trial*).ti,ab,sh.	1010
34	single blind method/	25632
35	double blind method/	147368
36	random allocation/	95709
37	placebos/	34063
38	(placebo or random*).ti,ab,sh.	1263924
39	randomized controlled trial/	467730
40	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	786522
41	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	145215
42	randomi?ed control trial*.tw.	6481
43	or/32-42	1565168
44	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	2187051
45	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	1071161

46	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	615678
47	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	340559
48	Clinical Trial, Phase I.pt.	18409
49	Clinical Trial, Phase II.pt.	29604
50	Clinical Trial, Phase III.pt.	14110
51	(registry or registries).ti,ab,kf,hw.	139501
52	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	53439
53	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	114108
54	(nonrandom* or non-random*).ti,ab,kf.	34084
55	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	2644
56	(all adj3 received).ab.	41192
57	or/44-56	3114626
58	31 and 43	120
59	31 and 57	278

### Appendix 3. Search strategy and results for Embase database

Database(s): **Embase** 1974 to 2018 Week 35

Search Strategy:

#	Searches	Results
1	exp Anemia, Sickle Cell/	32009
2	(h?emoglobin s or h?emoglobin sc or h?emoglobin se or h?emoglobin ss or h?emoglobin c or h?emoglobin d or Hb s or Hb sc or Hb se or Hb ss or Hb c or Hb d or sc disease*).tw.	5794
3	(sickle cell or sicklemlia or sickled or sickling or meniscocyt* or drepanocyt*).tw.	29569
4	1 or 2 or 3	38361
5	Blood Transfusion/	108332
6	Erythrocyte Transfusion/	23021
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	135137
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	77239
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	38387
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	43111
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1555
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	28985
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	273982
14	Blood Component Transfusion/	2629
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	19765
16	14 not 15	2279
17	ERYTHROCYTES/	112741
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	256379

19	17 or 18	278120
20	16 and 19	523
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	22304
22	((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	4095
23	13 or 20 or 21 or 22	279695
24	exp pain/	1146280
25	(pain or painfull).tw.	789805
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	82887
27	exp length of stay/	150699
28	(hospital adj3 (admission or stay)).tw.	169748
29	(patient adj3 (admission or stay)).tw.	12514
30	or/24-29	1690290
31	4 and 23 and 30	2325
32	randomized controlled trial/	508600
33	(RCT or randomi#ed or randomi#ation).ab,ti,kw,hw.	1062285
34	(random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or substitut* or treat*)).ab,kw.	560662
35	trial.ti.	248694
36	crossover procedure/	56042
37	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dumm*)).ti,ab,kw,hw.	276112
38	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	99658
39	or/32-38	1386841
40	prospective study/ or retrospective study/ or longitudinal study/ or cohort analysis/ or cross-sectional study/ or case control study/ or population based case control study/	1771952
41	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 study).ti,ab,kw.	1282224
42	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	790240
43	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab,kw.	500633

44	(registry or registries).ti,ab,kw,hw.	183687
45	(nonrandom* or non-random*).ti,ab,kw.	42777
46	((control* adj2 before adj2 after) or CBA study).ti,ab,kw.	3333
47	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kw.	80316
48	(all adj3 received).ab.	75969
49	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 1 clinical trial/	126474
50	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kw.	205403
51	or/40-50	3180246
52	31 and 39	245
53	31 and 51	599

## Appendix 4. Search strategy and results for ClinicalTrial.gov

#	Searches	Search column
#1	Anemia, Sickle Cell OR Sickle Beta Thalassemia OR Sickle Cell Anemia OR Sickle Cell trait	Condition or disease
#2	SCD OR SCA OR Sickle	Other terms
#3	Transfusion OR blood OR RBC OR hematocrit OR erythrocyte	Intervention/treatment
#4	pain OR hospitalisation OR hospitalization OR (hospital AND (admission OR stay)) OR crisis OR VOC OR ((vaso OR vein OR vena OR venous) AND (occlusive OR occlusive OR interruption OR obstruction)) OR survival OR quality of life	Outcome Measures
	#1 or #2 or #3 or #4	

\*Advanced Search option without any restrictions except search strings listed.