APPENDIX A. SEARCH STRATEGY

anemia	anemia anaemia anemia/
congestive heart failure/ coronary heart disease/ ischemic heart disease	cardiac failure chf congestive heart failure coronary heart disease ischemic heart disease heart failure/ coronary disease/ myocardial ischemia/
Erythropoiesis-stimulating agents	anti-anaemi* antianaemi* antianemi* anti-anemi* aranesp darbepoetin darbepoietin darbopoetin epo epoetin epogen epoietin eprex Erythopoiesis-stimulating agents erythropoesis erythropoetin erythropoiesis erythropoietin ESA ESAs hematinics neorecormon nesp procrit recormon rheupo erythropoetin/
Iron - IV or PO	ferric ferrous iron iron/
red blood cell transfusion	red blood cell transfusion Erythrocyte Transfusion/
benefits	

harms	safe safety side-effect* undesirable effect* treatment emergent tolerability toxicity adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes) /adverse effects /poisoning /toxicity /chemically induced /contraindications /complications thromboembolism thromboembolism/
threshold hemoglobin value	threshold hemoglobin value
RCT	1 randomized controlled trial.pt. 2 controlled clinical trial.pt. 3 randomized.ab. 4 placebo.ab. 5 drug therapy.fs. 6 randomly.ab. 7 trial.ab. 8 groups.ab 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10 exp animals/ not humans.sh. 11 9 not 10 [Cochrane's Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format]
human	not (not human)

Databases: MEDLINE, Cochrane, EMBASE

ESA Benefits – search strategy

Database(s):**Ovid MEDLINE® and Ovid OLDMEDLINE®** 1947 to November Week 1 2010**, Ovid MEDLINE® In-Process & Other Non-Indexed Citations** November 11, 2010

#	Searches	Results
1	anemia.mp. or exp Anemia/	149879
2	anaemia.mp.	22339
3	1 or 2	157901
4	cardiac failure.mp. or exp Heart Failure/	77416
5	chf.mp.	8843
6	congestive heart failure.mp.	28353
7	coronary heart disease.mp. or exp Coronary Disease/	177123
8	ischemic heart disease.mp. or exp Myocardial Ischemia/	321932
9	4 or 5 or 6 or 7 or 8	407842

10	3 and 9	2677
11	anti-anaemi*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	33
12	antianaemi*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	30
13	antianemi*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	174
14	anti-anemi*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	94
15	aranesp.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	83
16	exp Erythropoietin/ or darbepoetin.mp.	18912
17	darbepoietin.mp.	43
18	darbopoetin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	3
19	epo.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	7585
20	epoetin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2037
21	epogen.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	61
22	epoietin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	51
23	eprex.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	126
24	erythropoesis.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	81
25	erythropoetin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	164
26	erythropoiesis.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	15771
27	erythropoietin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	23192
28	ESA.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1138
29	ESAs.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	475
30	hematinics.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2350
31	neorecormon.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	31
32	nesp.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	73
33	procrit.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	33
34	recormon.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	30
35	Erythropoiesis-stimulating agent.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	152
36	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	37740

37	randomized controlled trial.pt.	305853
38	controlled clinical trial.pt.	83372
39	randomized.ab.	218942
40	placebo.ab.	127996
41	drug therapy.fs.	1433066
42	randomly.ab.	161893
43	trial.ab.	227198
44	groups.ab.	1067718
45	37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	2717428
46	exp animals/ not humans.sh.	3609973
47	45 not 46	2313774
48	10 and 36 and 47	225

ESA Benefits – search strategy, continued

Database(s):**EBM Reviews - Cochrane Central Register of Controlled Trials** 4th Quarter 2010

Date searched 11/15/10

#	Searches	Results
1	anemia.mp. or exp Anemia/	4561
2	anaemia.mp.	985
3	1 or 2	5004
4	cardiac failure.mp. or exp Heart Failure/	4150
5	chf.mp.	1152
6	congestive heart failure.mp.	2523
7	coronary heart disease.mp. or exp Coronary Disease/	9300
8	ischemic heart disease.mp. or exp Myocardial Ischemia/	17485
9	4 or 5 or 6 or 7 or 8	23230
10	3 and 9	96
11	anti-anaemi*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	0
12	antianaemi*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1
13	antianemi*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	16
14	anti-anemi*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	5
15	aranesp.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	25
16	exp Erythropoietin/ or darbepoetin.mp.	1291
17	darbepoietin.mp.	9
18	darbopoetin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	9
19	epo.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	602
20	epoetin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	603
21	epogen.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	2
22	epoietin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	18
23	eprex.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	22
24	erythropoesis.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	5
25	erythropoetin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	32
26	erythropoiesis.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	449
27	erythropoietin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1903
28	ESA.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	51
29	ESAs.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	18
30	hematinics.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	398
31	neorecormon.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	19
32	nesp.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	23

33	procrit.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	13
34	recormon.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	7
35	Erythropoiesis-stimulating agent.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	28
36	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	2764
37	randomized controlled trial.pt.	284694
38	controlled clinical trial.pt.	79466
39	randomized.ab.	147977
40	placebo.ab.	100112
41	randomly.ab.	76867
42	trial.ab.	102732
43	groups.ab.	156434
44	37 or 38 or 39 or 40 or 41 or 42 or 43	419005
45	10 and 36 and 44	33

ESA Benefits – search strategy, continued
Database: **EMBASE**
Date searched 11/15/10

#	Query	Results
11	#7 AND #10	105
10	#8 OR #9	346115
9	random$ OR factorial$ OR crossover$ OR cross AND over$ OR 'cross over$' OR placebo$ OR doubl$ AND adj AND blind$ OR single$ AND adj AND blind$ OR assign$ OR allocat$ OR volunteer$ AND [embase]/lim	40406
8	'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp	310032
7	#5 AND #6	1015
6	'anti anami$' OR antianaemi$ OR antianemi$ AND o$r AND 'anti anemi$' OR 'aranesp'/exp OR 'darbepoetin'/exp OR 'darbepoietin'/exp OR 'darbopoetin'/exp OR epo OR 'epoetin'/exp OR 'epogen'/exp OR 'epoietin'/exp OR 'eprex'/exp OR 'erythopoiesis stimulating' AND agents OR erythropoesis OR erythropoetin OR 'erythropoiesis'/exp OR 'erythropoietin'/exp OR esa OR esas OR 'hematinics'/exp OR 'neorecormon'/exp OR 'nesp'/exp OR 'procrit'/exp OR 'recormon'/exp OR rheupo AND [embase]/lim	70423
5	#1 AND #4	5587
4	#2 OR #3	376323
3	'heart failure'/exp OR 'coronary artery disease'/exp	352502
2	cardiac AND failure OR chf OR congestive AND 'heart'/exp AND failure OR coronary AND 'heart'/exp AND 'disease'/exp OR ischemic AND 'heart'/exp AND 'disease'/exp AND [embase]/lim	43081
1	'anemia'/exp AND [embase]/lim	141383

ESA harms – search strategy
Database(s):**Ovid MEDLINE® and Ovid OLDMEDLINE®** 1947 to November Week 1 2010**, Ovid MEDLINE® In-Process & Other Non-Indexed Citations** November 11, 2010

#	Searches	Results
1	anemia.mp. or exp Anemia/	149879
2	anaemia.mp.	22339
3	1 or 2	157901

4	cardiac failure.mp. or exp Heart Failure/	77416
5	chf.mp.	8843
6	congestive heart failure.mp.	28353
7	coronary heart disease.mp. or exp Coronary Disease/	177123
8	ischemic heart disease.mp. or exp Myocardial Ischemia/	321932
9	4 or 5 or 6 or 7 or 8	407842
10	3 and 9	2677
11	anti-anaemi*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	33
12	antianaemi*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	30
13	antianemi*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	174
14	anti-anemi*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	94
15	aranesp.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	83
16	exp Erythropoietin/ or darbepoetin.mp.	18912
17	darbepoietin.mp.	43
18	darbopoetin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	3
19	epo.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	7585
20	epoetin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2037
21	epogen.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	61
22	epoietin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	51
23	eprex.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	126
24	erythropoesis.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	81
25	erythropoetin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	164
26	erythropoiesis.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	15771
27	erythropoietin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	23192
28	ESA.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1138
29	ESAs.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	475
30	hematinics.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2350
31	neorecormon.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	31
32	nesp.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	73
33	procrit.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	33

34	recormon.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	30
35	Erythropoiesis-stimulating agent.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	152
36	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	37740
37	exp Thromboembolism/ or thromboembolism.mp.	47359
38	(adverse effects or poisoning or toxicity or chemically induced or contraindications or complications).fs.	2846319
39	(adverse adj2 (effect or effects or reaction or reactions or event or events or outcomes or outcome)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	179933
40	(safe or safety or side-effect* or undesirable effect* or treatment emergent or tolerability or toxicity).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	675202
41	37 or 38 or 39 or 40	3311276
42	10 and 36 and 41	280

ESA harms – search strategy, continued

Database(s):**EBM Reviews - Cochrane Central Register of Controlled Trials** 4th Quarter 2010

Date searched: 11/15/10

#	Searches	Results
1	anemia.mp. or exp Anemia/c	4561
2	anaemia.mp.	985
3	1 or 2	5004
4	cardiac failure.mp. or exp Heart Failure/	4150
5	chf.mp.	1152
6	congestive heart failure.mp.	2523
7	coronary heart disease.mp. or exp Coronary Disease/	9300
8	ischemic heart disease.mp. or exp Myocardial Ischemia/	17485
9	4 or 5 or 6 or 7 or 8	23230
10	3 and 9	96
11	anti-anaemi*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	0
12	antianaemi*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1
13	antianemi*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	16
14	anti-anemi*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	5
15	aranesp.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	25
16	exp Erythropoietin/ or darbepoetin.mp.	1291
17	darbepoietin.mp.	9
18	darbopoetin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	9
19	epo.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	602
20	epoetin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	603
21	epogen.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	2
22	epoietin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	18
23	eprex.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	22
24	erythropoesis.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	5
25	erythropoetin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	32
26	erythropoiesis.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	449
27	erythropoietin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1903

28	ESA.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	51
29	ESAs.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	18
30	hematinics.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	398
31	neorecormon.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	19
32	nesp.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	23
33	procrit.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	13
34	recormon.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	7
35	Erythropoiesis-stimulating agent.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	28
36	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	2764
37	exp Thromboembolism/ or thromboembolism.mp.	2067
38	(adverse adj2 (effect or effects or reaction or reactions or event or events or outcomes or outcome)).mp.	48156
39	(safe or safety or side-effect* or undesirable effect* or treatment emergent or tolerability or toxicity).mp.	95206
40	37 or 38 or 39	114226
41	10 and 36 and 40	10

ESA harms – search strategy, continued

Database: **EMBASE**

Date searched: 11/15/10

#	Query	Results
11	#7 AND #10	412
10	#8 OR #9	1154469
9	safe OR 'safety'/exp OR 'side effect$' OR undesirable AND effect$ OR treatment AND emergent OR tolerability OR 'toxicity'/exp OR (adverse AND adj2 AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)) AND [embase]/lim	432305
8	'complication'/exp OR 'side effect'/exp OR 'adverse drug reaction'/exp OR 'drug toxicity'/exp	899447
7	#5 AND #6	1015
6	'anti anami$' OR antianaemi$ OR antianemi$ AND o$r AND 'anti anemi$' OR 'aranesp'/exp OR 'darbepoetin'/exp OR 'darbepoietin'/exp OR 'darbopoetin'/exp OR epo OR 'epoetin'/exp OR 'epogen'/exp OR 'epoietin'/exp OR 'eprex'/exp OR 'erythopoiesis stimulating' AND agents OR erythropoesis OR erythropoetin OR 'erythropoiesis'/exp OR 'erythropoietin'/exp OR esa OR esas OR 'hematinics'/exp OR 'neorecormon'/exp OR 'nesp'/exp OR 'procrit'/exp OR 'recormon'/exp OR rheupo AND [embase]/lim	70423
5	#1 AND #4	5587
4	#2 OR #3	376323
3	'heart failure'/exp OR 'coronary artery disease'/exp	352502
2	cardiac AND failure OR chf OR congestive AND 'heart'/exp AND failure OR coronary AND 'heart'/exp AND 'disease'/exp OR ischemic AND 'heart'/exp AND 'disease'/exp AND [embase]/lim	43081
1	'anemia'/exp AND [embase]/lim	141383

Iron benefits and harms

Database(s):**Ovid MEDLINE® and Ovid OLDMEDLINE®** 1947 to November Week 1 2010**, Ovid MEDLINE® In-Process & Other Non-Indexed Citations** November 11, 2010

#	Searches	Results
1	anemia.mp. or exp Anemia/	149879
2	anaemia.mp.	22339
3	1 or 2	157901
4	cardiac failure.mp. or exp Heart Failure/	77416
5	chf.mp.	8843
6	congestive heart failure.mp.	28353
7	coronary heart disease.mp. or exp Coronary Disease/	177123
8	ischemic heart disease.mp. or exp Myocardial Ischemia/	321932
9	4 or 5 or 6 or 7 or 8	407842
10	3 and 9	2677
11	exp Iron/ or iron.mp.	133944
12	ferric.mp.	18656
13	ferrous.mp.	12391
14	11 or 12 or 13	145012
15	10 and 14	400

Iron benefits and harms – search strategy, continued

Database(s):**EBM Reviews - Cochrane Central Register of Controlled Trials** 4th Quarter 2010
Date searched: 11/15/10

#	Searches	Results
1	anemia.mp. or exp Anemia/	4561
2	anaemia.mp.	985
3	1 or 2	5004
4	cardiac failure.mp. or exp Heart Failure/	4150
5	chf.mp.	1152
6	congestive heart failure.mp.	2523
7	coronary heart disease.mp. or exp Coronary Disease/	9300
8	ischemic heart disease.mp. or exp Myocardial Ischemia/	17485
9	4 or 5 or 6 or 7 or 8	23230
10	3 and 9	96
11	exp Iron/ or iron.mp.	3384
12	ferric.mp.	365
13	ferrous.mp.	604
14	11 or 12 or 13	3566
15	10 and 14	24

Iron benefits and harms – search strategy, continued

Database: **EMBASE**

Date searched: 11/15/10

#	Query	Results
11	#5 AND #10	593
10	#8 OR #9	112969
9	ferric OR ferrous OR 'iron'/exp AND [embase]/lim	85359
8	'iron'/exp	88060
5	#1 AND #4	5587
4	#2 OR #3	376323
3	'heart failure'/exp OR 'coronary artery disease'/exp	352502
2	cardiac AND failure OR chf OR congestive AND 'heart'/exp AND failure OR coronary AND 'heart'/exp AND 'disease'/exp OR ischemic AND 'heart'/exp AND 'disease'/exp AND [embase]/lim	43081
1	'anemia'/exp AND [embase]/lim	141383

RBC transfusion benefits and harms – search strategy

Database(s):**Ovid MEDLINE® and Ovid OLDMEDLINE®** 1947 to November Week 1 2010**, Ovid MEDLINE® In-Process & Other Non-Indexed Citations** November 11, 2010

Date searched: 11/12/10

#	Searches	Results
1	anemia.mp. or exp Anemia/	149879
2	anaemia.mp.	22339
3	1 or 2	157901
4	cardiac failure.mp. or exp Heart Failure/	77416
5	chf.mp.	8843
6	congestive heart failure.mp.	28353
7	coronary heart disease.mp. or exp Coronary Disease/	177123
8	ischemic heart disease.mp. or exp Myocardial Ischemia/	321932
9	4 or 5 or 6 or 7 or 8	407842
10	3 and 9	2677
11	red blood cell transfusion.mp. or exp Erythrocyte Transfusion/	5368
12	10 and 11	46

RBC transfusion benefits and harms – search strategy continued

Database(s):**EBM Reviews - Cochrane Central Register of Controlled Trials** 4th Quarter 2010

Date searched: 11/12/10

#	Searches	Results
1	anemia.mp. or exp Anemia/	4561
2	anaemia.mp.	985
3	1 or 2	5004
4	cardiac failure.mp. or exp Heart Failure/	4150
5	chf.mp.	1152
6	congestive heart failure.mp.	2523
7	coronary heart disease.mp. or exp Coronary Disease/	9300
8	ischemic heart disease.mp. or exp Myocardial Ischemia/	17485
9	4 or 5 or 6 or 7 or 8	23230
10	3 and 9	96
11	red blood cell transfusion.mp. or exp Erythrocyte Transfusion/	360
12	10 and 11	6

RBC transfusion benefits and harms – search strategy continued
Database(s):**EMBASE**
Date searched: 11/12/10

#	Query	Results
7	#5 AND #6	205
6	'erythrocyte transfusion'/exp	8844
5	#1 AND #4	5587
4	#2 OR #3	376323
3	'heart failure'/exp OR 'coronary artery disease'/exp	352502
2	cardiac AND failure OR chf OR congestive AND 'heart'/exp AND failure OR coronary AND 'heart'/exp AND 'disease'/exp OR ischemic AND 'heart'/exp AND 'disease'/exp AND [embase]/lim	43081
1	'anemia'/exp AND [embase]/lim	141383

Hemoglobin threshold – search strategy
Database(s):**Ovid MEDLINE® and Ovid OLDMEDLINE®** 1947 to November Week 1 2010**, Ovid MEDLINE® In-Process & Other Non-Indexed Citations** November 11, 2010

#	Searches	Results
1	(hemoglobin adj3 threshold*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	75

Hemoglobin threshold – search strategy continued
Database: **EMBASE**
Date searched: 11/12/10

#	Query	Results
7	#5 AND #6	16
6	threshold AND 'hemoglobin'/exp AND [embase]/lim	972
5	#1 AND #4	5587
4	#2 OR #3	376323
3	'heart failure'/exp OR 'coronary artery disease'/exp	352502
2	cardiac AND failure OR chf OR congestive AND 'heart'/exp AND failure OR coronary AND 'heart'/exp AND 'disease'/exp OR ischemic AND 'heart'/exp AND 'disease'/exp AND [embase]/lim	43081
1	'anemia'/exp AND [embase]/lim	141383

Hemoglobin threshold – search strategy continued
Database(s):**EBM Reviews - Cochrane Central Register of Controlled Trials** 4th Quarter 2010
Date searched: 11/12/10

#	Searches	Results
1	(hemoglobin adj3 threshold*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	14

APPENDIX B. INCLUSION/EXCLUSION CRITERIA

1. Is the full text of the article in English?
   Yes.....Proceed to #2
   No..... Code **X1**. STOP

2. Does the study population include adult patients with congestive heart failure or coronary heart disease, and anemia or iron deficiency?
   Yes.....Proceed to #3
   No..... Code X2. Proceed to #8

3. Is the article an intervention study (or a systematic review/meta-analysis of intervention studies) comparing the effects of ESAs, iron, or red blood cell transfusions with usual care or placebo; or an observational study of the effects of red blood cell transfusions?
   Yes.....Proceed to #4
   No.....Go to #5

4. Does the study report outcomes that include mortality, hospitalization, exercise tolerance, cardiovascular events, quality of life, or adverse effects of treatment?
   Yes.....Code I4. Go to #6
   No ..... Code X4. Go to #7

5. Is the article an observational study that reports data on the harms of using ESAs or iron?
   Yes.....Code I5. Proceed to #6
   No..... Code X5. Proceed to #7

6. Does the article describe or analyze the costs of treatment or implementation?
   Yes..... Add Code C. STOP
   No.....STOP

7. Does the article describe or analyze the costs of treatment or implementation?
   Yes..... Add Code C. STOP
   No.....Proceed to #8

8. Is the article potentially useful for background, discussion, or reference-mining?
   Yes.....Code B. STOP
   No.....STOP

APPENDIX C. QUALITY ASSESSMENT TABLES

Appendix C, Table 1. Assessment of methodologic characteristics and risk of bias in randomized controlled trials of ESA therapy in patients with CHF or CHD

Study ID	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented?	Were incomplete outcome data adequately addressed?	Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?	Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?	Summary assessment: risk of bias (Low, Unclear, High)
Bellinghieri, 1994[27]	Unclear	Unclear	No	No	Unclear	No serious baseline imbalances. Randomized, but very little baseline characteristics presented though the baseline gender imbalance raises concerns that groups may not have been equal at baseline.	Overall: high risk of bias
Besarab 1998[26]	Unclear	Unclear	Yes - low risk of bias for mortality outcome, probably low risk of bias for hospitalization, MI outcomes. High risk of bias for physical function outcome given that blinding of participants and outcome assessors is unlikely to have occurred	Low risk of bias - data for all patients enrolled is reported and an intention to treat analysis was done	It is unclear why a composite outcome was chosen. Functional status data were incompletely reported (no comparative data, only that functional status increased with increasing Hct levels) —> high risk of bias for functional status outcomes, but probably low risk of bias for mortality outcome	No serious baseline imbalances between groups.	Overall: low risk of bias
Comin-Colet, 2009[12]	No - high risk of bias - allocation by preference of the participant. Because preference for treatment could be associated with unmeasured confounders such as better self-management skills etc, this is a significant methodologic limitation which threatens the validity of the results.	No	No - high risk of bias for subjective outcomes	Yes	Unclear	No serious baseline imbalances between groups	Overall: high risk of bias
Ghali, 2008[19]	Yes	Yes	Yes	Yes	Unclear	No serious baseline imbalances between groups	Overall: low risk of bias
Kourea, 2008[17]	Unclear	Unclear	Yes - though single blind, it was placebo controlled and evaluation of QOL and depression surveys was done by blinded personnel	Yes	Unclear	No serious baseline imbalances between groups	Overall: Unclear risk of bias

Study ID	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented?	Were incomplete outcome data adequately addressed?	Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?	Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?	Summary assessment: risk of bias (Low, Unclear, High)
Mancini, 2003[24]	Unclear	Unclear	Personnel and outcome assessors were not blinded High risk of bias especially for QOL outcomes	Yes, though no ITT done, only 3 patients did not complete treatment	No - high risk of bias - no protocol available. The QOL outcome is not completely reported - no actual values, only that x % "improved" and the definition of improvement is not provided.	No serious baseline imbalances between groups	Overall: high risk of bias
Palazzuoli, 2006[28]	Unclear	Unclear	Yes	Yes	Unclear	No serious baseline imbalances between groups. It is unclear if there is any overlap between patients in this study and Palazzuoli 2009 - if so, then possible multiple publication bias	Overall: Unclear risk of bias, but duplicates Palazzuoli 2007 results
Palazzuoli, 2007[21]	Unclear	Unclear	No (for 12 month outcomes) - high risk of bias for 12 month outcomes such as NYHA class. Blinding stopped after 4 month mark.	No - high risk of bias. Not clear that ITT done. Nowhere in the results is the denominator actually reported so it is unclear what the final n was used to calculate results.	No - no protocol available. The study includes 12 month NYHA scores as an outcome, but there are no objective measures of exercise duration which one might expect as another secondary outcome measure.	No serious baseline imbalances between groups. It is unclear if there is any overlap between patients in this study and Palazzuoli 2009 – if so, then possible multiple publication bias	Overall: high risk of bias. Duplicates Palazzuoli 2006 results with some additions.
Palazzuoli, 2009[15]	Unclear	Unclear	Blinding of personnel and outcome assessors is unclear past the 4 month mark after which intervention drug was continued, but the control group saline injections were discontinued. This could create high risk of bias for outcomes such as NYHA class.	No - high risk of bias. No ITT done. 7 of 58 enrolled patients did not make it to f/u and though outcomes are briefly and incompletely described for these patients they are not included in analyses. Additionally, only 48 of the 58 pts were included in the hospitalization outcome and the reasons for the discrepant numbers are not explained.	No - high risk of bias. No protocol available. The incomplete reporting of all enrolled patients raises suspicion that not all outcomes were reported. Further, there are signals from within paper that this is so (eg - edema development was a secondary end point but is not reported in results). Other secondary end points are incompletely described ("no significant changes in myocardial events was seen")	No serious baseline imbalances between groups.	Overall: high risk of bias
Parissis, 2008[18]	Yes	Unclear	Yes - single blind. Personnel not blinded, but outcome assessors were	Yes	Unclear	No serious baseline imbalances between groups. It is unclear if there is any overlap between patients in this study and Parissis 2009 – if so, then possible multiple publication bias	Overall: low risk of bias

Study ID	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented?	Were incomplete outcome data adequately addressed?	Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?	Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?	Summary assessment: risk of bias (Low, Unclear, High)
Parissis, 2009[16]	Yes	Unclear	Yes - single blind. Personnel not blinded but outcome assessors were	Yes	Unclear	No serious baseline imbalances between groups. It is unclear if there is any overlap between patients in this study and Parissis 2008 - if so, then possible multiple publication bias	Overall: low risk of bias
Pfeffer, 2009[14]	Yes	Unclear	Yes	Yes - 13% attrition, but equally balanced between two groups	Unclear	No serious baseline imbalances between groups	Overall: low risk of bias
Ponikowski, 2007[23]	Yes	Yes	Yes	Yes	Unclear	No serious baseline imbalances between groups Some evidence of spin: QOL assessed by three measures and improvement seen only in one measure, not the other two, yet conclusions suggest ESA improved health related quality of life	Overall: low risk of bias
Silverberg, 2001[25]	Unclear	No "Randomization… not done in a blinded fashion"	No	Unclear - Nowhere in the results is the denominator actually reported so it is unclear what the final n was used to calculate results.	Unclear	No serious baseline imbalances between groups	Overall: high risk of bias
Van Veldhuisen, 2007[22]	Yes	Yes	Yes	Yes	Unclear	No serious baseline imbalances between groups	Overall: low risk of bias

Appendix C, Table 2. Assessment of methodologic characteristics and risk of bias in randomized controlled trials of RBC transfusion for anemia in patients with CHF or CHD

Study ID	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?	Summary assessment: risk of bias (Low, Unclear, High)
Bracey, 1999[65]	Unclear: last digit of HR# determined group assignment	Unclear, concealment method not described	Study not described as blinded.	Yes	Yes	No serious baseline imbalances between groups.	Overall: Unclear risk of bias
Bush, 1997[67]	Unclear: randomization method not specified	Yes (sealed envelopes)	Study not described as blinded. Surgeons and anesthesiologists were not blinded.	Yes	Yes	No serious baseline imbalances between groups.	Overall: Low risk of bias
Carson, 1998[68]	Yes: automated telephone-response system at a separate research institute.	Yes: automated telephone-response system at a separate research institute.	Outcome assessors were blinded; blinding was not otherwise specified for patients or care personnel.	Yes	Yes	No serious baseline imbalances between groups.	Overall: Low risk of bias
Carson, 2009[69]	Unclear: randomization method not described (abstract only)	Not described (abstract only)	Not described (abstract only)	Not described (abstract only)	Yes	No serious baseline imbalances between groups.	Overall: Probably low; study is based on the pilot trial above (Carson 1998)
Cooper, 2011[40]CRIT trial	Unclear: randomization method not specified	Yes (opaque envelopes)	No: "Blinding of treatment assignment was not feasible"	Yes; 6.7% loss to follow-up	Yes	More smokers in conservative group (10% v 33%); more diabetes in liberal group (81% v 54%); P-values not specified.	Overall: Low risk of bias
Hajjar, 2010[66]	Yes (random numbers table)	Yes (opaque envelopes)	Patient and outcome assessors were blinded to group assignment. Anesthesiologist and ICU health care workers were not blinded.	Yes	Yes	No serious baseline imbalances between groups.	Overall: Low risk of bias
Hebert, 2001[39]TRICC trial	Unclear: randomization method not specified	Unclear, concealment method not described	Outcome assessors were blinded; care personnel were not blinded; patient blinding not specified.	Yes	Yes	No serious baseline imbalances between groups.	Overall: Low risk of bias
Johnson, 1992[64]	Yes (random numbers table)	Unclear, concealment method not described	Surgeons and anesthesiologists were blinded until patient in ICU. Blinding of outcome assessor and patient not specified.	Yes. No in-hospital deaths occurred.	Yes	No serious baseline imbalances between groups.	Overall: Low risk of bias
Weisel, 1984[63]	Unclear: randomization method not specified	Unclear, concealment method not described	Use of blinding was not stated.	Yes	Yes	No serious baseline imbalances between groups.	Overall: Low risk of bias

Appendix C, Table 3. Assessment of methodologic characteristics and risk of bias in observational studies of RBC transfusions for anemia in patients with CHD/CHF, stratified by patient population

Author Year	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?				Adequate duration of follow-up?
						Propensity matching	Account for bleeding	Account for timing of transfusion	Comments	
Percutaneous Coronary Intervention										
Chase, 2008[48] Multicenter Canada	Yes	No	Yes	Yes	Yes	Yes	No	No	Multivariate analysis did not account for some important confounders such as CHF	30 day and 1 year
Doyle, 2008[47] Mayo clinic USA	Yes	Not reported	Yes	No. Hospital complication registry but method of follow-up not stated	Not reported	No	No	No	Confounders not reported	Unclear, 30 day mortality reported, but graphs show 5-6 year mortality trends.
Jani, 2007[49]	Yes	No	Yes	Yes	Yes	Yes	Yes	No		Yes
Jolicoeur, 2009[50]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes		Yes
Kim, 2007[45] Single center USA	Yes	No	Yes	Yes	Yes	Yes	Yes	No		1 year
Kinnaird, 2003[44] Single center USA	Yes	Probably No. Lost 14%. Difference in loss between groups not reported.	Yes	Yes	Yes	No	Yes	No		1 year
Maluenda, 2009[36] Single Institution USA	Yes	Not reported	Yes	Yes	Probably yes	No	Yes	No		30 days and 1 year.
Maluenda, 2009[37]	Unknown. Abstract only reports # of charts reviewed. Probably yes as is likely same cohort as above.	Not reported	Yes.	No.	Probably yes as likely is same registry as above. But unknown based on this abstract.	Abstract only, may be same population as other Maluenda reference				1 year
Maluenda, 2009[38]	Unknown Abstract only reports # of charts reviewed. Probably yes as is likely same cohort as above.	Not reported	Yes	No.	Probably yes as likely is same registry as above. But unknown based on this abstract.	Abstract only, may be same population as other Maluenda reference				1 year

Author Year	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?				Adequate duration of follow-up?
						Propensity matching	Account for bleeding	Account for timing of transfusion	Comments	
Nikolsky, 2009[51]	Yes	No	Yes	Yes	Yes	Yes	Yes	No		Yes
Yatskar, 2007[46] Multicenter USA	Yes	No	Yes	Mostly yes. NHLBI registry. Telephone follow-up. But unclear why they looked at "Hematoma Related Transfusion" rather than transfusion.	Probably yes. Again, didn't look at transfusions, only hematoma related transfusions.	No	No – only examined transfusions for hematoma, but not for other causes or for transfusion without bleeding.	No	Confounders not reported and appears a number of important confounders were probably not accounted for	1 year
Acute Coronary Syndrome/Acute MI										
Aggarwal, 2011[60]	Partly - unclear whether transfusion administration was prospectively collected data for all potentially eligible patients.	No	Yes	No, but primary outcome was in-hospital death.	Yes, probably	No	Yes	No		Yes
Alexander, 2008[55]	Yes	No	Yes	Yes	Yes	No	No	No		Yes
Aronson, 2008[58]	Yes	Not reported	Yes	Yes	Unclear if investigators doing chart review on repeat admissions were blinded to whether patient had transfusion.	Yes	No	No		Yes
Rao, 2004[52]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes		Yes
Sabatine, 2005[57]	Yes	No	Yes	Yes	Yes	No	Yes	No		Yes
Shishehbor, 2009[56]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Also conducted sensitivity analyses to determine impact of "hidden" biases and found there would have to be "enormous" hidden biases to account for results	Yes
Singla, 2007[54]	Yes	No	Yes	Yes	No, 30 day event rates limited to VA hospitals only.	No	No	No		Yes

Author Year	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?				Adequate duration of follow-up?
						Propensity matching	Account for bleeding	Account for timing of transfusion	Comments	
Wu, 2001[59]	Yes	No, probably - primary outcome 30 D mortality assessed using Medicare Enrollment database, but proportion with complete vital status at 30 D unclear.	Yes	Yes	Yes, probably.	Yes	No	Partly – conducted additional analysis excluding patients who died within two days of admission.	Unclear how well transfusion administration was captured by claims data.	Yes
Yang, 2005[53]	Yes	Unclear - CRUSADE QI initiative relies on retrospective chart review.	Yes	No	No - in-hospital outcomes only, unclear whether post-discharge deaths were accounted for.	No	No	No		No
Congestive Heart Failure										
Garty, 2009[61]	Yes	No	Yes	Yes	Yes	Yes	No	No		Yes
Kao, 2011[62]	Yes	No	Yes	Yes	Yes	No	No	No		Yes
Critical Illness										
Hebert, 1997[71]	Unclear - consecutive patients, but 40% were retrospectively identified and patient identification methods not well-described.	Unclear	Yes	No	Unclear	No	No	No		Yes
Surgery										
Bursi, 2009[41]	Yes	Unclear - number of patients with complete 30 day survival information not reported	Yes	Partly	Partly - 30 day mortality assessed through review of death certificates and phone interviews, but not clear they looked at death registries	Yes	Yes	Yes		Yes
Carson, 1998[81]	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear		Yes
Glance, 2011[70]	Yes	No	Yes	Yes	Yes	Yes	No	No	Did not account for post-operative transfusions.	Yes

APPENDIX D. PEER REVIEW COMMENTS AND RESPONSES

Reviewer	Comment	Response
Question 1: Are the objectives, scope, and methods for this review clearly described?		
1	No: I am worried about a few things in the current iteration of the review: 1) defining the population upfront; 2) defining the outcomes upfront; 3) justification of the inclusion of observational data. Defining the population – the document refers to patients with "CHF" and "CHD" but does not drill down and define these. CHF can include those with asymptomatic low LVEF or those with symptoms of CHF but with normal LVEF. Similarly, CHD can include acute coronary syndrome, PCI, or those with stable angina. I think these clinical entities need to be defined upfront.	We've clarified these definitions in the "study selection" section of Methods. The entities had been defined (fairly broadly) up front, but we agree this was not well-reported in the manuscript.
1	If the studies are heterogeneous in their inclusion of these populations, then this should be specifically mentioned.	We've added more detail to the "data abstraction" section of Methods to clarify that we've collected and reported the clinical characteristics of study populations. We also added a sentence to the second paragraph of Discussion clarifying that most ESA studies were in patients with systolic heart failure. The applicability of the evidence review findings to various patient populations is also further delineated in the GRADE table, and in the clinical applications section.
1	Also, why examine non-anemic patients with iron deficiency if the primary purpose is to study the treatment of anemia?	Clarified this in "study selection" section.
1	Defining the outcomes – the document examines several outcomes but no justification is provided for why they were chosen.	Clarified that we are defining "health outcome" as those that are patient-centered and apparent to the patient (in contrast to intermediate physiologic outcomes). The list of outcomes was discussed with and approved by the Technical Expert Panel during the topic development phase.
1	Justification of observational data – on pages 7 and 8, there is a section on Study Quality, and the answers to all of the questions posed would result in observational data being "low quality." This is entirely justified, but there are other ways to evaluate observational data like the appropriateness and robustness of the statistical methods. The authors should consider including some measure of observational data quality.	We've added a table describing the methodologic characteristics of each of the observational studies. We've added the quality assessment description to "study quality" section of Methods.
2	Agree with adding ortho surgery data as large RCT recently completed.	The data had not been available, but we will include if enough data available.
3	Yes.	
Question 2: Is there any indication of bias in our synthesis of the evidence?		
1	The only bias is in the observational studies that are included (see above).	Noted and discussed above.
2	Seemed to be more pro-ESA than the data supports	Noted
3	No.	
Question 3: Are there any published or unpublished studies that we may have overlooked?		
1	No.	Noted.
2	The ortho FOCUS trial	See comment 5 rows below regarding the FOCUS trial.
3	No.	Noted.

Reviewer	Comment	Response
Question 4: Please write additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.		
1	The section on iron therapy doesn't seem to have a summary of what the overall findings are. This would be helpful.	Thanks – yes, an accidental omission – this was added to the beginning of the iron section.
1	Page 39 – MINT is an ongoing trial and likely will not be published for several years. There is a trial that has been presented called FOCUS that will be published soon. (see http://www.theheart.org/article/1024017.do for a report of the presented results).	Thanks for the clarification. The results were amended accordingly. We report the FOCUS results available in an abstract and acknowledge the full document has yet to be published.
1	Page 40 – an important distinction between the Wu study and the Rao study are that Wu looked at *baseline* anemia while Rao examined the lowest hct value occurring during hospitalization. In addition, patients with active bleeding were excluded from the Wu study.	We've clarified these distinctions in this section of the discussion.
1	The section on Clinical Applications should be more prescriptive (see below). It's tough to actually get at what the recommendation is because it is obscured a bit by more description of the data.	We've stopped short of providing prescriptive recommendations of what should and should not be done intentionally as we'd feel more comfortable developing clinical recommendations in conjunction with our stakeholders/ clinical partners.
2	Page 2- need to give number of paper rejected	Thank you – we had accidentally omitted this from the executive summary.
2	Page 2 – ESA – to me the evidence is clear that ESA are associated with harm and not "may be". This is especially true in diabetic patients	The harm of targeting near-normal hemoglobin, especially in diabetic patients, seems clear after trials like TREAT, but these were not exclusively focused on treatment of anemic heart disease patients. The harms of using ESAs in heart disease populations are not as well elucidated. The language is meant to reflect this uncertainty and the fact that it most closely applies to those with chronic kidney disease. However, we did change the language to be a bit more direct (changed "possibility" to "finding," and "may be" to "is".
2	Page 9 – the hematocrit to hemoglobin correction of 10:1 makes no sense – the Hbg:Hct is 1:3 roughly.	Thank you – this was a typo – corrected.
2	Page 12 – again I think the case ESA cause harm is proven	Please see response to page 2 comment above.
2	Page 16 – would strongly disagree that 6MWT is not influence by blinding – reams of data in the sports medicine literature supports placebo effect!	Thank you – yes, we had mis-stated this. Meant to say lack of personnel blinding alone, given that outcome assessors were blinded, shouldn't carry high risk of bias for these outcomes. Patients were blinded, and control patients received placebo injections. We've clarified this in the table.
2	Page 21- is there data to support the notion that longer use of ESA is associated with greater harm?	It would be hard to determine this from the studies. The two studies mentioned with long follow-up periods also differed in patient population and treatment from the other smaller, shorter duration ESA trials. The mortality curves in Besarab did begin to separate several months into treatment and continued to diverge 1-2 years into treatment.
2	Page 26 – any data for increased risk of cancer? Was suggested in TRICK study and certainly seen in the oncology trials…	No, not that was reported in these trials. Of note, many excluded patients with malignancy.
2	Page 26 – just a comment – are the ongoing trials even ethical given what we know about high Hct goals and bad outcomes with ESA…	Interesting point, but outside the scope of our review. It is a different patient population.

Reviewer	Comment	Response
2	Page 29 – Although old, I have found the discussion in this paper the best framework for understanding the complex interplay of transfusions for cardiac disease: *Prudent strategies for elective red blood cell transfusion. Welch HG, Meehan KR, Goodnough LT. Ann Intern Med. 1992 Mar 1;116(5):393-402*	Thanks for this suggestion.
2	Page 32 – any suggestion of confounder of ACS management and risk of transfusion – i.e. if more patients have PCI that did worse with more transfusions??	One of the main confounders would be risk of bleeding associated with management – either procedural or med-related. Not all studies accounted for bleeding, but some did and we've added a table clarifying some of the methodologic characteristics of observational transfusion studies, including whether or not they accounted for bleeding complications.
2	Page 38 – the FDA ESA recommendation is even more aggressive than stated: *In controlled trials with CKD patients, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dL.* *No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.* *ESA labels now recommend:* *For patients with CKD, consider starting ESA treatment when the hemoglobin level is less than 10 g/dL. This advice does* not define *how far below 10 g/dL is appropriate for an individual to initiate. This advice also does* not recommend *that the goal is to achieve a hemoglobin of 10 g/dL or a hemoglobin above 10 g/dL. Individualize dosing and use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions. Adjust dosing as appropriate.*	Agree. We've tried to clarify the language further by inserting the phrase "if they are to be used at all".
2	Page 39: - the "10/30" was base on an off the cuff recommendation by a Mayo Anesthesiologist in WWII (Vox Sang. 2010 Jan;98(1):2-11)	Thank you. We've inserted this reference.
2	Page 40 – given that most ACS patients in the USA get PCI should transfusions be proscribed in them for hbg > 8-9??	This is a question for policy- and guideline-makers. The data summarized here are still largely of poor quality because it is mostly observational data.
2	Page 41 – The person with the ferritin of 50 is truly iron deficiency and needs some form of iron replacement - also needs a GI work-up – maybe a ferritin of 123 would make the point better	We felt the data was not as strong for patients with ferritin > 100. The Anker study included patients with higher ferritins, but most had ferritin well below 100 and the applicability of the results of this IV iron trial are strongest for patients with low ferritins.
2	Page 42 – I though the trial for ESA for STEMI was distinctly negative - *JAMA. 2011 May 11;305(18):1863-72. Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction: REVEAL: a randomized controlled trial.* *Najjar SS, Rao SV, Melloni C, Raman SV, Povsic TJ, Melton L, Barsness GW, Prather K, Heitner JF, Kilaru R, Gruberg L, Hasselblad V, Greenbaum AB, Patel M, Kim RJ, Talan M, Ferrucci L, Longo DL, Lakatta EG, Harrington RA; REVEAL Investigators.* – also stroke - *Stroke. 2009 Dec;40(12):e647-56*	This and 2 other recent trials examined one-time high-dose ESA use in ACS patients but these were not focused on treatment of anemic patients. As such, they fell outside of the scope of our review. Inclusion of the statement alluding to these studies in our discussion is probably confusing and we've deleted it.

Reviewer	Comment	Response
3	Overall excellent review. The "emerging themes" concept is great as it does not leave the reader hanging in his/her approach to the individual patient. Love the way you broke out the high quality studies in fig 3 and 4.	Noted. Thanks.
3	On page 2- need to fill in # of studies rejected. Page 11- first box on right needs the N filled in.	Done.
3	We can develop practice guidelines around this but would not promulgate quality measures just yet.	Noted.
4	Overall --very readable, a seemingly transparent, honest assessment of the literature leaving this reader confident in the findings and the interpretations.	Noted.
4	Never easy to give weight to benefits and harms, or benefits versus harms, the problem was not clearly resolved in this analysis. I've no suggestions and in general thought the balance reached by the authors was reasonable.	Noted.
4	Except for the one ongoing study of 80 patients, all (or the vast,vast majority) patients apparently had recognized systolic dysfunction. In some CHF series, up to half have normal ejection fractions. . While I can't think why this would group would fare differently with treatments for anemia, available studies don't apply. . In some clinical trials evaluating arrhythmia patients, a clinical history of CHF was a more powerful predictor of outcome than ejection fraction measurements.	Agree. We've added statements to the ESA "summary" paragraph in results, the ESA discussion, and the Future studies sections clarifying that this evidence base applies most directly to those with reduced systolic function.
4	No data on influence of very common and potentially important contributors to outcomes....smoking, lung disease, cardiovascular medications, arrhythmias (particularly atrial fibrillation), others....	We limited the ESA and iron sections to trials only. We examined each trial for important baseline differences, though most were adequately randomized. This is more of an issue for the observational transfusion studies and we have evaluated the methodologic characteristics – including accounting for important confounders – of these studies.
Question 5: Are there any clinical performance measures, programs, quality improvement measures, patient care services, or conferences that will be directly affected by this report? If so, please provide detail.		
1	Absolutely. The use of blood is high in the VA system as is the use of ESAs. By providing this document, the use of these therapies with limited benefit should be curbed resulting in safer care for veterans at lower cost.	Noted.
2	Yes – this report has wide implications for multiple areas of care	Noted.
3	Each individual institution/system will need to assess its use of ESA's, iron and transfusions in these populations.	Noted.
Question 6. Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.		
1	I think the section on Clinical Applications should be more prescriptive. Also the clinical scenarios are a bit strange. I would prefer to see broader categories, or if this is too difficult, a table with the first column being the clinical situation and the subsequent columns addressing ESAs, Iron, and Blood transfusion. The cells then could have a (+), (-), or "Unk" for whether the evidence supports or refutes use or if there are no data.	We intended the GRADE table to show the level of evidence in various broad clinical categories for each of the interventions.
2	I think the transfusion part could stand alone as a journal article	Noted.
3	Target not only the cardiology and hospitalist leaders, but the P&T and blood bank chairs at system levels.	Noted.