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Red blood cell transfusion to treat or prevent complications in sickle cell disease: an overview of Cochrane reviews

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

To summarize the evidence in Cochrane reviews of the effectiveness and safety of red cell transfusions versus no transfusion, or restrictive (to increase the total haemoglobin) versus liberal (to decrease the haemoglobin S level below a specified percentage) transfusion, for treatment or prevention of complications experienced by people with SCD.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) is an inherited blood disorder, which can lead to life-threatening complications. People with sickle cell disease experience episodes of severe pain, and other complications including anaemia, end-organ damage, pulmonary complications, kidney disease, and increased susceptibility to infections and stroke (Pleasants 2014). It is one of the most common severe monogenic disorders in the world, due to the inheritance of two abnormal haemoglobin (beta globin) genes (Rees 2010). Populations originating from sub-Saharan Africa, the western hemisphere (South America, the Caribbean, and Central America), the Middle East, India and parts of the Mediterranean are predominantly affected.

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CONTRIBUTIONS OF AUTHORS

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Patricia Fortin: protocol development, searching, selection of studies, eligibility and quality assessment, data extraction and analysis.
Sally Hopewell: protocol development and methodological expert.
Marialena Trivella: protocol development and statistical expert.

DECLARATIONS OF INTEREST

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Reductions in infant and child mortality and increasing migration from highly affected countries have made this a worldwide problem (Piel 2012). Over 12,500 people in the United Kingdom and 100,000 in the USA are estimated suffer from the disease (NICE 2010; Pleasants 2014). A recent study estimated that approximately 305,800 babies were born with SCD in 2010, of which two thirds were born in Africa, and this could increase by 25% to approximately 404,200 by 2050 (Piel 2012).

The term 'sickle cell disease' refers to all genotypes that cause the clinical syndrome. There are three main types of SCD. Sickle cell anaemia is the most common form of the disease (up to 70% of cases of SCD in people of African origin) and is due to the inheritance of two beta globin S (βS) alleles (haemoglobin (Hb)SS). The second most common genotype (up to 30% of cases in people of African origin) is haemoglobin SC disease (HbSC disease) it is due to the co-inheritance of the βS and βC alleles and tends to be a more moderate form of the disease. The third major type of SCD occurs when βS is inherited with a β-thalassaemia allele, causing HbS/β-thalassaemia. (Rees 2010). People who have inherited a thalassaemia null mutation (HbSß°) have a disease that is clinically indistinguishable from sickle cell anaemia, whereas people with HbS β^+ thalassaemia have a milder disorder. In high-income nations, people with SCD are expected to live into their 40's, 50's and beyond, whereas in low-income countries including some African nations it is estimated that between 50% to 90% of children born with HbSS die before their fifth birthday (Gravitz 2014; Grosse 2011).

In people with SCD experiencing low oxygen levels, acidity and cellular dehydration, the HbS molecules polymerise and begin to distort the red blood cells taking on the appearance of sickle-shaped cells. The main determinant of disease severity is the rate and extent of this HbS polymerisation (Rees 2010). This is exemplified by co-inheritance of genetic factors that affect the intracellular HbS or fetal haemoglobin concentration, for example the protective effects of co-inherited α-thalassaemia (Rumaney 2014; Steinberg 2012) or hereditary persistence of fetal haemoglobin (Akinsheye 2011; Steinberg 2012). Sickling of red blood cells results in two main events: blockage of blood flow resulting in organ and tissue ischaemia; and haemolytic anaemia (Sparkenbaugh 2013). Both of these processes are thought to lead to increased inflammation and an increased tendency to develop a clot (Frenette 2007; Rees 2010). Blockage of blood flow is mediated via a dynamic interaction between sticky HbS containing red cells, the vessel wall, and white cells (Rees 2010). Sickle red blood cells also have a shorter lifespan of 10 to 12 days versus 120 days for normal red blood cells due to intravascular and extravascular haemolysis, leading to anaemia (Kato 2006a). Chronic intravascular haemolysis leads to decreased levels of nitric oxide within the blood, development of pulmonary hypertension and ischaemic strokes (Kato 2006a; Kato 2006b).

Description of the interventions

Individuals with SCD experience a variety of both acute and chronic complications as a result of the disease. Complications may be quite severe and include acute chest syndrome, acute cerebrovascular accident (CVA), acute and chronic pain, ocular or renal complications, chronic leg ulcers, priapism, avascular necrosis, pulmonary hypertension, and chronic respiratory and hepatobiliary complications (Expert Panel Report 2014). The course of the

disease is highly variable with some people having a relatively mild course with fewer complications and longer survival and others having frequent severe complications and shortened survival. Blood transfusions are a mainstay of treatment in SCD and 90% of adults will have received at least one red blood cell transfusion (Chou 2013a).

Red blood cell transfusions can be given to treat complications of SCD, e.g. acute chest syndrome (this often involves a single transfusion episode), or they can be part of a regular long-term transfusion programme to prevent complications of SCD (Yawn 2014). People with SCD can be placed on a long-term transfusion programme to prevent recurrence of a complication they have already experienced or to prevent the first episode of a complication e.g. stroke in children with abnormal transcranial dopplers (Adams 1998). Both a single transfusion episode or chronic transfusion programmes can use either a simple transfusion regime or an exchange transfusion regime (Josephson 2007). In addition to restrictive (to increase the total haemoglobin) or liberal (to decrease the haemoglobin S level below a specified percentage) red cell transfusions, other therapies may include drug therapy as an alternative to red cell transfusions such as hydroxyurea for anaemia, pain and acute chest syndrome; or adjuvant red cell transfusion therapies such as analgesics for pain, oxygen for chest complications and fluid replacement for pain crisis.

Red blood cell transfusions have reduced complications and improved the quality of life in people with SCD; however, they can also cause adverse events that are sometimes serious (Josephson 2007). The benefits of transfusion therapy must be balanced against risks including infections, iron overload, alloimmunisation, acute or delayed haemolytic transfusion reactions, and increased complexity of compatibility testing (Chou 2013a, Chou 2013b; Porter 2013; Scheunemann 2010; Ubesie 2012).

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How the intervention might work

Transfusing normal red blood cells to people with SCD who are anaemic, can increase the oxygen carrying capacity of the blood (Swerdlow 2006; Wagner 2007).

Sickled red blood cells increase blood viscosity (resistance to flow) through intrinsic properties of the sickled cells, as well as through abnormal interactions of these cells with white cells, platelets, the vessel wall, and clotting factors. Transfusion of normal donor red blood cells is used to mitigate these effects (Yawn 2014) and several regimens are used in current clinical practice. These include ’simple’ transfusion in which normal red cells are given to decrease anaemia without removal of the individual’s blood. In people with SCD who do not have severe anaemia ’simple’ blood transfusions can cause hyperviscosity syndrome because they raise the haemoglobin, but only marginally lower the HbS percentage (Schmalzer 1987).

Exchange transfusion involves removing some of the individual’s own blood and transfusing allogeneic blood, thereby lowering the concentration of HbS through dilution. This reduces the effects of a given haemoglobin level on blood viscosity. A full exchange transfusion involves a full blood volume exchange by manual or automated apheresis, this allows for rapid lowering of the HbS level to 30 per cent or less, and correction of anaemia. A partial (limited) exchange transfusion refers to manual removal of some of the individual’s own

blood, this is less effective in lowering the HbS level but is more easily performed when automated exchange is not available. In order to lower the HbS below 30 per cent, repeat partial exchange transfusions may be necessary.

A restrictive (conservative) transfusion policy involves giving a simple transfusion to reach a pre-specified target haemoglobin. A liberal (aggressive) transfusion policy involves giving a transfusion to reduce HbS percentage below a pre-specified threshold. In people with SCD with severe anaemia 'simple' blood transfusions can lead to a significant reduction in HbS percentage without the need for an exchange transfusion. In a trial of people with SCD due to have an operation, 36% of participants randomised to the 'aggressive' transfusion arm (to reduce HbS percentage to 30 or below) were treated with a 'simple' transfusion pre-operatively (Vichinsky 1995).

Why it is important to do this overview

For people with SCD red cell transfusions can reduce end-organ damage and be lifesaving by treating or preventing life-threatening complications (e.g. treating acute aplastic crisis or preventing strokes in children), but it may also be associated with serious complications. There are many indications for transfusion therapy in SCD; however, because of the inherent risks, an understanding of the evidence for its use for specific SCD complications is required. There is also wide variation in transfusion practices in SCD and some indications for transfusion therapy have been studied in randomised controlled trials and others based on observational studies or anecdotal evidence (Josephson 2007). Several Cochrane reviews addressing SCD complications such as stroke (Wang 2013), acute chest syndrome (Alhashimi 2010), chronic chest complications (Cho 2014), and pre-operative transfusions (Hirst 2012) have been published. Providing an overview of these reviews will make the information more accessible for people with SCD and health professionals.

In this overview we will identify gaps in the evidence base to inform recommendations for new systematic reviews and clinical trials research. We will also summarize evidence on reported outcomes to make recommendations for standardizing outcomes for new research and reviews. We will appraise the reviews and summarize their quality and strength of evidence and consider both common indications for transfusion as well as indications where transfusion is not commonly indicated but may be occasionally used. We will also consider the type of transfusion, restrictive or liberal, that may be most appropriate for a particular complication and whether transfusions are intermittent or chronic and used for prevention or treatment.

OBJECTIVES

To summarize the evidence in Cochrane reviews of the effectiveness and safety of red cell transfusions versus no transfusion, or restrictive (to increase the total haemoglobin) versus liberal (to decrease the haemoglobin S level below a specified percentage) transfusion, for treatment or prevention of complications experienced by people with SCD.

METHODS

Criteria for considering reviews for inclusion

Types of reviews—We will include Cochrane reviews of randomised or quasi-randomised controlled trials published in the *Cochrane Database of Systematic Reviews* part of *The Cochrane Library*, that review the use of red cell blood transfusions for treatment or prevention of the various complications of SCD such as stroke, acute chest syndrome, chronic chest complications.

Participants—We will include Cochrane reviews of people of all ages with known SCD.

Interventions—We will include Cochrane reviews that compare the following.

1. Red cell transfusions versus no red cell transfusions
2. Red cell transfusions plus standard care versus standard care (e.g. analgesia, intravenous fluids, oxygen)
3. Red cell transfusion versus disease-modifying drug therapy (e.g. hydroxyurea)
4. Restrictive (to increase the total haemoglobin) versus liberal (to decrease the haemoglobin S level below a specified percentage) red cell transfusion strategy

Primary outcomes—

1. Mortality from any cause
2. Serious adverse events (SAEs) as a result of sickle cell-related complications (e.g. neurological, ophthalmological, respiratory, orthopaedic, vascular, hepatic or renal complications, vaso-occlusive pain crisis, priapism, infections). We plan to report a summary count of total SAEs related to sickle cell-related complications, as well as reporting the types of complications that make up this summary measure.
3. Adverse events (serious and non-serious) associated with transfusions (e.g. acute and delayed transfusion reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, transfusion-associated dyspnoea, alloimmunisation, iron overload, problems of venous access). We plan to report a summary count of all adverse events related to transfusions, as well as reporting the types of complications that make up this summary measure.

Secondary outcomes—

1. Other adverse events (AEs) as a result of sickle cell-related complications.
2. Red cell transfusion requirement (Number of units or millilitres required or number of red cell transfusion episodes)

3. Quality of life (using validated instruments)
4. Hospital length of stay including length of stay in critical care and hospital readmissions

Search methods for identification of reviews

We will do a broad search of the *Cochrane Database of Systematic Reviews* (http://www.cochranelibrary.com/cochrane-database-of-systematic-reviews/table-of-contents-cdsr.html) using text words, sickle cell disease, blood, transfusion in the title, abstract and keywords and we will also use MeSH descriptors including,'anemia. sickle cell', 'erythrocyte transfusion'. We will focus on retrieving all relevant published systematic reviews and identify published protocols (*see* Appendix 1 for *Cochrane Database of Systematic Reviews* search strategy).

We plan to repeat this search biennially to update the overview in order to include new reviews and updates of included reviews.

Data collection and analysis

Selection of reviews—Two authors will independently evaluate all reviews retrieved in the search for eligibility using the criteria listed in the Criteria for considering reviews for inclusion in the above section. We will resolve conflicts through discussion to arrive at a consensus or by using third party adjudication.

Data extraction and management—Two overview authors will independently extract data using the DistillerSR software (DistillerSR 2014). Data will be extracted on a form designed to summarise key characteristics of each review. We will abstract data on the objectives of each review, any diagnostic criteria, inclusion criteria (e.g. participants, details of intervention, comparison, outcomes, type of trials and length of follow up), date of last search, frequency of updates, number of included trials, number of participants for each comparison and statistical outcome data. We will also include narrative text of the results if meta-analyses using the Review Manager software are not available (RevMan 2014).

We will extract data from included reviews where possible, but we will contact the review authors or extract data from the relevant trials ourselves if information is missing or unclear. Data obtained from authors or studies will be integrated with data obtained from the review and the source of the data will be highlighted.

We will report these data in a series of summary tables including a 'Characteristics of included reviews' table, and also report details of the quality assessment of individual reviews in a table, as recommended in chapter 22 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Assessment of methodological quality of included reviews

Methodological quality of included reviews—Two overview authors will assess the methodological quality of the included reviews using the 11 domains in AMSTAR (Shea 2007;Appendix 2) and use these domains to interpret the results of the review. We will not

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exclude reviews based on their methodological quality. We will not conduct sensitivity analysis to explore the consequences of combining reviews of varying methodological quality because all included reviews are Cochrane reviews we are not expecting significant overlap between comparisons. A recent systematic review of the measurement properties of AMSTAR found that the interrater reliability of AMSTAR was very satisfactory (Pieper 2015). As more guidance is provided for its use, and additional validity studies that link systematic review methodological quality to the strength of conclusions (Pieper 2015), we will use AMSTAR in future updates of this overview until a more reliable tool becomes available. AMSTAR domains include:

1. an *a priori* design;
2. duplicate review and data abstraction;
3. a comprehensive search was performed;
4. status of publication used as an inclusion criteria;
5. a list of included and excluded studies provided;
6. characteristics of included studies provided;
7. scientific quality was assessed and documented;
8. scientific quality was used appropriately in formulating conclusions;
9. appropriate methods were used to combine the findings of trials;
10. publication bias was assessed;
11. conflict of interest included.

Quality of evidence in included reviews—Two overview authors will assess and summarize the quality of evidence included in the 'Summary of Findings Table' and the'Risk of Bias' tables according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and recommendations in the *Cochrane Handbook of Systematic Reviews of Interventions*, respectively (Balshem 2011; Higgins 2011a; Schünemann 2011). Assessments will include information on outcomes across studies and based on trial design, directness of evidence, precision and consistency of results, and publication bias. Where possible we will grade the outcomes based on assessments provided in the original reviews. Differences will be resolved through discussion or third party adjudication.

Data synthesis—Our unit of analysis will be the included systematic reviews. We will present all statistical outcome data if available, if this is not possible we will present data as a narrative synthesis. We will report the evidence for each intervention from the reviews using the GRADE approach (Balshem 2011; Schünemann 2011). Comparisons presented will be determined by the data available in the reviews.

We will include an 'Overview of reviews' table which is in a format similar to the 'Summary of findings' table as recommended in chapter 22 of the *Cochrane Handbook for Systematic*

Reviews of Interventions (Higgins 2011b). These will include the primary outcomes of this overview for each intervention.

Where possible, data from reviews will be classified into subgroups based on:

- the indication for red cell transfusion is for prevention or treatment of SCD complications;
- acute or chronic red cell transfusions;
- restrictive (to increase the total haemoglobin) or liberal (to decrease the haemoglobin S level below a specified percentage) transfusion;
- by age of participants (children, adolescents, adults);
- patient characteristics (i.e. pregnant, undergoing surgery, type of SCD).

We do not plan to conduct any indirect comparisons or network meta-analyses.

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External sources

- NIHR Cochrane Programme Grant 13/89/09 - Safe and appropriate use of blood components, UK.

Appendix 1. The Cochrane Database of Systematic Reviews search strategy

#1	MeSH descriptor: [Anemia, Sickle Cell] explode all trees
#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*”)
#3	(“sickle cell” or sicklemia or sickled or sickling or meniscocyt* or drepanocyt*)
#4	#1 or #2 or #3
#5	MeSH descriptor: [Blood Transfusion] this term only
#6	MeSH descriptor: [Erythrocyte Transfusion] explode all trees
#7	((blood or erythrocyte* or “red cell*” or “red blood cell*” or RBC*) near/5 (transfus* or infus* or unit*))
#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

#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

#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”)

#11 hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*

#12 (red cell* or erythrocyte* or blood or RBC*) and transfus*:ti

#13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

#14 MeSH descriptor: [Blood Component Transfusion] this term only

#15 MeSH descriptor: [Erythrocytes] this term only

#16 (red cell* or red blood cell* or erythrocyte* or RBC*)

#17 #14 and (#15 or #16)

#18 ((transfus* or red cell* or red blood cell* or RBC*) near/10 (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*))

#19 (((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

#20 #13 or #17 or #18 or #19

#21 #4 and #20

Appendix 2. AMSTAR checklist

AMSTAR - a measurement tool to assess the methodological quality of systematic reviews.

1. Was an ’*a priori*’ design provided?

The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined or *a priori* published research objectives to score a ’yes’.

☐ Yes

☐ No

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- ☐ Can’t answer
- ☐ Not applicable

2. Was there duplicate study selection and data extraction?

There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: two people do study selection, two people do data extraction, consensus process or one person checks the other’s work.

- ☐ Yes
- ☐ No
- ☐ Can’t answer
- ☐ Not applicable

3. Was a comprehensive literature search performed?

At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, Embase, and MEDLINE). Key words or MESH terms (or both) must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

Note: If at least two sources + one supplementary strategy used, select ’yes’ (Cochrane register/Central counts as two sources; a grey literature search counts as supplementary).

- ☐ Yes
- ☐ No
- ☐ Can’t answer
- ☐ Not applicable

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language, etc.

Note: If review indicates that there was a search for ’grey literature’ or ’unpublished literature’, indicate ’yes’. SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey or unpublished literature.

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☐ Yes

☐ No

☐ Can’t answer

☐ Not applicable

5. Was a list of studies (included and excluded) provided?

A list of included and excluded studies should be provided. Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select ’no’.

☐ Yes

☐ No

☐ Can’t answer

☐ Not applicable

6. Were the characteristics of the included studies provided?

In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes.

The ranges of characteristics in all the studies analysed e.g., age, race, sex, relevant socioeconomic data, disease status,duration, severity, or other diseases should be reported.

Note: Acceptable if not in table format as long as they are described as above.

☐ Yes

☐ No

☐ Can’t answer

☐ Not applicable

7. Was the scientific quality of the included studies assessed and documented?

’A priori’ methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study (’low’ or ’high’ is fine, as long as it is clear which studies scored ’low’ and which scored ’high’; a summary score/range for all studies is not acceptable).

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☐ Yes

☐ No

☐ Can’t answer

☐ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating Note: Might say something such as “the results should be interpreted with caution due to poor quality of included studies”. Cannot score ’yes’ for this question if scored ’no’ for question 7.

☐ Yes

☐ No

☐ Can’t answer

☐ Not applicable

9. Were the methods used to combine the findings of studies appropriate?

For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

Note: Indicate ’yes’ if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity or variability between interventions.

☐ Yes

☐ No

☐ Can’t answer

☐ Not applicable

10. Was the likelihood of publication bias assessed?

An assessment of publication bias should include a combination of graphical aids (e.g. funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

Note: If no test values or funnel plot included, score ’no’. Score ’yes’ if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

☐ Yes

- ☐ No
- ☐ Can't answer
- ☐ Not applicable

11. Was the conflict of interest included?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Note: To get a 'yes', must indicate source of funding or support for the systematic review AND for each of the included studies.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

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Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.

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* *Indicates the major publication for the study*

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