

PAPER C

A SUMMARY OF WORK BY THE SYSTEMATIC REVIEW INITIATIVE : 2014/15

The Systematic Review Initiative was established in 2002, following concern about the lack of a supporting infrastructure for the development of the evidence base for transfusion in England. The need for an evidence base had been highlighted in the successive 'Better Blood Transfusion' Health Service Circulars. In the second of these, 'systematic review and research into the clinical and cost-effectiveness of transfusion practice including alternatives to donor transfusion' was included as a recommendation that required specific work. In the third, a specific objective was to "increase the evidence base for transfusion practice".

The Systematic Review Initiative (SRI) is based in Oxford and has a remit to perform systematic reviews of the literature covering randomised trials in transfusion medicine. Approximately half of the work of the SRI is undertaken in collaboration with The Cochrane Collaboration. The SRI was initially funded by the NBA Trust Funds but since 2005 the SRI has been funded through the blood pricing mechanism. The SRI has one full time and four part time core members of staff. All other staff members (for full details please see Appendix 4) contribute a set number of hours on a weekly basis to the SRI.

EXECUTIVE SUMMARY

The focus of our work over the last year has been to complete the large number of reviews that were in progress at the 2014 Steering Group meeting and to continue with our work on the Transfusion Evidence Library.

In 2014/15:

- ❑ six systematic reviews and six protocols work were completed and published;
- ❑ four systematic reviews and three protocols are completed and undergoing peer review;
- ❑ we explored the impact of all our published reviews (PAPER D);
- ❑ we have continued with our work programmes, as detailed in PAPERS E1 (core work programme) and E2 (NIHR Cochrane programme grant);
- ❑ the Transfusion Evidence Library now contains references to **851** high-quality transfusion medicine systematic reviews, **5,638** fully indexed randomised controlled trials and 11 clinical commentaries;
- ❑ we recruited two systematic reviewers for the NIHR Cochrane programme grant; lost one and are in the process of re-recruiting to the vacant post;
- ❑ our Assistant Information Specialist left (February 2015) and we have successfully recruited to the post;
- ❑ we continue in our relationship with the Centre for Statistics in Medicine, Oxford.

ACTIVITY OF THE SYSTEMATIC REVIEW INITIATIVE: 2014 - 15.

1. Systematic Reviews

Published 2014 - 15: see appendix 1 for full citation details.

Protocols:

- Adverse effects of small-volume red blood cell transfusions in the neonatal population. *Systematic Reviews* 2014
- [NIHR] Alternative agents versus prophylactic platelet transfusion for preventing bleeding in patients with disorders after chemotherapy or stem cell transplantation. [update]. *Cochrane Database of Systematic Reviews*
- [NIHR grant] Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy or stem cell transplantation [update]. *Cochrane Database of Systematic Reviews*
- [NIHR grant] Comparison of a restrictive versus liberal red cell transfusion policy for patients with myelodysplasia, inherited or acquired aplastic anaemia, and other congenital bone marrow failure disorders [new]. *Cochrane Database of Systematic Reviews*.
- [NIHR grant] Comparison of a therapeutic-only versus prophylactic platelet transfusion strategy for prevention of bleeding in patients with haematological disorders after chemotherapy or stem cell transplantation [update]. *Cochrane Database of Systematic Reviews*
- [NIHR grant] Comparison of different doses of prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy or stem cell transplantation [update]. *Cochrane Database of Systematic Reviews*

Systematic Reviews

- Current evidence of the efficacy of cell-based therapies in heart failure. *Circulation Journal* 20015
- Meta-analysis of cell therapy trials for patients with heart failure – an update. *Circulation Research* 2015.
- Red blood cell transfusion for people undergoing hip fracture surgery. *Cochrane Database of Systematic Reviews* 2015.
- The impact of electronic decision support on transfusion practice: a systematic review. *Transfusion Medicine Reviews* 2015.
- Transfusion of fresher versus older red blood cells for all conditions. *Cochrane Database of Systematic Reviews* 2015.
- Transfusion interventions in critical bleeding requiring massive transfusion: a systematic review. *Transfusion Medicine Reviews* 2015

Completed and currently undergoing peer review

- Fresh frozen plasma for cardiovascular surgery. *Cochrane Database of Systematic Reviews*. – has been in this state since last year, despite 3 re-submissions and an updated search run in March 2015.
- Intracranial haemorrhage in haematology patients receiving myeloblastic chemotherapy or stem cell transplantation.
- [NIHR grant] Comparison of different platelet count thresholds prior to insertion of central lines [protocol; new; rapid]. *Cochrane Database of Systematic Reviews*
- [NIHR grant] Comparison of prophylactic versus therapeutic fresh frozen plasma prior to insertion of central lines [protocol; new; rapid]. *Cochrane Database of Systematic Reviews*
- [NIHR grant] Granulocytes for preventing infection in patients with neutropenia or neutrophil dysfunction [update]. *Cochrane Database of Systematic Reviews*
- [NIHR grant] Transfusion therapy for complications in sickle cell disease [protocol; new; review of reviews]. *Cochrane Database of Systematic Review*
- Stem cells and acute myocardial infarction. [update] (Cochrane Heart Group).

Title registered with a Cochrane review group

- [NIHR grant] Red cell transfusions in patients with sickle cell disease and renal impairment [new; rapid]. *Cochrane Database of Systematic Reviews*
- [NIHR grant] Comparison of alternative agents versus prophylactic platelet transfusion for prevention of bleeding in patients with chronic bone marrow failure disorders [new; rapid]. *Cochrane Database of Systematic Reviews*

Ongoing activity

We have twelve systematic reviews and one secondary paper that are ongoing. Five of the thirteen are being led by members of the SRI; eight are being led by a Clinical Fellow and the SRI are providing methodological assistance and support as required. For a full list of these projects, please see PAPER E1.

For a list of, and details of progress of the systematic reviews within the NIHR Cochrane Programme grant, please see PAPER E2.

2. Searching Activities

a. Hand searching

Since 2006 we have only undertaken the prospective hand searching of conference abstracts, and since 2008 have retrieved only those abstracts addressing areas within the SRI Group scope. See Appendix 2 for a list of publications hand searched. The findings of this hand searching provide an excellent resource for people interested in the practice of transfusion medicine. Details of all relevant SRs and RCTs identified through hand searching have been indexed and are now

available on the Transfusion Evidence Library (www.transfusionevidencelibrary.com). As of May 2015, the library contains records of 920 RCTs and 52 SRs identified through hand searching alone.

b. Additional Searching

The information science workload continues to grow. One aspect of this workload is updating search results while a review is in preparation. Our policy has always been to run a full search at the beginning of the review process and another full search close to expected submission. Frequently Carolyn Dorée has been running 2 or 3 additional searches during the course of a review. During the past year, Carolyn has been encouraging review authors to set up PubMed auto alerts to highlight any new studies published during the course of the review so that only two full searches per review are required. This policy has lapsed somewhat this year, in part due to the lengthy Cochrane review process and we need to address the number of searches which are undertaken for each review over the coming year.

This year has also seen an increase in the number of searches designed and undertaken with the introduction of the NIHR Cochrane Programme Grant. The workload for the grant has been staggered so as to accommodate the search activities alongside core SRI work and the Transfusion Evidence Library.

In addition to the comprehensive searching undertaken for all in-house systematic reviews, the SRI (through Carolyn) acts as an occasional resource for individuals/research groups wanting to undertake searching on a given topic by developing and amending search strategies, running the searches on a wide range of relevant databases and screening the hits generated for relevance to the given topic. During 2014/15 Carolyn devised and/or updated the search strategies and performed searches for the following:

- non-SRI Cochrane review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion (JL Carson et al) – update search (April 2015).

3. The Transfusion Evidence Library.

In January 2013, our funders the UK Blood Forum agreed that we could seek a commercial partner for the re-development of the Transfusion Evidence Library. Our partner since mid-2013 has been Evidentia Publishing, a company specialising in developing, marketing and selling bespoke electronic specialist libraries.

The Transfusion Evidence Library is freely available to users in the UK (including blood service staff and the wider NHS) and is sold internationally (see PAPER H for a list of sales), through Evidentia Publishing, to health services, professional societies, blood transfusion organisations, academic institutions and individuals. Sales were steady through the year, but were not as high as Evidentia Publishing had hoped; we are therefore being asked to consider what mechanisms could

be used to increase sales during the next few months (and years). A report by Evidentia Publishing detailing the sales of the TEL to date and future plans is provided in PAPER H.

An important element of our ongoing marketing campaign is to attract new customers - and retain current subscribers - by adding value to the library in various ways. One such initiative is the Transfusion Evidence Alert, an email which is sent each month to over 14,000 people within the transfusion community containing 10 of the most interesting new systematic reviews and RCTs from the library. This has continued to be a great success, and has both increased awareness of and visits to the library. In order to tailor these alerts to the individual, Evidentia has developed Personal Accounts by which a user can register by email, select an area(s) of interest within transfusion and then sign up to receive monthly Personal Evidence Updates of the most recent studies relevant to them.

A further development during 2014-15 is our 'Clinical Commentaries'. These are commentaries on new systematic reviews and RCTs (listed in the TEA) which are written by a clinician and listed alongside the systematic review or RCT reference on the Transfusion Evidence Library. Each commentary is a short discussion of the objective, findings and implications of the paper in question. We are trying to match papers to interested clinicians in order to maximise the value of the commentaries.

In March 2015, we ran a 6-week user survey for the Transfusion Evidence Library, which was promoted widely during this period. Unfortunately, we received only 13 responses, an insufficient number to analyse, with no offers to join our user focus group. We are now looking into promoting the TEL through attendance at conferences in partnership with Evidentia Publishing.

Currently the Transfusion Evidence Library contains 855 systematic reviews and over 5,600 randomised controlled trials relevant to transfusion medicine. During 2014-15 the backlog of RCTs (from 1950-1996) relevant to transfusion was screened and processed by the SRI information specialists, and the library now contains all MEDLINE RCTs from 1950 onwards.

4. NIHR Cochrane Programme grant

The NIHR Cochrane programme grant started on 1st July 2014. The grant will see us deliver 28 systematic reviews over the duration of the grant. The principal investigator is Dr Lise Estcourt. Susan Brunskill is supporting in managing much of the HR and contract side of the grant and Carolyn Doree is the primary Information Specialist for the reviews. Details of the systematic reviews to be undertaken and their progress to date is available in PAPER E2.

The reviews are being undertaken with either the Cochrane Haematological Malignancies Group [n = 22], the Cochrane Cystic Fibrosis Group [n= 8] and the Cochrane Gynaecological Cancer group [n=2]. The reviews are either new [n = 19] or updates to existing Cochrane reviews [n = 11]. The style of the new reviews are either standard [n = 8], rapid [n = 9] or review of reviews [n = 3]. The methodology for rapid reviews was defined a priori in the grant application.

We are receiving statistical and methodological support and training from the Centre for Statistics in Medicine for the duration of the grant. This support is fortnightly and takes place in their offices. We have subcontracts in place with all external groups, except Cochrane Gynaecological Cancer group. We are using the review programme Distiller to manage the early stages of the review process and Review Manager to present the protocol and systematic review to the Cochrane review group.

The grant allows us to employ two NHS band 7 systematic reviewers [to a total of 1.3 WTE]. Recruiting to these posts has been difficult and taken considerable resource. We advertised in June 2014 and found two suitable systematic reviewers. One, Patricia Fortin, relocated from Canada to take up the 0.8 WTE post. Meeting the visa and permit requirements meant a delay of 8 months, and a re-advertisement of the post, but Patricia started with us on 16 February 2015 and is proving to be an excellent addition to the SRI. The second systematic reviewer started with us in late September 2014 on a 0.5 WTE contract. Unfortunately, this reviewer left us, with mutual consent on 7 May 2015. The post was re-advertised on 6th May 2015: with interviews scheduled for 17th June 2015. As a result of the difficulty and delays in recruitment, NIHR have granted us a 6 month extension to the grant, seeing the grant finish on 31st December 2017.

A current concern and a projected future difficulty is the length of time it is taking Cochrane to work through the peer review and editorial review process. This has undoubtedly got longer and more involved. Whilst this may increase the quality of the final review, it is a significant resource issue for the SRI and causes significant delays getting protocols and reviews peer reviewed. It also has a knock on effect on the currency of each search date. We are monitoring the situation and in an effort to facilitate the process have developed a generic protocol and review proforma for both Cochrane groups; each proforma includes the nuances that are expected by the respective group.

5. Links with groups outside the NHSBT

We have continued to develop the national and international links established over the previous years during 2014/15. This has predominantly been collaboration on systematic reviews:

- Dr Stephen Hibbs, an academic foundation trainee, Oxford and Drs Rick Kaufman (Boston), Mark Yazer (Pittsburgh) and Nathan Nielsen (clinical fellow in Boston) (electronic decision support in transfusion medicine);

- Dr Jon Bailey, trauma academic clinical fellow and Dr Nicola Curry, Consultant Haematologist, Oxford (the acute management of trauma haemorrhage [update]);
- Dr Kathryn Oakland, research fellow, lower gastroenterology, Oxford (the management of acute lower gastrointestinal bleeding);
- Dr Akshay Shah, critical care academic fellow, Oxford (Oral or parenteral iron supplementation to treat anaemia in adult critical care patients);
- Dr Annemarie Docherty, critical care academic fellow, Edinburgh (Transfusion thresholds in patients with cardiovascular disease);
- Dr Jason Tay, Consultant Haematologist/ Associate Scientist, Clinical Epidemiology Program (Restrictive versus liberal red blood cell transfusion triggers for patients with a haematological malignancy treated with intensive chemotherapy and/or stem cell transplantation);
- Dr Kirstin Wilkinson, a Consultant Cardiac Anaesthetist (red blood cell and congenital heart failure review);
- Drs Clare Pulford and Sarah Cook, Consultant Physician, Trauma/Geratology and Registrar in Geriatrics, Oxford and Dr Ali Shokoohi, Haematology Locum Consultant, Bath (hip fracture);
- Dr Ravinder Sandu, Cardiac Registrar, Liverpool (FFP for cardiovascular surgery);
- Drs Erica Wood, Zoe McQuilten and Sunelle Englebrecht and colleagues, Monash University, Melbourne, Australia (Patient Blood Management);
- Dr Jez Fabes, Intensivist Registrars, London (prohaemostatic coagulant factors);
- Drs Dean Fergusson, Alan Tinmouth and Jason Tay, Canada (transfusion triggers for patients with a haematological malignancy);
- Graham Smith, Blood Transfusion Service Manager, Frimley Park Hospital (iron supplementation in donors & donor deferral);

6. Talks and Presentations

Over the last year, members of, and reviewers within the SRI have been asked to give talks and presentations at national and international conferences. See appendix 3 for a full list of talks, presentations and conference abstracts.

7. Other activities

- Charlie Lythgoe, our Assistant Information Specialist left us for librarianship at Oxford Brookes University in February 2014. Her post has been ably filled by Catherine Kimber who started with us on 13th April 2015.
- Sheila Fisher increased her working hours with the group to 0.5 WTE from 1st January 2015.

- We have continued our successful and very rewarding relationship with the Centre for Statistics in Medicine, Oxford. They provide statistical and methodological support for all our systematic reviews, as well as discussions about future clinical trials.

8. Where next - work plan for 2015/16

To accompany this report there is an additional paper which will be discussed at the SRI Steering Group meeting:

PAPER E1	A summary of ongoing core work activities
PAPER E2	NIHR Cochrane Programme Grant reviews and their progress
PAPER F	Our Cochrane reviews: their status and our plans
PAPER G	SRI Procedures and policies – new to 2015

APPENDIX 1: SRI Publications 2014-15

Adverse effects of small-volume red blood cell transfusions in the neonatal population. Keir A, Pal S, Trivella M, Lieberman L, Callum J, Shehata N, Stanworth S. *Systematic Reviews* 2014; 3;92

Current evidence of the efficacy of cell-based therapies in heart failure. Harvey E, Fisher SA, Doree C, Taggart DP, Martin-Rendon E. *Circulation Journal* 20015; 79(2); 229-36

Meta-analysis of cell therapy trials for patients with heart failure – an update. Fisher SA, Doree C, Mathur A, Martin-Rendon E. *Circulation Research* 2015; 116 (8); 1361-77

Red blood cell transfusion for people undergoing hip fracture surgery. Brunskill SJ, Milette SL, Shokoohi A, Pulford EC, Doree C, Murphy MF, Stanworth S. *Cochrane Database of Systematic Reviews* 2015; 21, 4.

The impact of electronic decision support on transfusion practice: a systematic review. Hibbs SP, Nielsen ND, Brunskill S, Doree C, Yazer MH, Kaufman RM, Murphy MF. *Transfusion Medicine Reviews* 2015; 29 (1); 14-23.

Transfusion of fresher versus older red blood cells for all conditions. Brunskill SJ, Wilkinson KL, Doree C, Trivella M, Stanworth SJ. *Cochrane Database of Systematic Reviews* 2015

Transfusion interventions in critical bleeding requiring massive transfusion: a systematic review. McQuilten Z, Creighton G, Englebrecht S, Gotmaker R, Brunskill SJ, Murphy MF, Wood EM. *Transfusion Medicine Reviews* 2015; 29 (2) 127-137.

APPENDIX 2: Journals and Conference Abstracts Hand searched by the SRI up to May 2014

Year 1 st published	Years to be hand searched	Years completed
CONFERENCE ABSTRACTS		
AABB: AMERICAN ASSOCIATION OF BLOOD BANKS [IN TRANSFUSION] [1948: 1 st CONFERENCE]	1980 ONWARDS	COMPLETED: 1980 – 2014
ASBMT: AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION (BMT TANDEM MEETINGS) [ONLINE]	2010	COMPLETED : 2010
ASH: AMERICAN SOCIETY OF HEMATOLOGY [IN BLOOD] [1958(?): 1 st CONFERENCE]	1986 ONWARDS	COMPLETED 1986 - 2013 (1958-1985 TO BE HANDSEARCHED BY HAEM MALIGNANCIES CRG)
BBTS: BRITISH BLOOD TRANSFUSION SOCIETY [IN TRANSFUSION MEDICINE] [1983: 1 st CONFERENCE]	1990 ONWARDS	COMPLETED 1988, 1990 – 2014
BSH: BRITISH SOCIETY OF HAEMATOLOGY [IN BJH]	1993 ONWARDS	COMPLETED: 1993 – 2014
DGTI: GERMAN SOCIETY FOR TRANSFUSION MEDICINE AND IMMUNOHEMATOLOGY CONGRESS [IN VOX SANGUINIS]	2010 ONWARDS	COMPLETED: 2010-2014
EBMT: EUROPEAN GROUP FOR BLOOD & BONE MARROW TRANSPLANTATION (IN BONE MARROW TRANSPLANTATION)	1997 – 2010	COMPLETED 1997 - 2010
EHA: EUROPEAN HEMATOLOGY ASSOCIATION [IN HAEMATOLOGICAL] [1994: 1 st CONFERENCE]	1994 ONWARDS	COMPLETED: 1994 - 2014
HSANZ: AUSTRALIA & NZ COMBINED ANNUAL SCIENTIFIC MEETING [ONLINE]	1999 ONWARDS	COMPLETED 1999 - 2012
ISBT: INTERNATIONAL [IN VOX SANG.] [1950: 1 st CONFERENCE - BIENNIAL]	1994 ONWARDS	COMPLETED 1988, 1994 – 2014
ISBT: REGIONAL CONGRESS, EUROPE [IN VOX SANGUINIS - BIENNIAL]	2005 ONWARDS	COMPLETED: 2005-2013
ISBT: REGIONAL CONGRESS, ASIA [IN VOX SANGUINIS - BIENNIAL]	2005 ONWARDS	COMPLETED: 2005-2013
ISTH: INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS [ONLINE- BIENNIAL]	2007 ONWARDS	COMPLETED: 2007-2014
NATA: NETWORK FOR THE ADVANCEMENT OF TRANSFUSION ALTERNATIVES [ONLINE]	2004 ONWARDS	COMPLETED: 2004 - 2015

APPENDIX 3: Talks, presentations and abstracts from the SRI (2013-14).

SUBJECT	TO WHOM	DATE
TALKS AND PRESENTATIONS		
Introduction to systematic reviews	MSc students, Bristol University [LE]	22 October 2014
Risk factors for bleeding in patients with haematological malignancies	RDM Annual Symposium, Prize Lecture, University of Oxford [LE]	04 February 2015
Platelet transfusion overview	State of the Science Symposium for NIH/NHLBI, NIH, Bethesda [MM]	25 March 2015
Pathogen Inactivation of Platelets: overview from the UK	AABB Symposium on Pathogen Inactivation of Platelets [MM]	28 April 2015
Comparison of a restrictive versus liberal red blood cell transfusion policy in myelodysplastic syndromes and other bone marrow failure disorders – a systematic review	13 th Annual Symposium on Myelodysplastic Syndromes, Washington DC [LE]	29 April 2015
Platelet transfusions the evidence	NHSBT consultants Annual Face to face meeting [LE]	11 May 2015

APPENDIX 4: SRI staff 2014-2015

