

PAPER C

A SUMMARY OF WORK BY THE SYSTEMATIC REVIEW INITIATIVE : 2015/16

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 has been funded by the NBA Trust Funds, the blood pricing mechanism and is now funded through the Clinical Directorate and the UK Forum. 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

In 2015/16:

- ❑ five systematic reviews were completed and published;
- ❑ five further systematic reviews are completed and undergoing peer review;
- ❑ we recruited a second systematic reviewer for the NIHR Cochrane programme grant;
- ❑ we explored the impact of all our published reviews (PAPER D);
- ❑ we have begun a larger project to assess/ understand the wider impact of the SRI (PAPER E);
- ❑ we have continued with our work programmes, as detailed in PAPER F1 (core work programme) and PAPER F2 (NIHR Cochrane programme grant);
- ❑ the Transfusion Evidence Library now contains references to 1,105 high-quality transfusion medicine systematic reviews, over 6,200 fully indexed randomised controlled trials and 18 clinical commentaries;
- ❑ we are working towards an open access model for the Transfusion Evidence Library;
- ❑ we have developed a plan for a stem cell library (akin to our Transfusion Evidence Library);
- ❑ we are working through the Priority Setting Partnership process for blood transfusion with the James Lind Alliance;
- ❑ we are currently reviewing the support we receive from the Centre for Statistics in Medicine, Oxford.

ACTIVITY OF THE SYSTEMATIC REVIEW INITIATIVE: 2015-16

1. Systematic Reviews

Published 2015-16: see appendix 1 for full citation details.

Systematic Reviews

- Cell therapy for heart disease: Trial sequential analyses of two Cochrane reviews. *Clinical Pharmacology and Therapeutics*.
- Fresh frozen plasma for cardiovascular surgery. *Cochrane Database of Systematic Reviews*.
- Interventions to reduce vasovagal reactions in blood donors: a systematic review and meta-analysis. *Transfusion Medicine*
- Stem cell treatment for acute myocardial infarction. *Cochrane Database of Systematic Reviews*.
- The impact of restrictive versus liberal transfusion strategies on patient outcomes in patients with cardiovascular disease excluding those undergoing cardiac surgery: A Systematic Review and Meta-analysis. *British Medical Journal*

Completed and currently undergoing peer review

- Adverse effects of small-volume red blood cell transfusions in the neonatal population has been submitted (late 2015) to *Transfusion*.
- Haematopoietic stem cell therapy: composition of graft and outcome has been submitted (June 2016) to *British Journal of Haematology*.
- In patients with critical bleeding requiring massive transfusion, what is the optimal dose, timing and ratio (algorithm) to red blood cells, of blood component therapy (FFP, platelets, cryoprecipitate or fibrinogen concentrate) to reduce morbidity, mortality and transfusion, update for the National Blood Authority, Australia.
- Oral or parenteral iron supplementation to treat anaemia in adult critical care patients has been submitted (June 2016) to *Critical Care*
- Stem cell therapy for chronic ischaemic heart disease and congestive heart failure: has been submitted (May 2016) to *The Cochrane Library* [update].

NIHR Cochrane Programme grant

See PAPER F2 for a list of the reviews and their progress.

Ongoing activity

We have 12 systematic reviews and one secondary paper that are ongoing. Five of the thirteen projects are being led by members of the SRI; seven are being led by a Clinical Fellow and the SRI is providing methodological assistance and support as required. For a full list of these projects, please see PAPER F1.

2. Searching Activities

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. Please

see Appendix 2 for a list of publications currently 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 systematic reviews and RCTs identified through hand searching have been indexed and are now available on the Transfusion Evidence Library (www.transfusionevidencelibrary.com). As of June 2016, the library contains records of 1,011 RCTs and 68 systematic reviews identified through hand searching alone.

b. Additional Searching

The information science workload has grown considerably over the past year as 23 of the 28 systematic reviews associated with the NIHR Cochrane Programme Grant are now in production. Although the workload for the grant has been staggered so as to accommodate searching activities associated with core SRI work and the Transfusion Evidence Library, information science support for external project has necessarily been limited.

During 2015/16 Carolyn devised and/or updated the search strategies and performed searches for the following:

- Cochrane review (non-SRI): 'Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion' (JL Carson et al) – update searches (December 2015 & May 2016).
- SuReInfo (Summarized Research in Information Retrieval in HTA) – searches performed & data extracted for chapter, 'Value of using different search approaches' (November 2015).
- BCSH Guideline – 'What is the evidence that supports the use of viscoelastic haemostatic assays in major haemorrhage?' (full information science support, June 2016).

3a 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 (TEL) is freely available to users in the UK (including blood service staff and the wider NHS) and is sold internationally (see PAPER G 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). We are also

working with Evidentia to develop an Open Access model for the Library. A report by Evidentia Publishing detailing the sales of the TEL to date and future plans is provided in PAPER G.

The Library is updated monthly with all the new RCTs and systematic reviews relevant to transfusion medicine. These are identified by a monthly MEDLINE Alert and then processed for entry on the Library. In February 2016, we set up a weekly PubMed alert in addition to the monthly MEDLINE search which means that relevant records are now added to the library more quickly after publication, and that the overall number of records added monthly has increased. On average 60-70 records are now added monthly, and currently the Transfusion Evidence Library contains 1,105 systematic reviews and over 6,200 randomised controlled trials relevant to transfusion medicine.

Another feature of the TEL is our 'Clinical Commentaries'. These are commentaries on new systematic reviews and RCTs which are written by a clinician and listed alongside the relevant systematic review or RCT on the Transfusion Evidence Library. Each commentary is a short discussion of the objective, findings and implications of the paper in question. We try to match papers to interested clinicians in order to maximise the value of these commentaries. This development has been in a state of flux owing to staff changes over the course of 2015, but we are planning a renewed focus on this activity during 2016-17, to increase the value of the library and to increase usage by publicising new Critical Commentaries.

Evidentia Publishing has now fully installed and implemented Google Analytics on the TEL site, so we can now gain a detailed picture of library usage. An analysis of the first six weeks of data shows our audience is predominantly in the younger age group, and while most of our users come from the USA and the UK there is also significant usage from Canada, Europe and Australia. Over the period of analysis, the library had ~1500 visits. However, the most revealing finding from the analytics was that our Transfusion Evidence Alert is the biggest driver of usage of the library, with approximately 90% of the library's usage coming in response to these monthly email alerts; e.g. on the day of the alert, the library saw ~300 uses, whereas a normal day would see in the region of 30 users. Meanwhile, promoting the library on social media has increased the usage by 10-30 daily users. Now that analytics have been implemented, we will continue to keep and analyse usage statistics on a regular basis.

The lessons learned from Google Analytics and social media analysis show that marketing activities and the "pushing" of information are much more important than previously realised. To increase the visibility and usage of TEL over the course of the year we have undertaken and planned a variety of internal and external marketing activities:

- Created a presentation on how the Library can help nurses fulfil their new revalidation requirements, and sent it to senior nurses within NHSBT.
- Stepped up our promotion activities on Twitter, using relevant hash tags, and producing themed postings for awareness days such as World Blood Donor Day.
- Printed new flyers for distribution at the European Conference on Donor Health and Management (ECHDM 16)
- Developed a contact list of librarians at UK universities and medical schools to promote the library.

We are working with a postgraduate publishing student from Oxford Brookes University to produce a Communication Strategy for the SRI which will include the TEL. We are hoping that this will give us a more formal framework for our marketing activities and identify new avenues for dissemination.

3b. The Stem Cell Evidence Library (STEMCEL)

Over the last 6 months we have developed a proposal for a haematopoietic stem cell library, akin to our Transfusion Evidence Library. This library, given the working title STEMCEL will be an open access resource from day one, and we will be seeking financial support through grants and sponsorship. We have received initial set up funds from within NHSBT, through the Specialist Services Division. An application has been made for funds from the Oxford BRC and we are awaiting the outcome of that application. We will also be seeking sponsorship from additional partners. We will be seeking to appoint a new member of staff to manage the identification and collation of content for the STEMCEL and also oversee such activities for the Transfusion Evidence Library.

A steering group, chaired by Professor Charles Craddock, Director of the Blood and Marrow Transplant Unit at the Queen Elizabeth Hospital Birmingham (QEHB) and Professor of Haematology at the University of Birmingham will meet for the first time in October 2016. Membership of this committee will also include representatives from NHSBT, University of Oxford and the British Society of Blood and Marrow Transplantation (BBMST). The inaugural meeting will address issues of the scope of the clinical content and study type, timelines, resource requirements and possible funding opportunities.

We have explored many options for the development of STEMCEL because our principal requirement was that it be an open access resource. Recently, after a successful meeting with Evidentia Publishing (developers of our Transfusion Evidence Library), we have begun to talk to them about being the developers of STEMCEL. If such a collaboration proves possible, it will help

the core SRI team in the initial phases of development as Evidentia Publishing are already familiar with an existing product that we wish to use as our starting point.

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 are available in PAPER F2.

The reviews are being undertaken with 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 = 21] or updates to existing Cochrane reviews [n = 11]. The style of the new reviews are either standard [n = 10], rapid [n = 8] or a 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 the Cochrane Gynaecological Cancer Group. We were using the review programme Distiller to manage the early stages of the review process, but have not renewed the contract from June 2016 as the Cochrane Collaboration now expect all their reviews to use the package Covidence and we are making the switch to, and getting familiar with Covidence. We use 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 1.2 WTE]. Patricia Fortin started with us on 16 February 2015 and Dr Reem Malouf on 8 October 2015. The grant will finish on 31st December 2017. Progress with the grant activities is good and we are on schedule to complete by the end of 2017.

As last year, a concern and a future difficulty is the length of time it is taking Cochrane to work through the peer review and editorial review process. This continues to be lengthy, very involved and idiosyncratic to the Cochrane review group. We continue to monitor timelines for the completion of the peer review and editorial processes, using the generic protocols and review proformas we developed in early 2015 for these Cochrane groups, with each proforma including the nuances that are expected by the respective groups.

5. Blood Transfusion Priority Setting Partnership & James Lind Alliance

In September 2015, we became involved in a priority setting partnership (PSP) for blood transfusion. Each PSP consists of a steering group made up of patient/carers (n = 6) and clinical representatives (n = 8), which is supported by staff from the James Lind Alliance. The role of a PSP is to identify questions about treatment which have not been answered by research to date, and then to prioritise these questions. Through consultation and a review of the literature, the steering group's aim is to translate these "uncertainties" into a top ten list of agreed research questions and then obtain funding for that research.

The first stage of the PSP process - a survey to identify treatment uncertainties and open to all involved with or interested in blood transfusion - has recently been completed. We are currently involved in the process of sifting through the survey responses to refine and catalogue the posed uncertainties into "collated indicative questions". Thereafter we will take the lead in seeking to identify what extent these refined questions have, or have not been, answered by previous research. This process is to begin in June 2016 and should take up to three months to complete.

6. Links with groups outside the NHSBT

We have continued to develop the national and international links established over the previous years during 2015/16. This has predominantly been collaboration on systematic reviews:

- Dr Stephen Hibbs, an academic foundation trainee, in relation to the Priority Setting Partnership James Lind Alliance work;
- Dr Kathryn Oakland, research fellow in 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 Kirstin Wilkinson, Consultant Cardiac Anaesthetist and Dr Jonathan Huber, Anaesthetist trainee (update to the FFP review);
- Drs Erica Wood, Zoe McQuilten and Sunelle Englebrecht and colleagues, Monash University, Melbourne, Australia (Patient Blood Management);
- Dr Jez Fabes, Intensivist Registrar, London (prohaemostatic coagulant factors);
- Dr Suzy Morton, Consultant Haematologist, Birmingham (CMV);
- Kath Coleman, Visiting medical student, Monash University, Australia (transfusion triggers: blood loss).

7. Talks and Presentations

Over the last year members of, and reviewers associated with 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.

8. Other activities

- Reem Malouf started as a systematic reviewer for the NIHR Cochrane Programme grant in October 2015.
- We 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. We are in the process of redefining the nature of the contract between the SRI and CSM for the coming year.
- The core team has attended several methodological training opportunities in the past year.

9. Where next - work plan for 2016/17

To accompany this report there are additional papers which will be discussed at the SRI Steering Group meeting:

PAPER F1	A summary of ongoing core work activities
PAPER F2	NIHR Cochrane Programme Grant reviews and their progress
PAPER G	Our Cochrane reviews: their status and our future plans.

APPENDIX 1: SRI Publications 2015-16

Core SRI systematic reviews:

Published:

The impact of restrictive versus liberal transfusion strategies on patient outcomes in patients with cardiovascular disease excluding those undergoing cardiac surgery: A Systematic Review and Meta-analysis. Docherty AB, O'Donnell R, Brunskill S, Trivella M, Doree C, Holst L, Parker M, Gregersen M, Pinheiro de Almeida J, Walsh TS, Stanworth SJ. *British Medical Journal*; 2016 Mar 29, 352:i1351.

Interventions to reduce vasovagal reactions in blood donors: a systematic review and meta-analysis. Fisher SA, Allen D, Doree C, Naylor J, Aangelantonio ED, Roberts DJ. *Transfusion Medicine*; 2016, 26(1):15-33.

Stem cell treatment for acute myocardial infarction. Fisher SA, Zhang H, Doree C, Mathur M, Martin-Rendon E, *Cochrane Database of Systematic Reviews*. 2015 Sep 30;9:CD006536

Cell therapy for heart disease: Trial sequential analyses of two Cochrane reviews. Fisher SA, Doree C, Taggart DP, Mathur A, Martin-Rendon E. *Clinical Pharmacology and Therapeutics*; 2016 Jul;100(1):88-101

Fresh frozen plasma for cardiovascular surgery. Desborough M, Sandu R, Brunskill SJ, Doree C, Trivella M, Monteodori A, Abrahams I, Stanworth S. *Cochrane Database Systematic Reviews*. 2015 Jul 14;7:CD007614.

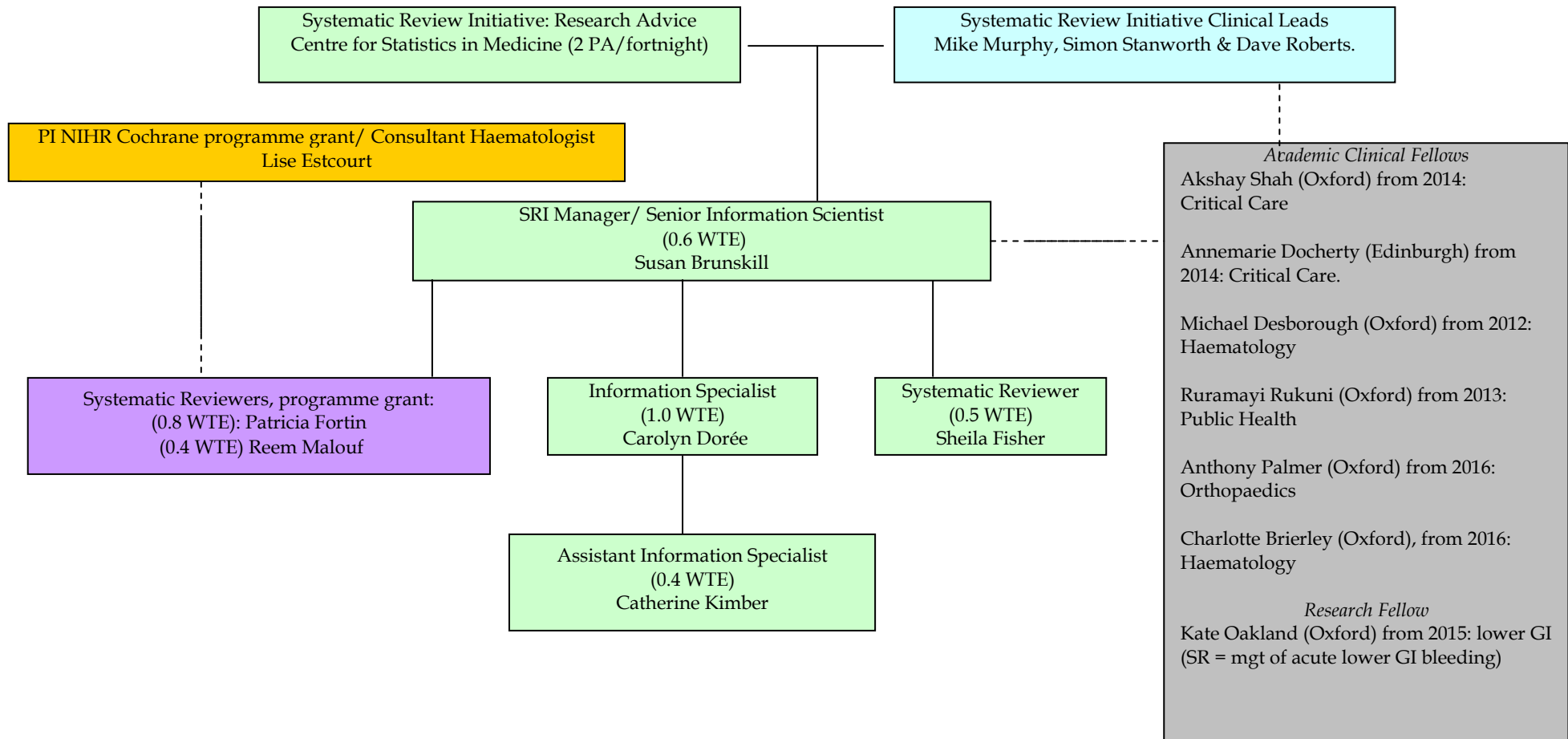
APPENDIX 2: Journals and Conference Abstracts Hand Searched by the SRI up to May 2016

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 – 2015
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 - 2015 (1958-1985 TO BE HANDSEARCHED BY HAEM MALIGNANCIES CRG)
ASPHO: ANNUAL MEETING OF THE AMERICAN SOCIETY OF PEDIATRIC HEMATOLOGY ONCOLOGY	2011 ONWARDS	COMPLETED 2011-2016
BBTS: BRITISH BLOOD TRANSFUSION SOCIETY [IN TRANSFUSION MEDICINE] [1983: 1 st CONFERENCE]	1990 ONWARDS	COMPLETED 1988, 1990 – 2015
BSH: BRITISH SOCIETY OF HAEMATOLOGY [IN BJH]	1993 ONWARDS	COMPLETED: 1993 – 2016
CSTM CANADIAN SOCIETY FOR TRANSFUSION MEDICINE	2009 ONWARDS	COMPLETED: 2009-2015
DGTI: GERMAN SOCIETY FOR TRANSFUSION MEDICINE AND IMMUNOHEMATOLOGY CONGRESS [IN VOX SANGUINIS]	2010 ONWARDS	COMPLETED: 2010-2015
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 - 2015
HSANZ: AUSTRALIA & NZ COMBINED ANNUAL SCIENTIFIC MEETING [ONLINE]	1999 ONWARDS	COMPLETED 1999 - 2015
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: 2005-2015
ISBT: REGIONAL CONGRESS, ASIA [IN VOX SANGUINIS - BIENNIAL]	2005 ONWARDS	COMPLETED: 2005-2015
ISH : INTERNATIONAL SOCIETY OF HEMATOLOGY	2010 ONWARDS	COMPLETED: 2010-2012, 2014 UNAVAILABLE, 2016 JOINT WITH BSH
ISHTM: INDIAN SOCIETY OF HEMATOLOGY AND TRANSFUSION MEDICINE	2010 ONWARDS	COMPLETED: 2010-2015
ISTH: INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS [ONLINE- BIENNIAL]	2007 ONWARDS	COMPLETED: 2007-2015
NATA: NETWORK FOR THE ADVANCEMENT OF TRANSFUSION ALTERNATIVES [ONLINE]	2004 ONWARDS	COMPLETED: 2004 - 2016

APPENDIX 3: Talks, presentations and abstracts from the SRI (2015-2016).

	TO WHOM	DATE
TALKS AND PRESENTATIONS		
Platelet Transfusions and their alternatives	Clinical trials Unit Biannual talk, Stoke Gifford. (LE)	June 2016
Cells at the moment of truth: recent findings from systematic reviews and meta-analyses (STEMI and heart failure)	13 th International Symposium on Stem Cell Therapy and cardiovascular Innovations, Madrid. (EMR)	May 2016
Restrictive vs. liberal blood transfusion thresholds in patients with cardiovascular disease: Systematic Review	South East Scotland Intensive Care Journal Club (AMD)	May 2016
Talk including the following 4 reviews: 1. Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review 2. Alternative agents versus prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after chemotherapy or stem cell transplantation 3. Desmopressin use for minimising perioperative allogeneic blood transfusion 4. Effect of restrictive versus liberal red cell transfusion strategies for any indication on bleeding outcomes: a systematic review and meta-analysis.	BEST meeting, Christchurch College, Oxford (MD)	April 2016
"Systematic Reviews"	Oxford Centre monthly talks: Clinical & Scientific staff (SB)	April 2016
Restrictive vs. liberal blood transfusion thresholds in patients with cardiovascular disease: Systematic Review	Edinburgh and East Scotland Society of Anaesthetists (AMD)	March 2016
Platelet Transfusions	MSc students Bristol (LE)	February 2016
Systematic reviews	MSc students Bristol (LE)	January 2016
Platelet transfusions	BBTS, London (LE)	November 2015
CONFERENCE ABSTRACTS		
Interventions to reduce vasovagal reactions in blood donors: A systematic review and meta-analysis.	2 nd European Conference on Donor Health and Management, Cambridge (DR & SF)	July 2016
Alternatives to prophylactic platelet transfusions	NATA, Dublin (LE)	April 2016
Prophylactic platelet transfusions in patients with haematological malignancies - lessons from the TOPPS trial	NATA, Dublin (LE)	April 2016
Restrictive vs. liberal blood transfusion thresholds in patients with cardiovascular disease: Systematic Review (abstract in Critical Care)	International Symposium of Critical Care and Emergency Medicine (ISICEM), Brussels. (AMD)	March 2016

APPENDIX 4: SRI staff 2015-2016



Funding Streams

- SRI core funding: mix NHSBT & UK Forum
- NHSBT core funding
- NHSBT & NIHR funding
- NIHR funding
- Other funding