Review report of MTG28 Spectra Optia for automatic red blood cell exchange in patients with sickle cell disease

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This medical technology guidance was published in January 2020.

All medical technology guidance is reviewed 3 years after publication.

This review report summarises new evidence and information that has become available since this medical technology guidance was published, and that has been identified as relevant for the purposes of this report. This report will be used to inform NICE's decision on whether this guidance needs to be updated at this time.

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1. Original objective of guidance

To assess the clinical and cost effectiveness of Spectra Optia for automatic red blood cell exchange in patients with sickle cell disease.

2. Current guidance recommendations

“1.1 The case for adopting Spectra Optia for automated red blood cell exchange in patients with sickle cell disease is supported by the evidence. Spectra Optia is faster to use and needs to be done less often than manual red blood cell exchange.

1.2 Spectra Optia should be considered for automated red blood cell exchange in patients with sickle cell disease who need regular transfusion.

1.3 NICE recommends collaborative data collection to generate further clinical evidence on some outcomes of treatment with Spectra Optia. In particular, there is a need for long-term data on how automated and manual exchange affect iron overload status and the subsequent need for chelation therapy.

1.4 Based on current evidence and expert advice on the anticipated benefits of the technology when used in patients with iron overload, cost modelling shows that in most cases using Spectra Optia is cost saving compared with manual red blood cell exchange or top-up transfusion. The savings depend on the iron overload status of the patient, and are more likely to be achieved if devices already owned by the NHS can be used to treat sickle cell disease. The estimated cost saving for adopting Spectra Optia is £18,100 per patient per year, which has the potential to save the NHS in England £12.9 million each year.”

3. Methods of review

The NICE guidance Information Services (gIS) identified 747 records following the literature search of 11 databases (detailed in Appendix C), reduced to 621 after deduplication. Following a first sift, NICE identified 73 records that were considered to be potentially within scope of the decision problem. These records were supplemented with records identified by the company (n = 45) and from clinical advisors (n = 10).

A single EAC reviewer (IW) performed a second sift to identify records that matched the criteria for inclusion in the original Assessment Report (reported in Table 3.1). Full peer reviewed papers of primary studies that met the scope were included regardless of study design with the exception of case reports, which were not included. Secondary papers, such as letters, editorials, and non-systematic reviews, were not included. Systematic reviews with meta-analyses were included, and the reference lists of systematic reviews without meta-analyses were searched for any additional studies not otherwise identified.

Included studies were broadly categorised into study type (comparative, non-comparative, or economic). Conference abstracts, posters and presentations were included but particular attention was given to studies that reported comparative data. A sample of data extracted from studies was checked against the original source by another reviewer (HC). Results were reported by outcome, with the principal outcomes of interest being the proportion of sickled cells (HbS%), iron overload, hospital resource use (including red blood cell [RBC] units), clinical outcomes (frequency of stroke, multi-organ failure, acute chest syndrome and pain crises), and complications associated with apheresis.

Table 3.1. Criteria for study inclusion.

	Inclusion criteria	Exclusion criteria
Population	Sickle cell disease patients requiring a medium or long-term exchange transfusion regime.	Sickle cell patients with an acute complication or crisis. Sickle cell patients not representative of the care pathway (e.g. patients on experimental medication, patients receiving stem cell therapy).
Interventions	Spectra Optia device Cobe Spectra device (predecessor)	Other apheresis technologies
Comparator	Manual red blood cell exchange or partial exchange.	"Top up" transfusions.
Outcomes	<u>Primary outcomes</u> • Percentage of total haemoglobin that is HbS (HbS%), relative to target percentage (usually <30%) • Duration of exchange procedure • Frequency of treatment • Patient haematocrit (measure relative to prescribed target for therapy) • Iron overload and requirement for chelation therapy • Clinical outcomes including frequency of stroke, multi-organ failure, acute chest syndrome and pain crises • Quality of life • Length of hospital stay • Staff time and staff group/grade • Frequency of top-up transfusion required to treat sickle cell complications <u>Secondary outcomes</u> • Ease of venous access, bruising and haematoma • Device-related adverse events • Hospital admissions • Donor blood usage • BMI and growth in children	
Study design	Primary studies reporting quantitative data. Systematic reviews.	Case reports. Narrative reviews, letters, editorials.
Language restrictions	English only.	
Search date	2015 onwards.	2014 and before. Studies dated 2015 cross-referenced against original Assessment Report and excluded if reported in this.

4. New evidence

4.1. Changes in technology

The company has reported there "have been no changes to the technology", nor have there been any changes to the model performance, mode of action, or CE marking status of the technology.

4.2. Changes in care pathways

There are no NICE clinical guidelines on red blood cell exchange (RBCx). There are NICE pathways on *Sickle cell disease: acute painful episode review*, but this is beyond the scope of the MTG28, which is concerned with long-term management of sickle cell disease.

The national programme of Haemoglobin Disorders Reviews, conducted by the West Midlands Quality Review Service (WMQRS), published quality standards in 2018 stating that all patients on long-term transfusions should have access to automated exchange transfusion and that protocols and audits for its use should be in place (West Midlands Quality Review Service, 2018). These quality standards were originally developed separately for children and adults' services, to support the Sickle Cell Society guidelines, published in 2008 as noted in the original Assessment Report, now updated in 2018 (Sickle Cell Society, 2018). This includes the following recommendations concerning transfusions in all people (children and adults) with sickle cell disease (EAC emphasis):

- "OS 26. All hospitals that admit SCD patients should have protocols and training in transfusion for SCD including manual exchange procedures.
- OS 27. Automated exchange transfusion should be available to all patients with SCD and should be provided by specialist centres.
- OS 28. Specialist centres should audit their use of blood transfusion in the acute and chronic setting to ensure its use is consistent with national guidance".

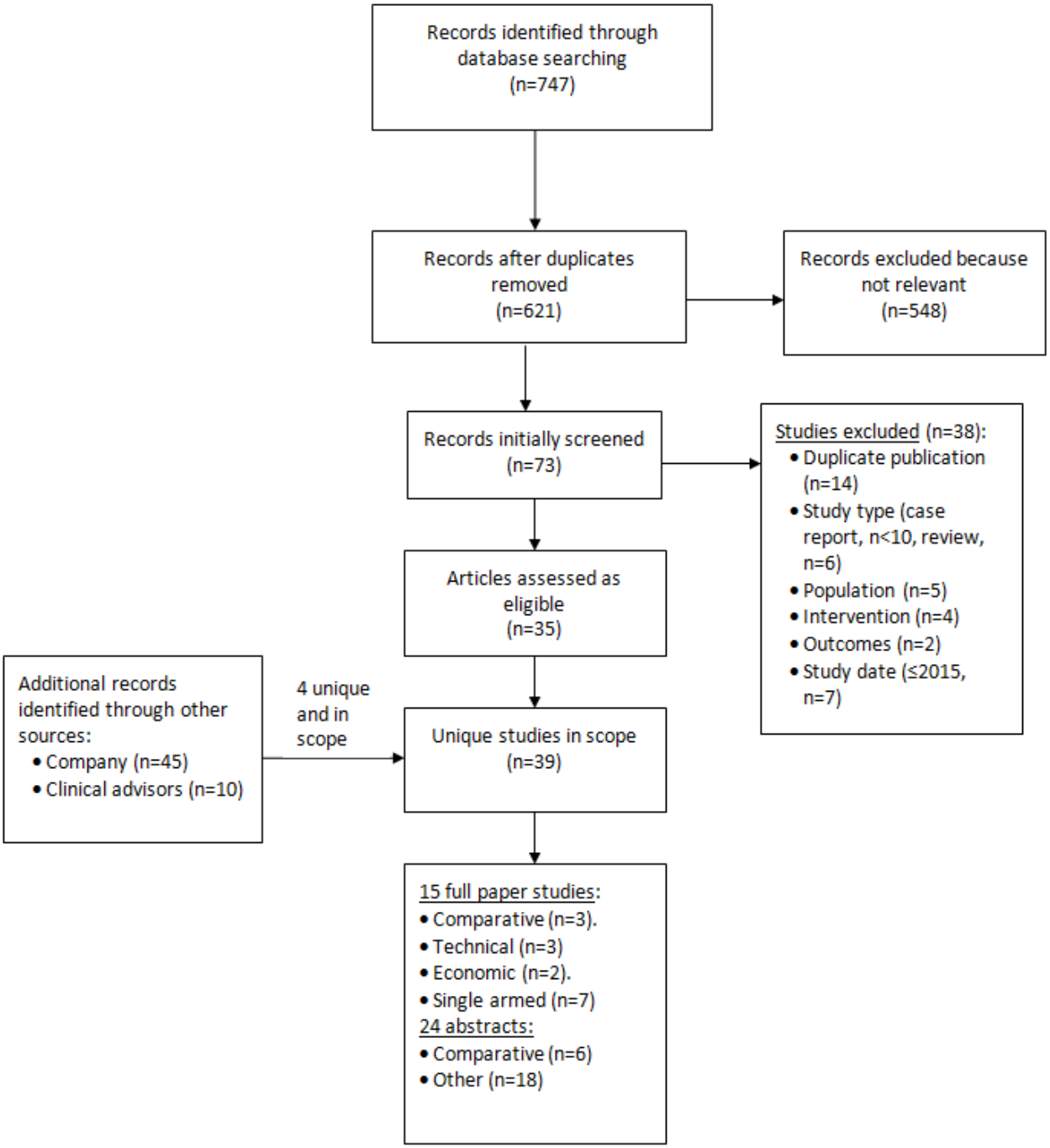
All four clinical experts stated that there had been no changes to patient pathways regarding automated RBCx. However, the original NICE guidance published in March 2016 had improved uptake and access of Spectra Optia. They noted that increased use of Spectra Optia has led to better clinical outcomes for patients, reduced use of iron chelation therapy, reduced number of blood packs required and improved availability meaning that patients did

not have to travel as far for treatment. The experts stated that there were no competing technologies and were not aware of the previous version of the technology (Cobe Spectra) being used in the NHS.

4.3. Results from MTEP MTG review

Study identification, sifting, and selection is illustrated as a PRISMA diagram (Moher et al., 2009) in Figure 4.1. The EAC considered 34 studies from the NICE gIS search were within the scope of the decision problem. These were supplemented by 4 studies identified by the company (n =3) or the clinical advisors (n = 1). No systematic reviews were identified. Sixteen studies were reported in full in peer reviewed journals, whilst 26 studies were available in abstract form only. Studies were categorised as being comparative (with manual RBCx), technical (comparison of Spectra Optia and Cobe Spectra technologies), single armed, or economic. All fully published studies and comparative studies were reported. Non-comparative studies published in abstract form only are listed in Table B5.

Figure 4.1. *PRISMA flow diagram illustrating study selection.*



4.4. New studies

4.4.1. *Overview of included studies*

Comparative studies

Three studies that compared automated RBCx with manual RBCx were published in full in peer reviewed journals. The study by Escobar *et al.* (2017) was a small retrospective cohort comparison that included 16 children and young adults (≤ 21 years) who received automated RBCx with Spectra Optia (37 exchanges) or manual RBCx (57 exchanges) between January 2011 and August 2016. The authors reported on the baseline characteristics of the patients, changes to the proportion of sickled cells (HbS%), and procedural outcomes. Clinical outcomes (e.g. changes in complication rates) were not reported.

The study by Woods *et al.* (2017) was also a retrospective cohort study in children with sickle cell disease (SCD), set in a single institution in the United States. The median age of patients was 11 years (range 2 to 21 years). Patients received manual RBCx (n = 17) or automated RBCx using the Cobe Spectra system (n = 20). However, the groups were not comparable at baseline, with several significant differences, most notably age (6.4 years in the manual group, compared with 12.1 years in the Cobe Spectra group). A focus of this study was the rate of catheter complications. However, control of HbS% and iron overload were also reported.

The study by Fasano *et al.* (2016) was a retrospective cohort study that compared automated RBCx (using the Spectra Optia or Cobe Spectra systems) with simple transfusions (also known as “top up transfusions”) and partial exchange. Patients were classified as belonging to one of these groups if they had received that modality for at least 6 months previously; however, prior to this they may have received a different treatment. The focus of this study was the effect of automated RBCx on reducing iron overload.

Six comparative studies were reported only in abstract form. Three of these were retrospective cohort studies (Ahmed et al., 2018, Araujo et al., 2019, Kelly et al., 2015), one was a cross-sectional study (Dierick, 2019), one was described as a prospective observational study (Nassim et al., 2016), and one was a cross over study (Nzouakou et al., 2018) . None of the studies specifically reported on the technology used to perform automated RBCx. The studies ranged widely in the number of people recruited, from 230 in the study by Ahmed *et al.* (Saudi Arabia), to just 5 patients in the study by Araujo *et al.* (Portugal). None of the abstract studies reported clinical outcomes, other than

to note the absence of adverse events. One of the studies focussed on health-related quality of life (HRQoL) (Dierick, 2019), whilst the aim of study by Nassim *et al.* (2019) was focussed on measurement of blood viscosity. The study by Nzoukou *et al.* was set in the UK (Nzouakou et al., 2018).

None of the comparative studies had an experimental design and thus the comparisons made were likely to be subject to a high degree of confounding and bias. The studies were mainly retrospective in design and were usually poorly reported. Retrospective studies, which use routine data collection, are inherently limited by the quality and completeness of data recorded. They are also particularly subject to reporting bias. In general, the populations were poorly described or mixed, and it is unlikely the compared groups were truly equivalent. In studies of children, age was shown to be a confounding variable. The abstracts were necessarily under-reported and did not adequately describe the interventional or comparative technologies. Therefore these factors combined make it difficult to ascribe an effect or outcome to a specific technological system under study.

An overview of the comparative studies is reported Table B1.

Technical studies

Three studies, published in full, reported comparisons between the Spectra Optia device, and its predecessor, Cobe Spectra (Buyukkurt et al., 2018, Kim et al., 2016, Poullin et al., 2016). These studies were retrospective and had the aims of comparing the procedural efficacy of the technologies in patients with SCD. In one study, Specta Optia was used in the depletion-exchange mode (Kim et al., 2016).

All the studies reported that the performances of the Cobe Spectra and Spectra Optia were broadly equivalent. This agrees with the conclusion of the EAC Assessment Report (Willits et al., 2015), which summarised that the Spectra Optia system represented an incremental developmental improvement over Cobe Spectra, and that for the purposes of health technology assessment, both systems could be considered to be equivalent. Therefore these studies and the issue of equivalence are not considered further in this report.

An overview of the technical studies is reported Table B2.

Single armed studies

Six non-comparative studies were published in full. Most of these were retrospective observational studies (Ballas and Lyon, 2016, Joshua Daniel et al., 2016, Tsitsikas et al., 2017b, Tsitsikas et al., 2016), one was a prospective study focussing on the effects of isovolaemic haemodilution (Hequet et al.,

2019), and one was a correlation study which analysed the relationship between automatic RBCx and ferritin levels and liver iron concentration (Myers et al., 2016). Most the studies used Spectra Optia although some used the predecessor technology, or the method of automated exchange was not explicitly stated. The studies were all limited in sample size, ranging from 50 participants (Hequet *et al.*) to 10 participants (Ballas and Lyon). Two studies were set in the same hospital of the UK (Tsitsikas et al., 2017b, Tsitsikas et al., 2016).

Single-armed observational studies offer only weak inference of causality, and require either explicit comparisons with uncontrolled data sources, such as historical data, or implicit extrapolation for their interpretation (e.g. before and after effect). In the case of Spectra Optia, this is confounded by the nature of RBCx, which features repeated administration, reflecting the chronicity of SCD. Thus single-armed studies may be used to support the absolute outcomes reported in individual arms of the comparative studies, but do not provide information on the comparative effectiveness of automated and manual RBCx.

An overview of the single armed studies is reported Table B3.

Economic studies

Two economic studies were identified that were fully published in peer reviewed journals (Dedeken et al., 2018, Tsitsikas et al., 2017a). Neither included decision analytic modelling, rather they were cost studies that were piggy-backed onto small single-armed observational studies. The study by Dedeken was set in Belgium and featured a “before and after” design with children (age range 9 to 16 years, n = 10) switching from manual to automated RBCx. The study by Tsitikas was set in the UK, and reported on data from 30 participants receiving automated RBCx (device not specified). Costs in this study were driven by hospital attendance for acute painful crises and RBC use.

An overview of the single armed studies is reported Table B4.

Other studies

Abstracts which were within scope but not included for further analysis because they were not comparative are listed in Table B5. Five abstracts not otherwise discussed were set in the UK. Ball (2018) presented a conference abstract which described the role of NHS Blood and Transplant in the uptake of automated RBCx to treat SCD (Ball, 2018). Another conference abstract reported on a small case series of 7 children receiving automated RBCx through the Therapeutic Apheresis Service (TAS), based in Leeds (Hughes et

al., 2017). A comparison of paediatric and adult services from Barts Hospital, London, was presented as a conference abstract (Nzouakou et al., 2016). Trompeter *et al.* reported the impact of automated RBCx on alloimmunisation rates in a large exchange programme in England (Trompeter and McMillan, 2015). Finally, Tsitikas reported 4 year results of a costing study in a conference abstract; however it is highly likely that this was the same population as the fully published paper (see Table B4).

4.4.1. *Results of included studies*

The key outcomes of interest in the assessment of Spectra Optia are its relative effect on physiological outcomes such as HbS% (an intermediate or surrogate measure), iron overload (informing the need for chelation), clinical outcomes (informing patient benefit and healthcare resource use), RBC usage (informing healthcare resource use) and procedural information, such as time of procedure and frequency of procedures (informing healthcare resource use). These outcomes, which were poorly evidenced in the Assessment Report (Willits et al., 2015), are the focus of this review.

The outcomes are reviewed on a study by study basis in Table B6 (comparative studies) and Table B7 (single-armed studies). A brief narrative summary of the outcomes reported by all included studies follows.

Abnormal haemoglobin (HbS%)

In the scope, this was fully described as “Percentage of total haemoglobin that is HbS (HbS%), relative to target percentage (usually <30%)”. Abnormal haemoglobin levels are an important outcome as they are a surrogate for the prevention of complications of SCD. For most indications, a target HbS% of 30% is aimed for post-procedures. This level is associated with reduced mortality and morbidity.

Most of the comparative studies reported this outcome, and in all the studies that reported this, the numerical reduction achieved was greater with automated RBCx than it was for manual RBCx. Of the fully published papers, Escobar *et al.* reported that automated RBCx resulted in a reduction of -46% compared with only -27% for manual RBCx; this difference was significant ($p < 0.001$). In the study by Woods et al, more patients achieved target HbS levels using automated RBCx (59%) compared with manual RBCx (50%), but this difference was not significant. Fasano *et al.* did not report any differences in HbS between partial or automated RBCx, or simple transfusion, but did not report temporal changes from a baseline, so this data was difficult to interpret. The abstracts that compared automated with manual RBCx were poorly reported, but did appear to show automated technologies are associated with larger decreases in HbS% (Ahmed et al., 2018, Araujo et al., 2019, Nassim et

al., 2016, Nzouakou et al., 2018). The single armed studies that reported this outcome all showed that automated RBCx reduced HbS% compared with pre-procedural levels (Ballas and Lyon, 2016, Hequet et al., 2019, Joshua Daniel et al., 2016, Tsitsikas et al., 2017b, Tsitsikas et al., 2016).

These results are consistent with the findings of the original Assessment Report (Willits et al., 2015) in that, although the studies suggest automated exchange is associated with improved removal of sickled cells, this evidence cannot be regarded as unequivocal. This is because of the poor methodological quality of the studies and their reporting, and the lack of experimental evidence available.

Iron overload

Changes to the risk of iron overload is usually measured by the intermediate outcome of blood ferritin levels (measured as absolute value or as a rate) and/or as liver iron concentration. This was the focus of one comparative study, which compared simple transfusion with automated and partial RBCx (Fasano et al., 2016). Automated RBCx, using either Spectra Optia or Cobe Spectra, was associated with significant reduction in both ferritin levels and liver iron content. The other fully published comparative studies specifically reported that automated RBCx did not induce iron overload (Escobar et al., 2017, Woods et al., 2017). One other comparative study, published as an abstract, reported significant improvements in ferritin levels in patients receiving automated compared with manual RBCx (Nzouakou et al., 2018).

The single-armed studies were less informative concerning the potential for automated RBCx to reduce iron overload. However, one study analysed the correlation between the duration a patient has been receiving RBCx and their liver iron concentration (Myers et al., 2016). No significant correlation was detected.

The original Assessment Report found that the evidence for automated RBCx reducing iron overload was equivocal (Willits et al., 2015). The study by Fasano *et al.* (2016), which was also identified as a pre-publication abstract in the Assessment Report, provide statistical evidence that automated RBCx reduces ferritin and liver iron concentrations, but the comparison was with simple top up transfusion and partial exchange, neither of which is iron neutral. Therefore the evidence for Spectra Optia reducing iron overload remains equivocal.

Clinical outcomes and adverse events

The primary function of the Spectra Optia device is to reduce the rate of adverse clinical outcomes associates with SCD, such as stroke, multi-organ

failure, acute chest syndrome and painful crises. There was a paucity of evidence on these outcomes, with no study providing quantitative, statistically informed data at an adequate level of granularity. There was also a lack of evidence published on procedural adverse events. One comparative study, published as an abstract, reported the odds of an adverse event occurring post-procedure were significantly higher with manual RBCx than with automated RBCx, but only once device malfunction was excluded (Kelly et al., 2015). A case series on men with priapism reported resolution of the acute condition in 7/10 patients (Ballas and Lyon, 2016); this was also supported by the authors of a UK study (Tsitsikas et al., 2017b). Another study by the same author reported a 70% reduction in painful crises associated with Spectra Optia use (Tsitsikas et al., 2016); this also has consequences for healthcare resource use.

In conclusion, the evidence for Spectra Optia leading to improved outcomes is unproven. This is due to a lack of sufficiently good quality evidence, rather than negative evidence.

Red Blood Cell Usage and Alloimmunisation

It is generally an accepted fact that automated RBCx requires greater RBC usage than manual exchange or simple transfusion. For instance, the study by Fasano *et al.* (2016) reported that automated RBCx required a mean of 6.8 RBC units, compared with 1.2 for a simple top up transfusion and 2.0 for a partial exchange. This is unsurprising, since these are not like for like comparisons. None of the studies included reported concerns over the alloimmunisation rate associated with increased RBC usage.

Procedural outcomes and healthcare resource use.

The study by Escobar was noticeable in that it reported that automated RBCx was associated with a slightly higher procedural duration than manual RBCx, although there was no statistical difference. This was contradicted by another comparative study, published as an abstract, which found a very large reduction in procedural time associated with automated RBCx (Araujo et al., 2019). Furthermore, the original EAC Assessment Report stated there was unequivocal evidence that Spectra Optia was associated with decreased procedural time (Willits et al., 2015), and there appears to be unanimity amongst clinical experts regarding this. Therefore the EAC considers the result reported by Escobar *et al.* was likely to be an erroneous finding.

The available evidence suggest that automatic RBCx is likely to decrease the requirement for exchange procedures, as it is more efficient at removing and replacing sickled cells. However, although the direction of results were consistent with this, the reduction in frequency reported in the included

studies was relatively small and not described as statistically significant (Fasano et al., 2016, Nzouakou et al., 2018). The evidence reported in the Assessment Report for reduced frequency of procedure was more convincing.

Probably the greatest potential for Spectra Optia to reduce healthcare resource use is by reducing future emergency admissions for complications of the sickle cell disorder, or to prevent the long-term complications of these. As noted, there was very little evidence reported on clinical outcomes. However, two UK studies (possibly with patient overlap) used a "before and after" approach to estimate emergency attendance rates for painful crises, and found these were reduced following the introduction of automated RBCx (Tsitsikas et al., 2017b, Tsitsikas et al., 2016).

Health-related Quality of Life (HRQoL)

One comparative study, presented only as an abstract, reported on HRQoL (Dierick, 2019). It reported that automated RBCx was associated with a 25% improvement in HRQoL compared with manual RBCx (0.70 vs. 0.55, $p < 0.001$). However, the method of HRQoL elicitation was not described so it is not possible to interpret this result further.

Economics

Two economic studies were identified (Table B4). The study by Dedeken *et al.* was based on a small observational study set in Belgium (n = 10) that compared automated RBCx with manual RBCx. Three costs were included; these were the costs associated with RBC usage; the costs associated with the procedure (1 day clinic costs); and the costs associated with chelation to reduce iron overload. Costs directly associated with the technology, Spectra Optia, were not included, nor were costs associated with complications of SCD and iron overload. A 2 year time horizon was reported. The authors reported that during the first year, automated RBCx was associated with a cost of 140,184 Euros, compared with 107,092 Euros for manual exchange. This cost expenditure was reported as non-significant. In the second year, the cost of automated RBCx decreased to 103,270 Euros, mainly because chelation could be stopped (thus saving 382 Euros compared with manual RBCx). However, this reduction was also not statistically significant.

The other economic study was set in the UK (Tsitsikas et al., 2017a). This analysis was based on a retrospective observational study (n = 30). Costing data was derived on Trust income paid by the local care commissioning group (CCG), Commissioning Dataset (CDS), and contract monitoring information. Up to 5 years of automated RBCx data was collected in some patients. Cost savings were based on the rate of emergency admissions due to complications; procedural costs were not included as an expense. Costs

associated chelation were not included. The authors reported that automated RBCx was cost expending in the first year only, at £188. After the first year, there were savings of £7186, £15,129, £17,060 and £22,147 corresponding to the second to fifth years respectively. This was due to reductions in emergency admissions to 20%, 48%, 58%, 71%,and 79% 1, 2, 3, 4 and 5 years after starting automated RBCx. Inclusion of the costs associated with increased RBC usage meant that automated RBCx was cost saving from the third year onwards only. However, reimbursement to the hospital did not cover the estimated procedural costs; thus the authors reported the trust lost between £600 and £800 for each exchange undertaken

4.5 Ongoing trials

No new or ongoing trials were identified by the NICE gIS search of Clinical trials.gov, WHO International Clinical Trial Registry Platform (ICTRP) and ISRCTN on the 8th October, 2019 (Appendix C).

4.6 Changes in costs

The main cost inputs of the economic model are listed in Table 4.1. Most of the costs used in the original assessment were from reference sources which have not changed materially above inflation, including the cost of blood, an important driver of the model.

The cost of chelation was also an important driver of the model. Annual costs of chelation were based on calculations subject to several assumptions, but are ultimately dependent on the cost of the chelation drug, deferasirox (Exjade). The available dosing formulation for this drug appears to have changed since the publication of MTG28. In the original economic analysis, Exjade was priced at £117.60 per pack of 28 125 mg tablets. This works out at a cost of £3.36 per 100 mg active substance. However, Exjade now only appears to be available as 90 mg, 180 mg, or 360 mg tablets available in packs of 30 (BNF, 2019). This works out at a cost of £4.67 per 100 mg active substance, an increase of 39%, and clearly above inflation. The anticipated effect of this would be to increase the cost-saving potential of Spectra Optia, through reduction in the need for chelation medicine.

The capital and servicing costs of Spectra Optia were included in the EAC-revised economic model, assuming a 7 year lifetime of the device. The manufacturer (Terumo BCT), advised that there have been no changes related to the cost of the device. Therefore, technology costs are assumed not to have changed. It should be noted that Spectra Optia is a multifunctional system, and can be used for other purposes such plasma exchange and stem cell harvesting, so not all costs should be attributed to RBCx and the treatment of SCD. Additionally, it is likely that many Trusts have already invested in a Spectra Optia device, and this is evidenced from feedback from the expert advisors. These trusts will not have additional capital outlays should they manage SCD patients with Spectra Optia.

In summary, most of the costs in the model have not changed significantly, although the increase in the costs associated with Exjade might favour Spectra Optia. As an example, in a 15 year old taking the maximum dose of Exjade, this could amount to an additional saving of nearly £6000 per annum.

Table 4.1. *Healthcare resource use and costs used in economic model.*

Resource identified	**Value used by company (baseline)**	**How value was derived (in Assessment Report)**	**EAC comment on potential for updated values**
Procedure times (minutes)	Adults Spectra Optia 110, manual RBCx 245, top up transfusions 300 Children Spectra Optia 86, manual RBCx 245, top up transfusions 180	Mean of several comparative and single armed (automated RBCx only) studies.	These values are consistent with a comparative study in adults set in the UK (Kuo et al., 2015) used in the Assessment Report, and were not controversial. There has not been sufficiently robust, generalisable evidence identified to update these figures.
Number of procedures per year	Spectra Optia 8.5, manual RBCx 12, top up transfusions 13	Mean value from clinical studies supplemented with evidence from clinical advisors.	These values were consistent with two comparative studies identified in the Assessment Report (Dedeken et al., 2014, Kuo et al., 2015). There has not been sufficiently robust, generalisable evidence identified to update these figures.
Number of packed RBCs per procedure	Adults Spectra Optia 7, manual RBCx 4, top up transfusions 2 Children Spectra Optia 5, manual RBCx 4, top up transfusions 2	Mean value from several comparative and single-armed studies.	There has not been sufficiently robust, generalisable evidence identified to update these figures.

Resource identified	Value used by company (baseline)	How value was derived (in Assessment Report)	EAC comment on potential for updated values
Number of staff per patient and staff grade	Spectra Optia 1.0 (grade 5), manual RBCx 1.5 (highly qualified), top up transfusions 0.5 (grade 5)	Estimates from clinical advisors.	No empirical evidence has been identified on staffing requirements and associated costs.
Cost of stroke	One off cost of £21,807 at 2.5 years	Estimate from Cherry *et al.* (2012) (Cherry et al., 2012)	The HTA value by Cherry *et al.* (2012) is likely to remain the most robust estimate, despite limitations. Applying inflationary costs to this figure, the cost of stroke is **£23, 094.**
Cost of hospital admissions	Mean hospital cost £1,354 (range £423 to £3,832)	Estimate from NHS reference cost data related to sickle cell inpatient stay with complication and comorbidity (HRG reference codes SA36A, SA36B and SA36C).	Cost estimates reflect a heterogeneous population of mixed characteristics (children and adults), indications (painful crises, acute chest syndrome) and treatments but excludes cost for those admitted without complications. The EAC has not revalued these costs, which are unlikely to have changed above inflationary adjustment.
Cost of chelation (per year)	Adults: £21,022 Children: £9,954	Drug costs calculated from drug regimens applying BNF unit prices and estimated body weights.	The cost calculation for chelation was complicated. The available tablet dose of deferasirox (Exjade) appear to have changed, making recalculation of these values more difficult (see below).

Resource identified	Value used by company (baseline)	How value was derived (in Assessment Report)	EAC comment on potential for updated values
		Monitoring costs were added by the EAC, based on costs from the HTA by Cherry *et al.* (2012).	
Additional cost of consumables	Spectra Optia: £167.84 (Spectra Optia exchange set) Manual RBCx and top up transfusions: no cost	Information from manufacturer.	Cost of consumables other than Spectra Optia exchange set assumed to common across modalities. The manufacturer has stated these costs have not changed.
Cost of blood	£120 per unit packed RBC (all modalities.	Information from NHS Blood and Tissue Services.	The most recent cost the EAC identified on the cost of a unit of RBC was **£124.46** (set in April 2017). The cost of RBC units is anticipated to decrease in future due to a drop in demand (NHS Blood and Transport, 2016).
Cost of technologies	Capital cost and maintenance contract of Spectra Optia not included in base case results. Manual RBCx and top up transfusions: no such costs.	Pricing information from manufacturer	Capital costs of Spectra Optia were included in the EAC base case of the model.

4.7 Other relevant information

During the literature searching, the EAC became aware of another technology that could be a potential competitor to the Spectra Optia system. The Fenwal Amicus Red Blood Cell Exchange system (Fresenius Kabi) has received FDA 510(k) clearance for marketing in the United States (see www.fresenius-kabi.com). Its CE mark status is unclear. The technology is indicated for "red cell exchange for the transfusion management of sickle cell disease in adults and children". Like Spectra Optia, it can also be used for therapeutic plasma exchange, mononuclear cell (MNC) collection and platelet collection.

The EAC identified 1 MHRA medical device alert published in December 2019 (MDA/2019/041), stating that an "inadequately broken anticoagulant 'frangible' may lead to clotting and inadequate therapy during apheresis procedures." The company had produced a field safety notice (FSN) describing a faulty connector for anticoagulant fluid bags in September 2018. It appears the MHRA alert indicated that users had not responded to the FSN in adequate numbers.

5. Conclusion

The clinical evidence to support the efficacy and cost saving potential of Spectra Optia in the original assessment was poor, comprising mostly retrospective studies, which did not adequately control for potential confounding and bias, and single-armed studies (Willits et al., 2017). The EAC has assessed the published literature since then, and has determined whilst the evidence base has increased in volume, it has not improved in quality. This is perhaps not surprising, as it was commented in the original Assessment Report that new, informative research on the technology was unlikely to be forthcoming, as there was a lack of clinical equipoise. That is, experimental research, such as randomised controlled trials, are unlikely to be performed as there are practical and ethical concerns of assigning people to a comparator arm when it is *self-evident* that the interventional technology is superior. Compared with manual RBC, clinical experts believe the main advantages of the Spectra Optia system are greater efficiency, increased success in achieving clinical targets (HbS, haemoglobin, and haematocrit), and reduced staffing requirements. Patients may benefit from reduced procedure duration and frequency, as well as an assumed reduction in serious complications associated with better control of SCD.

Whilst it is generally not possible to unequivocally prove these benefits using the available data from low methodological quality observational studies, evidence (direction of results) does generally support this, as does anecdotal evidence from providers and users. It should be noted that many costs

associated with serious long-term complications of SCD were not modelled, but if Spectra Optia were to improve these, even marginally, large savings might be gained. Additionally, as the cost of chelation has increased but the cost of RBC units has remained stable, this is also likely to improve the cost-saving potential of Spectra Optia.

The Spectra Optia system was given positive recommendations for use in MTG28. Since then, it appears the technology has been commissioned in several trusts and the therapeutic apheresis service (TAS), based in Birmingham, Bristol, Leeds, Liverpool, London, Manchester, Oxford, and Sheffield. Providers may be reimbursed through Commissioning for Quality and Innovation (CQUIN, B13), although this may not be adequate to recoup all provider costs (Tsitsikas et al., 2017a). Thus, Spectra Optia is increasingly becoming an established treatment in people with SCD. The company have stated that there are 41 NHS users of Spectra Optia.

In conclusion, the EAC did not identify any new evidence from the literature base which it considered were likely to inform or change current recommendations. The comparative study by Kuo *et al.* (2015), set in the UK, remains the most informative evidence, despite its limitations. The EAC did not identify any changes in costs that would likely negatively impact on the cost-saving potential of Spectra Optia. It is possible that increased cost of chelation drugs could increase the cost saving potential of the technology. Therefore, the EAC recommends that MTG28 is put on the static list.

Appendix A – Relevant guidance

NICE guidance – published

NICE CG143, *Sickle cell disease: managing acute painful episodes in hospital*, covers the management of acute painful sickle cell episodes. However, transfusions and RBCx for chronic management of SCD are not covered by this guideline.

NICE guidance – in development

None identified.

Guidance from other professional bodies

The West Midlands Quality Review Service and UK Forum on Haemoglobin Disorders published quality standards in 2018 stating that all patients on long-term transfusions should have access to automated exchange transfusion and that protocols and audits for its use should be in place (West Midlands Quality Review Service, 2018). These quality standards are based on the guidelines from The Sickle Cell Society, last updated in 2018 (Sickle Cell Society, 2018) and the guidelines for clinical care of sickle cell disease in children published by the NHS (NHS Screening Programmes, 2010).

Appendix B – Details of studies and ongoing trials

Table B1 *Characteristics of comparative studies.*

Study reference and location	Study design	Population	Intervention	Comparator	Principal outcomes	Comment
(Escobar et al., 2017) Portugal	Retrospective cohort study	Children and young adults (≤ 21 years) with SCD (n=16)	RBCx with SO (n=37 procedures)	Manual RBCx (n=57 procedures)	HbS levels Ferritin levels RBC usage Vascular access used	Published in a peer reviewed journal.
(Woods et al., 2017) United States	Retrospective cohort study	Children aged 2 to 21 years with SCD (n=37)	RBCx with CS (n=20 patients)	Manual RBCx (n=17 patients)	Catheter-related complications HbS levels Ferritin levels Need for chelation	Published in a peer reviewed journal.
(Fasano et al., 2016) United States	Retrospective observational study	Children (aged with SCD (n=28)	Automated RBCx with CS or SO (n=10).	Partial manual RBCx (n=6) Simple (top up) transfusion (n=20)	Serum ferritin levels Alloimmunisation HbS levels Procedural outcome	Published in a peer reviewed journal. Patients crossed over between groups. Patients defined as belonging to group after 5 months continuous treatment.
(Ahmed et al., 2018) Saudi Arabia	Retrospective cohort study	Adults with painful vaso-occlusive crises secondary to SCD (n=230)	Automated RBCx	Manual RBCx	HbS levels Mortality and major procedural complications	Poster abstract.
(Araujo et al., 2019) Portugal	Retrospective cohort study	Patients with SCD, further information not specified (n=5)	Automated RBCx (n=46 procedures)	Partial RBCx (n=42 procedures)	HbS targets and levels Ferritin level	Conference abstract

Study reference and location	Study design	Population	Intervention	Comparator	Principal outcomes	Comment
					Procedure duration Annual requirements for RBCx RBC units Costs	
(Dierick, 2019) United States, UK, France	Cross-sectional study	Patients with SCD, further information not specified (n=40)	Automated RBCx	Manual RBCx	HRQoL Patient and clinician reported benefits	Conference abstract
(Kelly et al., 2015) United States	Retrospective cohort study	Children with SCD receiving RBCx for stroke prevention (n=49)	Automated RBCx	Manual RBCx	Adverse events Alloimmunisation	Conference abstract
(Nassim et al., 2016) United states	Prospective observational study	Adults with SCD receiving RBCx (n=43)	Automated RBCx (n=31 patients)	Manual RBCx (n=12 patients)	Blood viscosity HbS levels Haematocrit	Conference abstract
(Nzouakou et al., 2018) UK	Cross-over study	Adults with SCD receiving RBCx (n=29)	Automated RBCx (n=29 patients)	Manual RBCx (n=29 patients)	HbS% RBC usage Serum ferritin	Conference abstract

Abbreviations: CS, Cobe Spectra; HbS, sickled haemoglobin; HRQoL, health-related quality of life; RBC, red blood cell; RBCx red blood cell exchange; SCD, sickle cell disease; SO, Spectra Optia.

Table B2. *Characteristics of technical studies (comparison of Cobe Spectra and Spectra Optia).*

Study reference and location	Study design	Population	Intervention	Comparator	Principal outcomes	Conclusion
(Buyukkurt et al., 2018) Turkey	Retrospective and cross-sectional observational study	Adults with SCD (n=165)	RBCx with SO (113 procedures)	RBCs with CS (227 patients	HbS levels (pre and post) Blood composition, haematocrit RBC replacement volume Procedure duration	"The recently introduced SO apheresis system is as effective and safe as the CS system"
(Kim et al., 2016) United States	Retrospective observational study	Adults with SCD (n=19)	RBCx with SO using IHD (57 procedures)	RBCs with CS using IHD (57 procedures)	Procedural parameters HbS Blood components Haematocrit Adverse events	"Performance characteristics of Spectra Optia for HbS, Hct and FCR were similar to COBE Spectra"
(Poullin et al., 2016)	Retrospective chart review	Teenagers and adults with SCD (n=23)	RBCx with SO (46 procedures)	RBCs with CS (46 procedures)	HbS (before and after) Haematocrit Transfused units Procedure duration	"Technical performance and packed RBC unit consumption were not compromised when switching from the COBE Spectra IHD/RBCx protocol to the depletion/RBCx protocol on the Spectra Optia."

Abbreviations: CS, Cobe Spectra; HbS, sickled haemoglobin; IHD, isovolaemic haemodilution; RBC, red blood cell; RBCx red blood cell exchange; SCD, sickle cell disease; SO, Spectra Optia.

Table B3. *Characteristics of single-armed studies (peer reviewed journal articles only).*

Study reference and location	Study design	Population	Intervention	Principal outcomes	Comment
(Ballas and Lyon, 2016) United States	Retrospective case series	Adults with priapism secondary to SCD (n=10)	Automated RBCx with a Haematonics V50 machine and CS.	%HbS Hb levels Haematocrit Clinical outcome	Small case series Priapism affects 89% of male >20 Years with SCD.
(Hequet et al., 2019) France	Prospective observational study	Mainly adults (92%) with SCD (n=50)	RBCx-IHD with SO (n=300) RBCx with SO (control, n=173)	Comparison of predicted and actual HbS and haematocrit Clinical tolerance	A comparison was made with a control RBCx not featuring depletion.
(Joshua Daniel et al., 2016) India	Retrospective observational study	Patients with SCD (n=21)	RBCx with SO	HbS levels (pre and post RBCx)	Of borderline generalisability due to setting and population.
(Myers et al., 2016) United States	Correlation study	Patients with SCD receiving erythrocytaphoresis therapy (n=29)	[Presumed] RBCx	Ferritin levels Liver iron concentration (evaluated with MRI)	Method of erythrocytaphoresis not stated.
(Tsitsikas et al., 2017b) UK, Homerton hospital	Retrospective observational study	Patients with SCD (n=21)	RBCx with SO	Emergency attendance Hbs (pre and post RBCx) Tolerance Alloimmunisation	Case series, little reporting of aggregate data. UK study
(Tsitsikas et al., 2016) UK, Homerton hospital	Retrospective observational study	Patients with SCD (n=50)	RBCx with SO (n=504 procedures)	HbS levels Blood components Alloimmunisation Iron loading Tolerability and safety Clinical outcomes (pain, leg ulcers, pulmonary hypertension)	Reporting of quantitative data not clear. UK study.

Study reference and location	Study design	Population	Intervention	Principal outcomes	Comment
Abbreviations: CS, Cobe Spectra; Hb, haemoglobin; HbS, sickled haemoglobin; IHD, isovolaemic haemodilution; MRI, magnetic resonance imaging; RBC, red blood cell; RBCx red blood cell exchange; SCD, sickle cell disease; SO, Spectra Optia.					

Table B4. *Characteristics of economic studies.*

Study reference and location	Study design	Population	Intervention	Principal outcomes	Comment
(Dedeken et al., 2018) Belgium	Observational costing study	Children with SCD switching from manual RBCx to automated RBCx (SO) (n=10)	RBCx with SO	Ferritin levels Procedural duration RBC requirement Frequency of treatment Costs	Costs in Euros. Costs came from 3 sources: RBC units, clinical costs, and chelation costs.
(Tsitsikas et al., 2017a) UK, Homerton hospital	Retrospective observational costing study	Adult patients with SCD (n=30)	Automated RBCx (technology not reported but assumed to be SO)	Days in hospital Chelation RBC requirement Overall costs	UK study which should be highly generalisable to national practice in the NHS.
Abbreviations: CS, Cobe Spectra; Hb, haemoglobin; HbS, sickled haemoglobin; IHD, isovolaemic haemodilution; MRI, magnetic resonance imaging; RBC, red blood cell; RBCx red blood cell exchange; SCD, sickle cell disease; SO, Spectra Optia.					

Table B5. *List of abstracts not included for analysis.*

Reference	Title	Abstract details
(*Abdelaal et al., 2016*)	Efficacy and tolerability of a depletion-red cell exchange program with the spectra optia in sickle cell disease patients.	*Transfusion,* 56**,** 83A.
(Ball, 2018)	NHS blood and transplant's role in delivering an automated red cell exchange service.	*Transfusion Medicine,* 28**,** 47.
(De Castro *et al.*, 2019)	Anatomy of an exchange transfusion program for adults with sickle cell disease.	*Journal of Clinical Apheresis,* 34**,** 150-151
(Hughes *et al.*, 2017)	Successful Implementation of red cell exchange for paediatrics with sickle cell disease using spectra optia.	*Transfusion Medicine,* 27**,** 48-49.
(Jain *et al.*, 2018)	Role of automated red cell exchange in acute and chronic complications of sickle cell disease.	*Blood,* 132.
(Karafin *et al.*, 2019)	A survey of current practices of red blood cell exchange transfusion for patients with sickle cell disease.	*Journal of Clinical Apheresis,* 34**,** 81.
(Lalefar and Hagar, 2015)	A comparison of hematologic parameters in patients with sickle cell disease undergoing red cell exchange using terumo bct spectra optia and cobe spectra apheresis systems.	*Blood,* 126**,** 4743.
(Marquez *et al.*, 2017)	Red blood cell depletion/exchange: Case presentation.	*Journal of Clinical Apheresis, 32, 105.*
(Miller *et al.*, 2015)	Safety and efficacy of elective automated red cell exchange transfusion programmes for patients with sickle cell disease at a single centre.	*British Journal of Haematology,* 169**,** 104.
(Moraga-Salazar and Mora-Fallas, 2019)	Apheresis and transfusion service perspective of a chronic red blood cell exchange program in a pediatric center in Costa Rica: A single-center 3-year experience.	*Transfusion,* 59**,** 186A.
(Nazli *et al.*, 2017)	Transition from manual simple exchange transfusion to automated Red Cell Exchange (RCX) program in sickle cell disease patients: Experience at a tertiary care hospital in Riyadh Ksa.	*Journal of Clinical Apheresis,* 32**,** 104-105.
(Nuttall Musson *et al.*, 2017)	How much blood and how often? Comparing two centres' regular automated exchange transfusion programmes for sickle cell disease.	*Transfusion Medicine,* 27**,** 50.
(Nzouakou *et al.*, 2016)	Annual review of transfusion targets in regularly transfused paediatric and adult sickle cell patients. Experiences from Bart's Health NHS Trust.	*British Journal of Haematology,* 173**,** 153-154.
(Su *et al.*, 2016)	Surveillance of post-procedure red cell gain/loss following red cell exchange procedures with and without depletion in pediatric sickle cell patients: A single institution experience.	*Journal of Clinical Apheresis,* 31**,** 96-97.
(Trompeter and McMillan, 2015)	Establishing alloimmunisation rates and safety of electronic issue in the largest automated exchange programme for sickle cell disease in England.	*Vox Sanguinis,* 109**,** 255.

(Tsitsikas *et al.*, 2016)	4 year cost-analysis of automated red cell exchange transfusion for management of recurrent painful crises in adult patients with sickle cell disease.	*Haematologica,* 101**,** 612-613.
(Wagner *et al.*, 2015a)	Efficacy and safety of a combined depletion/exchange procedure with a new cell separator in patients with sickle cell disease: A single centre experience.	*Transfusion Medicine and Hemotherapy,* 42**,** 28.
(Wagner *et al.*, 2015b)	Evaluation of a combined depletion/exchange procedure with a new erythrocytapheresis device in patients with sickle cell disease.	*Cytotherapy,* 17**,** S26.

Table B6. *Summary of key results of comparative studies.*

Study reference	Sample size	Physiological parameters (in particular, HbS%)	Effect on iron overload	Clinical outcomes (major SCD-related and procedural complications)	RBC usage and alloimmunisation	Procedural outcomes
(Escobar et al., 2017) Portugal	16 patients RBCx with SO (n=37 procedures) Manual RBCx (n=57 procedures)	HbS% Automated: Pre: 66.3 ± 14.6 Post: 35.8 ± 11.4 Manual Pre: 56.0 ± 9.2 Post: 41.3 ± 11.1 Change aRBCx:-46.2 ± 11.0% vs. mRBCx: -27.2 ± 7.8 (p<0.001)	"Although not a main endpoint of our study, ferritin levels of our patients on chronic RBCx were always in the normal range and so no iron-overload complications were observed."	Not reported.	"After 154 packed RBC units transfused in RBCx, there was no record of alloantibodies development or transfusion reactions".	Duration of procedure aRBCx: 95 ± 39 (range 33 to 196) minutes. mRBCx: 89 ± 28 (range: 55 to 180) minutes.
(Woods et al., 2017) United States	aRBCx with CS: 20 children mRBCx: 17 children	aRBCx: goal HbS achieved in 59% visits (IQR, 28.4%, 91.1%) mRBCx: goal HbS achieved in 50% visits (IQR 29.7%, 90.3%, p=0.4). Six patients with nonadherence to scheduled aRBCx appointments switched to mRBCx.	"There was no difference in long-term iron control between aRBCx recipients and mRBCx recipients as measured by serum ferritin, with aRBCx recipients having a median ferritin of 999 ng/ml (IQR 685.5 to 2,669) compared with 1,579 ng/ml for those who had never had	Total catheter complication rate (incidence/1000 catheter days): aRBCx: 1.00 (IQR 0.68 to 1.42) mRBCx: 0.00	Not reported.	Duration of procedure "Among the 20 patients who received aRBCx during the study period, the median proportion of time receiving aRBCx was 63% (IQR 39%, 100%).

Study reference	Sample size	Physiological parameters (in particular, HbS%)	Effect on iron overload	Clinical outcomes (major SCD-related and procedural complications)	RBC usage and alloimmunisation	Procedural outcomes
			aRBCx (IQR 649 to 2,496, p=0.9)"			
(Fasano et al., 2016) United States	Children with SCD requiring chelation, on chronic RBCx (n=28)	HbS% aRBCx: 34.7 (30.3 to 38.3) TUT: 33.4 (27.4 to 40.6) pRBCx: 36.3 (33.4-40.4) p=0.732	Change in ferritin (ng/mL/month) aRBCx: -91 (-141 to -48) TUT +15 (+17 to +145) pRBCx: +38 (+24 to +105) p=0.003 Change in LIC aRBCx: -5.7 (-10.7 to -0.5) TUT: +1.3 (-1.6 to +4.3) pRBCx: +2.3 (-6.5 to +8.9) p=0.004	Not reported	Alloimmunisation rate (AlloAbs/100 transfusion episodes): aRBCx: 0.63 TUT: 0 pRBCx: 0.5 Number of units per procedure: aRBCx: 6.8 (3 to 9) TUT: 1.2 (1 to 3) pRBCx: 2.0 (1 to 3)	Days between transfusions aRBCx: 30.1 (28.5 to 32.3) TUT: 28.8 (27.0 to 30.5) pRCBx: 28.2 (24.2 to 30.0) p=0.100
(Ahmed et al., 2018) Saudi Arabia	230 patients	aRBCx: median 31%(range 8% to 50%) mRBCx median 44 % (range 31% to 74%. "[aRBCx achieved] mean HbS level of 28%(range 8%-50%) and nearly two thirds (67%)	Not reported	"No mortalities or major procedure related complication [were] reported"	Not reported	Not reported

Study reference	Sample size	Physiological parameters (in particular, HbS%)	Effect on iron overload	Clinical outcomes (major SCD-related and procedural complications)	RBC usage and alloimmunisation	Procedural outcomes
		reached to as low as 31% HbS level with only one session of aRBCx, and was associated with rapid improvement of the oxygenation within the first 2 hours of the procedure"				
(Araujo et al., 2019) Portugal	5 patients aRBCx: 46 procedures mRBCx: 42 procedures	Preprocedure: aRBCx: median 38.4% (range 18.3% to 52.9%) mRBCx: median 42.6% (range 31.3% to 59.1%) HbS increased in 11.4% subsequent procedures.	aRBCx: median ferritin: 1315 ng/ml mRBCx: 1356 ng/ml	No major SCD events reported.	aRBCx: median 4 RBC units mRBCx: median 2 RBC units "No major complication or alloimmunization was observed"	aRBCx: mean 60 minutes procedure, repeated 21 days. mRBCx: mean 360 minutes procedure, repeated 24 days.
(Dierick, 2019) United States, UK, France	40 patients with SCD	Not reported	Not reported	aRBCx resulted in a 25% improvement in HRQoL compared with mRBCx (0.70 vs. 0.55, p<0.001)	Not reported	Not reported
(Kelly et al., 2015) United States	49 children	Not reported	Not reported	aRBCx: 33 AE in 5240 transfusions. mRBCx: 38 AE in 4227 transfusions. The OR of any AE with mRBCx compared with aRBX was 1.5 (95% CI 0.88 to	"odds of RBC alloimmunization was significantly lower with aRBX"	Not reported

Study reference	Sample size	Physiological parameters (in particular, HbS%)	Effect on iron overload	Clinical outcomes (major SCD-related and procedural complications)	RBC usage and alloimmunisation	Procedural outcomes
				2.55). Excluding citrate and machine malfunction, the OR of any AE with mRBCx compared to aRBX was 2.5 (95% 1.39 to 4.55, p=0.002).		
(Nassim et al., 2016) United states	43 adult SCD patients aRBCx: 31 patients mRBCx: 12 patients	"Both aRBCx and mRBCx procedures decreased HbS level, leucocytes and platelets counts, and increased HbA level (p ranging from < 0.01 to < 0.001). The decrease in HbS (p < 0.001) levels….. was higher in the aRBCx than in the mRBCx group".	mRBCx was associated with a significant increase in haematocrit, haemoglobin, and blood viscousity compared with mRBCx.	Not reported	Not reported	Not reported
(Nzouakou et al., 2018) UK	29 adults with SCD (cross over study)	aRBCx: median pre-exchange HbS: 46% (range 18% to 64%) Post exchange: 15% (range 7% to 25%) mRBCx: median pre-exchange	Ferritin (after 1 year treatment) aRBCx: 1263 µg/l (range 27 to 7229) mRBCx: 1466 µg/l (range 36 to 7042) p=0.0006)	Not reported	aRBCx: 33 ml/kg RBC mRBCx: 20 ml/kg RBC	Time between procedures: aRBCx 22 to 188 days 9 (range 4 to 9) per year mRBCx: 14 to 83 days

Study reference	Sample size	Physiological parameters (in particular, HbS%)	Effect on iron overload	Clinical outcomes (major SCD-related and procedural complications)	RBC usage and alloimmunisation	Procedural outcomes
		HbS: 52% (range 23% to 73%) Post exchange: 36% (range 15 to 54%)				11 (range 6 to 15) per year

; TUT, top up transfusion.

Table B7. *Summary of key results of single-armed studies (published peer reviewed articles only).*

Study reference	Sample size	Physiological parameters (in particular, HbS%)	Effect on iron overload	Clinical outcomes (including procedural AEs)	RBC usage and alloimmunisation	Procedural outcomes, healthcare resource use
(Ballas and Lyon, 2016) United States	10 patients with priapism as a complication of SCD	HbS% Pre: 55±20.4 Post: 25.5±16.1 Hct (%) Pre: 22.8±5.5 Post: 26.8±4.8	No aggregated data presented.	7/10 patients responded (but most required additional treatment). 2/10 partial response 2/10 failed response	No aggregated data presented.	Not reported.
(Hequet et al., 2019) France	Mainly adults (92%) with SCD (n=50)	Post-procedure Hct: H32%±1% (predicted 31%±1%) HbS% Pre: 47%±7% Post: 9%±2% No significant difference in patients who received standard aRBCx or IHD.	Ferritin levels ranged from 10 to 4400 µg/L (median, 340)	Not reported	Not reported	Not reported.
(Joshua Daniel et al., 2016) India	Patients with SCD (n=21)	HbS% Pre: “between 73 to 85%” Post: “22 to 29%”	Not reported	Not reported	Not reported	Not reported
(Myers et al., 2016) United States	Patients with SCD receiving erythrocytaphoresis therapy (n=29)	Not reported	“LIC was associated with serum ferritin (r=0.697, P<0.001) but was not	Not reported	Not reported	Not reported

Study reference	Sample size	Physiological parameters (in particular, HbS%)	Effect on iron overload	Clinical outcomes (including procedural AEs)	RBC usage and alloimmunisation	Procedural outcomes, healthcare resource use
	Note: Correlation study.		associated with the total number of LTE procedures (r=-0.088, P=0.656) or total number of simple transfusions (r=0.316, P=0.108). The total number of LTE procedures was not associated with serum ferritin (r=0.040, p=0.838), the total number of simple transfusions (r=-0.258, p=0.184), or LIC group (r=-0.111, p=0.566)"			
(Tsitsikas et al., 2017b) UK, Homerton hospital	Patients with SCD (n=21) Case series	HbS "Mean pre-transfusion HbS achieved was 41% (32 to 57%)"	"The procedures were overall well tolerated with no evidence of iron loading	"Immediate effect on priapism and pulmonary hypertension".	The authors reported alloimmunisation rate of 0.065/100 units of red cells	Emergency hospital attendance (reduction) 1 year: 25% 2 years: 43% 3 years: 65% 4 years: 74% 5 years: 80%
(Tsitsikas et al., 2016) UK, Homerton hospital	Patients with SCD (n=50)	HbS% Pre: 44% Post: 9% Hb	"Patients with no previous iron overload remain unaffected, whereas	"Twenty-seven patients (55%) did not experience any problems	RBC usage 12.3 units per procedure (12 to 14 range).	Reduced hospital attendance.

Study reference	Sample size	Physiological parameters (in particular, HbS%)	Effect on iron overload	Clinical outcomes (including procedural AEs)	RBC usage and alloimmunisation	Procedural outcomes, healthcare resource use
		Pre: 93 g/L Post: 105 g/L	patients with significant hepatic siderosis are able to chelate effectively"	while on the program" Vasovagal symptoms in 35% patients. 70% of patients had a reduction in the number and severity of painful rises requiring hospital attendance.	<u>Alloimmunisation</u> "Three of the 50 (6%) patients developed a total of four new antibodies while on aRBCx, representing a rate of formation of new antibodies of 0.065/100 units of red cells".	

Abbreviations: AE, adverse event; aRBCx, automated exchange; CI, confidence interval; CS, Cobe Spectra; Hb, haemoglobin; HbS, sickled haemoglobin; Hct, haematocrit; HRQoL, health-related quality of life; IHD, isovolaemic haemodilution; IQR, inter-quartile range; LIC liver iron concentration; mRBCx, manual exchange; OR, odds ratio; pRBCx, partial red blood cell exchange; RBC, red blood cell; SCD, sickle cell disease; SO, Spectra Optia; TUT, top up transfusion.

Appendix C – Literature search strategy

<table>
<tr><th>Adverse events sources</th><th>Date searched</th><th>Results and search terms</th></tr>
<tr><td>FDA medical devices:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm from this page search:

MAUDE database, - search on device and manufacturer, but the information needs to relate to the device. We might also be able to restrict searching to the most recent version of the device e.g. Sherlock 4 (rather than just ‘Sherlock’)

Do not include results that are pre the date limit</td><td>8th Oct 2019</td><td>MAUDE Adverse Event Reports:

<table>
<tr><th>Manufacturer</th><th>Brand name</th><th>Date received</th></tr>
<tr><td>TERUMO BCT</td><td>SPECTRA OPTIA</td><td>08/23/2019</td></tr>
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FDA (2018) 510(k) Premarket Notification: Spectra Optia Apheresis System (K181049)</td></tr>
</table>

		FDA (Sept 2018) Voluntary Medical Device Safety Alert: SPECTRA OPTIA APHERESIS SYSTEM:
MHRA: http://www.mhra.gov.uk/index.htm *Search for the indication. if getting no results for the device name*	8th Oct 2019	MHRA (2018) Urgent FIELD SAFETY NOTICE: IV Pole Collar for Spectra Optia® Apheresis System MHRA (2018) Urgent Field Safety Notice: Spectra Optia procedures with Correct Connect ACD-A Solution
Ongoing trials sources Clinical trials.gov http://clinicaltrials.gov/ct2/home WHO International Clinical Trial Registry Platform (ICTRP): (covering a number of registries) http://apps.who.int/trialsearch/ ISRCTN http://www.isrctn.com/	8th Oct 2019	No new trials identified

Include completed trials that are within the date parameter specified by the analyst		

Databases*	**Date searched**	**No retrieved**	**Version/files**
MEDLINE (Ovid)	18th Oct 2019	95	Ovid MEDLINE(R) <1946 to October 17, 2019>
MEDLINE In-Process (Ovid)	18th Oct 2019	24	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to October 17, 2019>
EMBASE (Ovid)	18th Oct 2019	164	Embase <1974 to 2019 Week 41>
Embase conferences	18th Oct 2019	425	Embase <1974 to 2019 Week 41>
Ovid ePubs	18th Oct 2019	6	Ovid MEDLINE(R) Epub Ahead of Print <October 17, 2019>
CDSR (Wiley)	18th Oct 2019	8	Issue 10 of 12, October 2019
**Database of Abstracts of Reviews of Effects – DARE (CRD)	18th Oct 2019	0	Up to 2015
HTA database (CRD)	18th Oct 2019	0	Up to 2018
CENTRAL (Wiley)	18th Oct 2019	23	Issue 10 of 12, October 2019
**NHS EED (CRD	18th Oct 2019	0	Up to 2015
Econlit (for economic searches)	18th Oct 2019	2	Econlit <1886 to October 03,2019>
Total		747	
Total after de-duplication		621	

Search strategies

Database:
Database: Ovid MEDLINE(R) <1946 to October 17, 2019>

Search Strategy:

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1 Anemia, Sickle Cell/ (20208)
2 Hemoglobin SC Disease/ (630)
3 Hemoglobin, Sickle/ (3078)
4 (sickle or sickling or sca or scd or h?emoglobin S*1 or hbs*1 or hb-s*1).tw. (43171)
5 (h?emoglobin adj3 thalass?emia).tw. (829)
6 (drepanocyt* or microdrepanocyt* or meniscocyt*).tw. (366)
7 or/1-6 (47126)
8 Exchange Transfusion, Whole Blood/ (4603)
9 Erythrocyte Transfusion/ (8577)
10 BLOOD COMPONENT REMOVAL/ (4491)
11 Cytapheresis/ (343)
12 ((blood cell*1 or red cell*1 or rbc or rbcs or rc or rcs or erythrocyt* or normocyt*) adj3 (exchang* or transfus* or deplet* or remov*)).tw. (12608)
13 (RBCX or RBCE or RCX or RCE).tw. (475)
14 (ARCET or RCET).tw. (12)
15 (erythrocytapheres* or erythroexchange*).tw. (187)
16 (EBT or EBTs).tw. (1275)
17 ((chronic or exsanguination* or substitution or total or replacement) adj (exchang* or transfus* or deplet* or remov*)).tw. (4319)
18 (apheres* or cytapheres* or cytopheres* or pheres*).tw. (6840)
19 ((blood cell*1 or red cell*1) adj3 separat*).tw. (1027)
20 or/8-19 (36324)
21 (spectra or spectrar or spectratm or spectrartm or optia* or cobe* or terumo* or caridian* or gambro* or automat* or auto or device* or manual*).tw. (661031)
22 7 and 20 and 21 (135)
23 spectra optia.tw. (77)
24 22 or 23 (207)
25 animals/ not humans/ (4601341)
26 24 not 25 (205)
27 limit 26 to english language (195)
28 limit 27 to ed=20150601-20191018 (95)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to October 17, 2019>
Search Strategy:
---

1 Anemia, Sickle Cell/ (0)
2 Hemoglobin SC Disease/ (0)
3 Hemoglobin, Sickle/ (0)
4 (sickle or sickling or sca or scd or h?emoglobin S*1 or hbs*1 or hb-s*1).tw. (4821)
5 (h?emoglobin adj3 thalass?emia).tw. (50)
6 (drepanocyt* or microdrepanocyt* or meniscocyt*).tw. (4)
7 or/1-6 (4859)
8 Exchange Transfusion, Whole Blood/ (0)
9 Erythrocyte Transfusion/ (0)
10 BLOOD COMPONENT REMOVAL/ (0)
11 Cytapheresis/ (0)
12 ((blood cell*1 or red cell*1 or rbc or rbcs or rc or rcs or erythrocyt* or normocyt*) adj3 (exchang* or transfus* or deplet* or remov*)).tw. (1212)
13 (RBCX or RBCE or RCX or RCE).tw. (70)
14 (ARCET or RCET).tw. (2)
15 (erythrocytapheres* or erythroexchange*).tw. (10)
16 (EBT or EBTs).tw. (186)
17 ((chronic or exsanguinatio* or substitution or total or replacement) adj (exchang* or transfus* or deplet* or remov*)).tw. (396)
18 (apheres* or cytapheres* or cytopheres* or pheres*).tw. (458)
19 ((blood cell*1 or red cell*1) adj3 separat*).tw. (55)
20 or/8-19 (2352)
21 (spectra or spectrar or spectratm or spectrartm or optia* or cobe* or terumo* or caridian* or gambro* or automat* or auto or device* or manual*).tw. (201817)
22 7 and 20 and 21 (14)
23 spectra optia.tw. (17)
24 22 or 23 (26)
25 animals/ not humans/ (0)
26 24 not 25 (26)
27 limit 26 to english language (26)
28 limit 27 to dt=20150601-20191018 (24)

Database: Ovid MEDLINE(R) Epub Ahead of Print <October 17, 2019>
Search Strategy:

---

1 Anemia, Sickle Cell/ (0)
2 Hemoglobin SC Disease/ (0)
3 Hemoglobin, Sickle/ (0)
4 (sickle or sickling or sca or scd or h?emoglobin S*1 or hbs*1 or hb-s*1).tw. (708)
5 (h?emoglobin adj3 thalass?emia).tw. (11)
6 (drepanocyt* or microdrepanocyt* or meniscocyt*).tw. (1)
7 or/1-6 (715)
8 Exchange Transfusion, Whole Blood/ (0)
9 Erythrocyte Transfusion/ (0)
10 BLOOD COMPONENT REMOVAL/ (0)
11 Cytapheresis/ (0)
12 ((blood cell*1 or red cell*1 or rbc or rbcs or rc or rcs or erythrocyt* or normocyt*) adj3 (exchang* or transfus* or deplet* or remov*)).tw. (260)
13 (RBCX or RBCE or RCX or RCE).tw. (8)
14 (ARCET or RCET).tw. (2)
15 (erythrocytapheres* or erythroexchange*).tw. (3)
16 (EBT or EBTs).tw. (36)
17 ((chronic or exsanguinatio* or substitution or total or replacement) adj (exchang* or transfus* or deplet* or remov*)).tw. (62)
18 (apheres* or cytapheres* or cytopheres* or pheres*).tw. (100)
19 ((blood cell*1 or red cell*1) adj3 separat*).tw. (6)
20 or/8-19 (466)
21 (spectra or spectrar or spectratm or spectrartm or optia* or cobe* or terumo* or caridian* or gambro* or automat* or auto or device* or manual*).tw. (17276)
22 7 and 20 and 21 (2)
23 spectra optia.tw. (4)
24 22 or 23 (6)
25 animals/ not humans/ (0)
26 24 not 25 (6)
27 limit 26 to english language (6)

Database: Embase <1974 to 2019 Week 41>
Search Strategy:
---
1 sickle cell anemia/ (32168)
2 sickle cell crisis/ (1208)
3 (sickle or sickling or sca or scd or h?emoglobin S*1 or hbs*1 or hb-s*1).tw. (71536)
4 (h?emoglobin adj3 thalass?emia).tw. (1080)
5 (drepanocyt* or microdrepanocyt* or meniscocyt*).tw. (298)
6 or/1-5 (78100)
7 exchange blood transfusion/ (5038)
8 erythrocyte transfusion/ (25869)
9 apheresis/ (13945)
10 cytapheresis/ (856)
11 ((blood cell*1 or red cell*1 or rbc or rbcs or rc or rcs or erythrocyt* or normocyt*) adj3 (exchang* or transfus* or deplet* or remov*)).tw. (24260)
12 (RBCX or RBCE or RCX or RCE).tw. (904)
13 (ARCET or RCET).tw. (33)
14 (erythrocytapheres* or erythroexchange*).tw. (321)
15 (EBT or EBTs).tw. (1568)
16 ((chronic or exsanguinatio$ or substitution or total or replacement) adj (exchang* or transfus* or deplet* or remov*)).tw. (6294)
17 (apheres* or cytapheres* or cytopheres* or pheres*).tw. (15522)
18 ((blood cell$1 or red cell*1) adj3 separat*).tw. (1391)
19 or/7-18 (71204)
20 (spectra or spectrar or spectratm or spectrartm or optia* or cobe* or terumo* or caridian* or gambro* or automat* or auto or device* or manual*).tw,dv. (1089366)
21 6 and 19 and 20 (440)
22 spectra* optia*.tw,dv. (627)
23 21 or 22 (998)
24 nonhuman/ not human/ (4508065)
25 23 not 24 (991)
26 limit 25 to (conference abstract or conference paper or "conference review" or editorial or erratum or letter or note or tombstone) (706)

27 25 not 26 (285)
28 limit 27 to english language (273)
29 limit 28 to dc=20150601-20191018 (164)
30 limit 26 to dc=20150601-20191018 (425) Conferences

EconLit

Database: Econlit <1886 to October 03,2019>
Search Strategy:
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1 [Anemia, Sickle Cell/] (0)
2 [Hemoglobin SC Disease/] (0)
3 [Hemoglobin, Sickle/] (0)
4 (sickle or sickling or sca or scd or h?emoglobin S*1 or hbs*1 or hb-s*1).tw. (146)
5 (h?emoglobin adj3 thalass?emia).tw. (0)
6 (drepanocyt* or microdrepanocyt* or meniscocyt*).tw. (0)
7 or/1-6 (146)
8 [Exchange Transfusion, Whole Blood/] (0)
9 [Erythrocyte Transfusion/] (0)
10 [BLOOD COMPONENT REMOVAL/] (0)
11 [Cytapheresis/] (0)
12 ((blood cell*1 or red cell*1 or rbc or rbcs or rc or rcs or erythrocyt* or normocyt*) adj3 (exchang* or transfus* or deplet* or remov*)).tw. (3)
13 (RBCX or RBCE or RCX or RCE).tw. (8)
14 (ARCET or RCET).tw. (0)
15 (erythrocytapheres* or erythroexchange*).tw. (0)
16 (EBT or EBTs).tw. (17)
17 ((chronic or exsanguinatio* or substitution or total or replacement) adj (exchang* or transfus* or deplet* or remov*)).tw. (18)
18 (apheres* or cytapheres* or cytopheres* or pheres*).tw. (4)
19 ((blood cell*1 or red cell*1) adj3 separat*).tw. (0)
20 or/8-19 (49)
21 (spectra or spectrar or spectratm or spectrartm or optia* or cobe* or terumo* or caridian* or gambro* or automat* or auto or device* or manual*).tw. (14949)

22 7 and 20 and 21 (2)
23 spectra optia.tw. (2)
24 22 or 23 (2)
25 limit 24 to yr="2015 -Current" (2)

Cochrane Library

ID Search Hits
#1 MeSH descriptor: [Anemia, Sickle Cell] this term only 635
#2 MeSH descriptor: [Hemoglobin SC Disease] this term only 24
#3 MeSH descriptor: [Hemoglobin, Sickle] this term only 18
#4 (sickle or sickling or sca or scd or h?emoglobin S*1 or hbs*1 or hb-s*1):ti,ab,kw 9097
#5 (h?emoglobin adj3 thalass?emia):ti,ab,kw 0
#6 (drepanocyt* or microdrepanocyt* or meniscocyt*):ti,ab,kw 34
#7 #1 or #2 or #3 or #4 or #5 or #6 9107
#8 MeSH descriptor: [Exchange Transfusion, Whole Blood] this term only 69
#9 MeSH descriptor: [Erythrocyte Transfusion] this term only 587
#10 MeSH descriptor: [Blood Component Removal] this term only 203
#11 MeSH descriptor: [Cytapheresis] this term only 14
#12 ((blood cell* or red cell* or rbc or rbcs or rc or rcs or erythrocyt* or normocyt*) near/3 (exchang* or transfus* or deplet* or remov*)):ti,ab,kw 13686
#13 (RBCX or RBCE or RCX or RCE):ti,ab,kw 51
#14 (ARCET or RCET):ti,ab,kw 0
#15 (erythrocytapheres* or erythroexchange*):ti,ab,kw 29
#16 (EBT or EBTs):ti,ab,kw 125
#17 ((chronic or exsanguinatio* or substitution or total or replacement) next (exchang* or transfus* or deplet* or remov*)):ti,ab,kw 187
#18 (apheres* or cytapheres* or cytopheres* or pheres*):ti,ab,kw 1199
#19 ((blood cell* or red cell*) near/3 separat*):ti,ab,kw 753
#20 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 15486
#21 (spectra or spectrar or spectratm or spectrartm or optia* or cobe* or terumo* or caridian* or gambro* or automat* or auto or device* or manual*):ti,ab,kw 81345

#22 #7 and #20 and #21 90
#23 (spectra optia):ti,ab,kw 32
#24 #22 or #23 121
#25 "conference":pt or (clinicaltrials or trialsearch):so with Cochrane Library publication date Between Jun 2015 and Oct 2019 388449
#26 #24 not #25 67 (23 in Central with 2015+ date limit, 8 in CDSR with 2015+ date limit)

CRD

☐	1	MeSH DESCRIPTOR Anemia, Sickle Cell	39
☐	2	MeSH DESCRIPTOR Hemoglobin SC Disease	1
☐	3	MeSH DESCRIPTOR Hemoglobin, Sickle	1
☐	4	(sickle or sickling or sca or scd or h?emoglobin S* or hbs* or hb-s*)	285
☐	5	((h?emoglobin near3 thalass?emia))	4
☐	6	(drepanocyt* or microdrepanocyt* or meniscocyt*)	2
☐	7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	285
☐	8	MeSH DESCRIPTOR Exchange Transfusion, Whole Blood	8
☐	9	MeSH DESCRIPTOR Erythrocyte Transfusion	96
☐	10	MeSH DESCRIPTOR BLOOD COMPONENT REMOVAL	25

☐	11	MeSH DESCRIPTOR Cytapheresis	3
☐	12	(((blood cell* or red cell* or rbc or rbcs or rc or rcs or erythrocyt* or normocyt*) near3 (exchang* or transfus* or deplet* or remov*)))	234
☐	13	(RBCX or RBCE or RCX or RCE)	2
☐	14	(ARCET or RCET)	0
☐	15	(erythrocytapheres* or erythroexchange*)	2
☐	16	(EBT or EBTs)	6
☐	17	(((chronic or exsanguinatio* or substitution or total or replacement) next (exchang* or transfus* or deplet* or remov*)))	12
☐	18	(apheres* or cytapheres* or cytopheres* or pheres*)	63
☐	19	(((blood cell* or red cell*) near3 separat*))	4
☐	20	(#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19)	325
☐	21	(spectra or spectrar or spectratm or spectrartm or optia* or cobe* or terumo* or caridian* or gambro* or automat* or auto or device* or manual*)	5148
☐	22	(#7 and #20 and #21)	3
☐	23	(spectra optia)	0
☐	24	#22 OR #23	3
☐	25	(spectra optia) FROM 2015 TO 2019	0

Notes:
Record any important decisions on how the strategy was developed *[May include notes from analysts or IS colleagues, links to correspondence, etc. For example, why particular search terms included/excluded. Consider annotating the search strategy if this is easier.]*

Appendix D – References

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Appendix 3. Background documents for this review

1. Medical technologies guidance document - https://www.nice.org.uk/guidance/mtg28

2. Assessment report – https://www.nice.org.uk/guidance/mtg28/documents/assessment-report

3. Scope of assessment – https://www.nice.org.uk/guidance/mtg28/documents/final-scope