National Institute for Health and Care Excellence

External Assessment Centre correspondence

Spectra Optia apheresis device for automatic red blood cell exchange in patients with sickle cell disease

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
n/a	**Seven initial clarification questions to Spectra Optia Sponsor. Submitted by EAC for discussion at sponsor introductory teleconference 02/07/2015, hosted by NICE:** 1) The Clinical evidence submission appears to have the following error – to confirm please: a. Page 24 of 186 and in References. Are the 2008 Sickle Society & Department of Health Standards referenced incorrectly as Beta Thalassaemia? We presume you mean the 2008 Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK and appear to have used these in the body of the submission. Please confirm. b. Table A2 (page 16) appears to have been truncated, could you report any missing content please?	**Verbal and written responses from Cedar representative Sue Peirce and Terumo representative Benit Maru to these seven initial clarification questions. Verbal responses are summarised in this log by the EAC:** a. The document title should be "Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK" (and in the references). I will change the entry in the reference list when submitting the economics. Do you want me to change this on page 24 as well? b. It should be replaced with: "System will calculate based on pre-procedure laboratory data and post-procedure target value."	Cedar to change the entry in the reference list when submitting the economics
n/a	2) Were any hand-searches of individual conferences carried out? If so, which conferences and which years?	Cedar electronically searched any conference abstract book obtained in order to review the article (sometimes the text of an abstract wasn't available or they would want to see if a table or	None.

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		figure was included). They also searched for the word 'exchange' throughout the pdf. There was also the 54th ASH meeting that is available online https://ash.confex.com/ash/2012/webprogram/): 18th Congress of the EHA 2013.pdf, 22nd Annual ASPHO 2009.pdf, 24th BSH meeting 2014.pdf, 25th ASA Meeting 2005.pdf, 30 ASA meeting abstracts 2009.pdf, 32nd ASA Meeting 2011.pdf, 34th ASA Meeting May 2013.pdf, 35th ASA Meeting Apr 2014.pdf, 36th ASA Meeting May 2015.pdf, 41st meeting of ESBMT 2015.pdf, 52nd BSH meeting - abstracts 2012.pdf, 54th Meeting BSH 2014.pdf, 55th Meeting of the BSH 2015.pdf, 5th Sickle Cell Disease Symposium 2011.pdf, AABB and CTTXPO meeting 2011.pdf, AABB Annual Meeting 2014.pdf, AABB and CTTXPO meeting 2010.pdf, AASA abstracts 2011.pdf, ASPHO meeting 2012.pdf, ASPHO meeting 2013.pdf, ASPHO meeting 2015.pdf	
n/a	3) We propose to hand search conference abstracts from the 'top three' worldwide conferences where clinical	The top three highlighted were:	None

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	evidence on Spectra Optia may have been presented. Could you please recommend which 'top three' conferences we should target for this purpose?	1. American Society of Haematology (ASH) 2. British Society of Haematology (BSH) 3. American Society for Apheresis (ASFA)	
n/a	4) We understand one of the main technical differences between Spectra Optia and its predecessor, COBE Spectra, is the extracorporeal blood volume (EBV) in the patient circuit. This is specified as 285ml in COBE Spectra and 185ml in Spectra Optia. With this in mind: a. We understand the claim that the smaller volume would benefit children and small adult patients. However, what is your view on the impact of smaller EBV for average or large adult patients and how this may change outcomes when considering COBE Spectra verses Spectra Optia (e.g. duration of procedure)? b. Several of the single armed papers on the COBE Spectra device are in children (studies p, q, t). How generalizable would COBE Spectra be to the Spectra Optia device in these cases?	a. The manufacturers highlighted in verbal response that there should be no difference in the duration of the procedure as duration is dependent on patient total blood volume, rather than EBV. Written response from Maru Benit: *Extracorporeal volume (ECV) is significantly lower on Spectra Optia than on Cobe Spectra. The benefits for paediatric patients are obvious but there is also a benefit for adult patients in the sickle cell population.* *As SCD patients are often of diminutive stature, low body weight and low hematocrit, there is a higher likelihood of the extracorporeal red cell mass exceeding 10% which should trigger the operator to consider a 'custom prime'. As the ECV is lower in Optia, the total blood volume of the patient can be significantly lower before the*	None

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		need for custom prime occurs. *The significant differences between the two systems with regards to custom prime is that Optia can calculate ECV and extracorporeal red cell mass and calculate this as a % of the patients total blood volume. This allows it to prompt the operator to consider a custom prime. Cobe Spectra does not calculate the ECV as a % of total blood volume nor the extracorporeal red cell mass and as such it is reliant on the operator running these calculations to decide if a custom prime should be performed. Thus it allows the operator to spend more time with the patient rather than doing calculations.* b. The manufacturers highlighted in verbal response that the two devices are equivalent for automatic red blood cell exchange. This is not the case for depletion though, where centres were doing their own modifications to protocol on COBE, to achieve a depletion exchange outside of the company specifications for the device. The Quirolo et al. 2015 paper provides detail on this and the data from this study helped guide the FDA approval for the RBCX function of	

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		the Spectra Optia system. Written response from Maru Benit: *The algorithms used in Spectra Optia were derived from those of the Cobe Spectra therefore procedure time and efficiency of exchange are similar.* *The only significant changes to the Spectra Optia algorithms in Red Cell Exchange are:* *- The Custom Prime calculation(see above).* *- Introduction of Depletion/Exchange to improve efficiency and as such reduce exposure to as many units of blood.*	
n/a	5) How was the Spectra Optia Automated Interface Management (AIM) Protocol developed from the COBE Spectra User Protocols? Can you explain in more specific detail which operational parameters/settings were matched between the two systems? Or is AIM more relevant to the therapeutic plasma exchange functionality?	The manufacturers highlighted in verbal response that the AIM protocol for Optia watches the plasma layer to make sure that RBCs do not seep into it. On COBE, the operator had to monitor this visually. Written response from Maru Benit: *The shortest answer is: In TPE AIM manages,*	None.

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		in RBCX AIM monitors the interface. *The long answer is: The Aim system is fully active in plasma exchange, monitoring the interface (division of cellular components and plasma) position, interpreting the position and adjusting the pumps to maintain the correct position. In red blood cell exchange, the AIM system purely monitors the position of the interface and alerts the operator if this position shifts. There is a secondary system on the Spectra Optia that also monitors the plasma line exiting the centrifuge that is designed to alert the operator if there are red cells in the plasma line. Therefore the operator does not have to monitor themselves, again allowing more time to be spent with the patient. Also freeing up time to run more than one procedure at a time.*	
n/a	6) Automated RBC exchange requires two peripheral venous lines or a central venous line. a. In practice, how much of an issue is this for the treatment of adults and children? Would patients who are unable to tolerate this be likely to have other different characteristics compared with those who can	a. Any type of venous line can be used for the Spectra Optia device, including femoral access. Ideally, peripheral veins would always be used, but this can be problematic, e.g. in children under 5kg and patients with prior vein collapse	None.

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	tolerate it? b. Are the Spectra Optia and COBE Spectra devices equivalent in this regard? In the paper by Perseghin et al. (2013), it is noted that 4 patients in the Spectra Optia group required a central line whilst none did in the COBE Spectra group	from previous transfusions. b. They are equivalent. The both work on anticoagulant infusion rates and gravitation flow, which varies depending on patient size etc.	
n/a	7) Can you give us any information on the economic model, such as what software will be used (Excel?) and which key parameters may be considered?	Cedar advised that they are using TreeAge for the economic model. They are performing a 3 arm comparison between automated exchange, manual exchange and top-up transfusions. They are further separating the arms into subgroups, including whether patients start with iron overload. The model will have a 5 year timeline and include installation costs, procedure time, units of blood per procedure and hospital admissions for complications of SCD such as acute chest syndrome (ACS), pain and recurrent stroke Cedar also highlighted that they have recently learned that 6 apheresis centres in the UK Blood and Transplant Service all use Spectra Optia machines and local trusts can potentially buy	Sue Peirce will look into the costs of buying an apheresis machine from one of the 6 centres in the UK. <u>EAC comment 27/07/2015</u> – this information on costs of Spectra Optia RBCX through the NHS Blood and Transplant Therapeutic Apheresis Service (TAS) was not present in the sponsor's economic evidence submission, received by the EAC on 16/07/2015. Hence further information sought directly from the TAS in Question

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		RBCX sessions from one of these centres.	8), below.
n/a	**Eleven questions from the EAC to the ratified Clinical Experts. These were emailed to each Expert individually in questionnaire form by the EAC, with responses collated into a single document for ease of reference.** **Dates of sending out the 11 questions to 9 ratified Clinical Experts: 10/07/2015 to 29/07/2015.** **Dates of receipt of 6 responses 13/07/2015 to 07/08/2015.**	Please see Appendix 1 for the Collated responses to these 11 EAC questions.	Informed Section 3.6.6 and other parts where referenced in the EAC Assessment Report
n/a	**8) In light of the information provided by the sponsor in response to question 7) at the introductory teleconference on 02/07/2015, the EAC contacted the NHS Blood and Transplant Service on 27/07/2015, seeking additional information on this route to patient access to RBCX using Spectra Optia.**	Comprehensive email response in reply received from Kay Harding, Senior Nurse Manager, NHS Blood and Transplant. Filton on 03/08/2015. Email transcribed in full for MTAC in Appendix 2 with pricing information for redaction in public documents highlighted in the pdf.	Informed sections 4.5.3 where referenced in the EAC Assessment Report

Appendix 1

MT271 Collated
responses to 11 EAC

Appendix 2

From: Harding Kay
Sent: 03 August 2015 16:36
To: Cole, Helen
Cc: Howell Catherine & PA
Subject: Query on behalf of NICE

Dear Helen,

To answer your query, NHSBT currently provides automated red cell exchange services from our units based in Bristol, Oxford, Sheffield, Leeds and Liverpool. We undertake a low level of activity across our service when compared to current/potential demand for services (last year we did approx. 170 procedures).
NHSBT treatment prices are agreed with the Department of Health national Commissioning Group as part of an annual price setting process. Our existing pricing is based on a full cost recovery methodology which includes direct, indirect and unallocated overhead costs. Treatments are charged to Trusts on a cost per procedure basis. The procedure price includes review and acceptance of the referral by one of our Consultant Haematologists and for a member of our team to undertake the actual automated exchange (we provide equipment and consumables). The price EXCLUDES the price of replacement fluids i.e red cells.
A red cell undertaken in one of our units is [redacted]. Different premiums apply if the procedure is undertaken in a different part of the hospital, at another hospital and/or out of hours. The maximum charge for a procedure undertaken in another hospital outside of normal working hours is [redacted].
I hope this information is helpful. We would prefer if the information on pricing was redacted in any public documents. Please do not hesitate to come back to me if I can be of further assistance.

Best wishes,

Kay

Kay Harding
Senior Nurse Manager
Therapeutic Apheresis Services
NHS Blood and Transplant