National Institute for Health and Clinical Excellence
Review of Technology Appraisal Guidance – No. 41
Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women

Personal statement of Dr Ann Benton FRCP FRCPath

I am a Consultant Haematologist and Lead for Blood Transfusion within Swansea NHS Trust, with a half time role as Lead Consultant for Better Blood Transfusion in Wales. My current responsibilities include:

- All aspects of general haematology clinical practice, including intensive chemotherapy for acute leaukaemia and autologous stem cell transplantation
- Trust Lead for Laboratory Haematology and Blood Transfusion
- Senior Clinical Tutor for the Graduate Entry Medicine programme at Swansea Clinical School
- Lead Consultant for Better Blood Transfusion Wales, strategic lead for the Welsh Blood Service Hospital Transfusion Practitioner Scheme
- Chair of UK NEQUAS Blood Transfusion Steering Committee
- Chair of UK Better Blood Transfusion Toolkit Editorial Board
- Member of UK Blood Stocks Management Scheme Steering Committee
- Member of Scottish National Blood Transfusion Service e-learning Editorial Board
- Member of UK National Audit (Blood Transfusion) steering group
- Member of Royal College of Pathologists Transfusion Medicine sub-committee
- Member of UK Transfusion Network
- Chair of Welsh Implementation Group for Blood Safety and Quality Regulations
- Member of Clinical Advisory Group for Blood Transfusion (Wales)
- Member of Blood Implementation Group (Wales)
- Member of Education sub-group for Blood Transfusion (Wales)

My perspective in relation to RAADP TA41 and the ‘expertise’ I possess for this area is thus based on my experience as a general haematologist in a District General/Teaching Hospital/Tertiary referral centre with responsibility for Blood Transfusion, the

requirements of my national role as the strategic lead for improving all aspects of Blood Transfusion Practice across Wales, and my understanding of Blood Transfusion issues on a UK wide platform through involvement with the various committees and working groups. As a member of the Royal College of Pathologists Transfusion Medicine sub-committee I was tasked to lead the submission to the review process on behalf of the Royal Colleges of Pathology and Medicine, and to contribute to the consultation on the recently provided report by the review team.
For me the key areas to consider from TA41 are as follows:

1) Is there evidence that the proposed intervention will be effective, and how will its effectiveness be assessed?
There is no doubt that the use of targeted anti-D therapy in situations of potential maternal exposure to foetal red cells in Rh D Negative women (both antenatal and post delivery), has reduced the incidence of sensitisation and thus significantly reduced the incidence of haemolytic disease of the newborn in subsequent pregnancies. However, there is no good clinical data on the impact of RAADP and the best available information comes from non-randomised community based studies by MacKenzie et al which suggest that the introduction of prophylactic ante-natal anti-D may further reduce the rate of sensitisation from 0.95% to 0.35%. Undoubtedly the reason for this lack of data is in part due to the fact that there is no easy and comprehensive method of identifying the true rate of sensitisation in Rh D Neg women as both sensitisation and HDN will only be identified in those women who go on to have subsequent pregnancies. Ideally the implementation of RAADP would have been accompanied by a strategy for identifying and quantifying the rate of sensitisation in all Pregnant Rh D neg women. Without a mechanism for collecting this data it is difficult to know how the effectiveness of implementing this technology can appropriately be assessed.
Recommendation:
Consideration be given to the mechanism required for establishing a robust means of data capture for the incidence of anti-RhD sensitisation

2) Implementation of the guidance was assessed to be relatively resource neutral, except for the additional cost of ‘drug’

This is not actually the case. Experience shows that achieving safe and appropriate implementation requires a significant multidisciplinary commitment both to establish and maintain the RAADP programme. In particular additional specialist midwifery, and laboratory technical resources are necessary along with a significant need for additional clerical support in both clinical and laboratory areas. A failure to identify such resources is likely to be a contributing factor in failure to implement the guidance.

Recommendation:

Recognition of the potential resource implications be included in revised guidance.

3) Feasibility of implementation?

Feedback from a broad spectrum of laboratory managers indicates that successful implementation is dependent on key factors (appendix 1)

Recommendation:

Appendix 1 be provided as part of any revised guidance as a practical ‘toolkit’ to encourage and support those who have not yet implemented, or who have struggled to implement effectively, to achieve compliance with the guidance.

4) Level of implementation?

TA 41 suggested local audit. There is some evidence available from local audits but outcomes can be difficult to compare, and many units have not yet undertaken any form of audit.

Recommendation:

Revised guidance should include a requirement to participate in national audit of implementation, including the technology used, level of uptake, adverse events, traceability, and information available to pregnant women.

It should also identify an appropriate mechanism/body to facilitate and monitor such audit.

5) Potential adverse effects of implementation?

There are two main areas of concern:

a) Technical issues and potential for missing significant allo-antibodies as identified in SHOT data

Recommendation:

The guidance should highlight the need for ongoing and regularly updated education, training and competency assessment of all involved in the assessment of feto-maternal haemorrhage and the administration of anti-D immunoglobulin

b) Transmission of vCJD & other as yet unidentified pathogens

Recommendation:

The guidance should reinforce the need for anti-D immunoglobulin to be subject to the same rigorous process of patient identification, documentation, traceability requirements and adverse event reporting as for all blood products

6) Which technology for anti-D?

There remains no definitive data from specific studies to identify which of the technologies, one dose or two, is most effective (if either). However, clinical data from UK and other countries (Canada particularly) suggest both as effective, but further work on several issues, such as uptake for two dose regimen, protective effect of one dose regimen in prolonged gestation, limiting donor exposure, and availability of anti-D, remain.

A national audit of implementation coupled with the process of data capture for rates of sensitisation would provide some of this information.

7) New technology for targeted ante-natal prophylaxis

The potential to develop foetal genotyping on maternal blood samples into a diagnostically useful test is certainly imminent, although not quite perfected. Once available, such technology would allow targeted AADP rather than RAADP, improving the efficacy of the intervention, avoiding unnecessary donor exposure in those women not carrying a RhD positive foetus, and reducing waste of product.

Recommendation:

Endorsement of further work on this technology, and acknowledgement that guidance may need future review if targeted AADP becomes reality

Appendix 1

Requirement	Comments
Planning: An essential aspect of implementing the RAADP program.	Defining a project team and ensuring all relevant groups are represented aids implementation.
Education: Ensure that all staff involved with antenatal care are fully aware of the program and their responsibilities within that program	This requires the implementation of structured education sessions that explain the changes being made and how best to implement them to ensure success. These education sessions and regular updates must be given to all professional groups involved in the RAADP program.
Defining Responsibility: Clear definition of various professional roles.	Ensures that all areas are covered and there is no confusion regarding who is responsible for what.
Communication: Appropriate mechanisms must be in place to ensure timely and appropriate information transfer between all groups of staff involved in the care of with each woman.	Close cooperation between the blood transfusion department and the antenatal carers is essential. The audit trail, traceability and appropriate interpretation of laboratory investigations is dependent on information sharing.
Resources: Ensure that appropriate staffing levels are available to maintain full audit trail of the products used. Clerical support will often be required.	Maintaining a full audit trail requires time and resource. This may be done using paper or electronically or a combination of both.
Eligibility: All women that are at risk must be identified and offered RAADP.	It may be helpful to ensure that appropriate clinical comments are printed on the antenatal blood transfusion reports to highlight the fact that the woman is eligible to be offered anti D immunoglobulin.
Audit: A full audit trail of any product issued	This is required to be able to trace any woman receiving a specific batch. This

must be maintained and include the dose and batch number of the anti-D immunoglobulin given to the woman.	information would be essential should a batch be recalled or batch traceability be required.
Effective implementation: Ensure that effective audit takes place to measure the success of the programs implementation.	e.g. % of Rh-negative women that are offered RAADP. % that receive the full program of doses
Documentation: Evidence of process and receipt, or not, of anti-D must be included in the woman's notes	It is also important to make sure that if a woman decides not to receive the RAADP that this is recorded for future reference.
Appropriate interpretation of investigations: Clear and appropriate clinical details must be supplied to the laboratory before investigations can be carried out.	Laboratory tests are often hindered by the lack of appropriate clinical details on requests for investigations. Appropriate clinical information is very important if the RAADP program is to be successful.
Information: All women should receive information about RAADP in a format that is understandable to all. This should include the benefits and risks.	Guidance 41 provided an information leaflet, but the survey by Harkness in 2005[6] identified 60 different information leaflets in use. The production of standard information should be considered through the use of a multidisciplinary group review of all current available leaflets.
Balance: Information and advice given to women must be free from bias as well as being factual.	Women often ask for advice on what they should do with regard to treatment. Any advice offered must be based on fact and not personal preference by the clinician looking after the patient.
Timing: Information on the RAADP should be given to women before booking or at an early stage in pregnancy, to allow opportunity to make informed choice.	Patient information leaflets should be made widely available in primary care so that RAADP is brought to the attention of women at a very early stage in their pregnancy.