Dear Dr Feinmann

I am responding on behalf or myself and [redacted] of NHS Blood and Transplant (the National Blood Service). We have received advice and help from [redacted] and [redacted]. [redacted] and I have also contributed as members of the Royal College of Pathologists to the RCPath submission. I have sent copy of these comments to [redacted] and [redacted].

This is the most thorough piece of work we have ever seen on anti-D prophylaxis. It is clear and well written.

There were four points we would like you to consider

1. The terminlogy of the opening couple of sentences may propagate the tendency to use the term Rhesus or Rh as synonymous with RhD. As you are aware the Rh system is a system of antigens that include Rhc, RhC, RhCw, RhD, Rhe and RhE etc. We understand that you need to express this clearly without getting bogged down with technical detail. We wondered, however, if you would consider changing the wording to reflect this. A suggestion being

" Human blood is classified according to two main systems: the ABO system, and the Rh system. The Rh system consists of several related proteins the most important of which is called the RhD antigen "

2. It is unrealistic to expect any test to have 100% sensitivity with no false negatives. This is particularly true when considering the difficulties in amplifying a fetal gene from maternal plasma with no reliable control for the presence of fetal DNA rather than DNA of maternal origin maternal. Obviously laboratories always strive to achieve this with minimal loss of specificity but this should be reflected in the document. On a related issue all the peer reviewed publications referenced in relation to the use of fetal genotyping utilise labour intensive techniques to assess
fetal risk in sensitised women . These techniques are not scalable but
peer reviewed articles of scalable techniques should follow soon as there have been recent abstracts at meetings.

We would therefore suggest rewording the section on p 38 as follows to take comment 2 into account

" In principle, this technology permits the screening of all non-sensitised RhD-negative pregnant women to enable antenatal prophylaxis to be targeted to only those carrying RhD-positive foetuses. However, to be feasible in practice, the test results must be able to cost effectively test large volumes of samples and yield as few as possible false negatives (i.e. cases in which the foetus appears to be RhD negative but is actually RhD positive). 100% accuracy is never likely be achieved. Studies published to date have involved processing small numbers of samples from previously sensitised women to see if the baby they are carrying in their current pregnancy is likely to be affected and the techniques used are not practical for testing all RhD negative women, both sensitised and unsensitised. The existence of false positives is less important, as it simply means that, as in current

practice, a RhD-negative woman carrying a RhD-negative foetus will be given unnecessary prophylaxis " .

3. Dr Osipenko using data presented at the RhD NIPD implementation meeting estimated that current costs of performing fetal genotyping for a population such as the UK are approximately £40. This estimate was based upon the available evidence and robust health economic analysis by a well recognised team. We are hopeful that this may however prove a pessimistic estimate for the UK as samples would not need to be taken specially (the test could be performed at the same time as routine pregnancy tests, requiring only an additional anticoagulated sample bottle +/- specific additional form). We estimate that appropriate large scale techniques actually cost <£10 for staff time, consumables and non consumables. Transport links to the International Blood Group Reference Laboratory in England are already in place for the regular transport of samples so it is unlikely that transport costs of implementation of NIPD will be enormous. Further work on specific health economic assessment is warranted in the UK in the near future. We have not suggested changing the script but were keen to check that this comment had been considered by the team. We suspect you would not want to amend the text.

4. We are not sure that it is primarily the accuracy of fetal genotyping that is in question in relation to cost-effective implementation and would therefore suggest another minor wording change to reflect this on p132:

" Finally, non-invasive foetal genotyping has not yet been demonstrated to be sufficiently practical and cost effective to enable its use to target provision of RAADP to only those non-sensitised RhD-negative women pregnant with RhD-positive infants. However, an appropriate test which is sufficiently accurate at an early enough gestational date may become available in the next few years."

Thank you for taking these comments into consideration. I have attempted to track the changes in the text of the attachment but have had some problems with this when saving the changes and colleagues have not been able to see them.

[redacted]
Consultant Haematologist
National Health Service Blood and Transplant Southmead Rd Bristol BS10 5ND

Tel [redacted]
Fax: [redacted]