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Primary Care Trust

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Dear Chris Feinmann

Re Review of TA41: Pregnancy - routine anti-D prophylaxis for rhesus negative women, Appraisal Consultation Documentation

Nottingham City PCT has been given the opportunity to comment on the Appraisal Consultation Document (ACD), and the accompanying evaluation report. You have asked that four questions be addressed.

i) Do you consider that all of the relevant evidence has been taken into account?

- *Yes, there has been an extensive and comprehensive review of the literature, and engagement with patients, clinicians and other stakeholders.*

ii) Do you consider the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact implications for the NHS are appropriate?

- *The resource impact implications for the NHS are likely to be appropriately covered.*

There are two areas where we would wish to comment on clinical and cost effectiveness which may indicate that benefits to patients and the NHS are more limited than suggested in the ACD.

Benefit and Harm
From the evaluation (page 83 and 84) the number needed to treat to prevent one foetal loss with this intervention is 5,790 (range of 5,730 to 8,690 given in the previous evaluation) with the benefit almost exclusively falling in subsequent rather than current pregnancies. This is an absolute risk reduction of 0.017% of a RhD negative mother having a foetal loss due to Rhesus incompatibility, which is an extremely small benefit. There is an additional obvious benefit of having a child unaffected by HND, but prevention of foetal loss appears to be associated with the greatest benefit according to the evaluation.

At the same time, for a mother, the number needed to cause (significant) harm can be calculated as 140,000 for one preparation, and for any harm as 69,000 for another, though there is usually marked under reporting of adverse events and the numbers needed to harm are almost certainly worse (page 40 of the evaluation). There are also observable changes in babies that cannot benefit from the intervention, but there is no apparent harm from this (also page 40).

There must be very few interventions that a patient would give informed consent to for such a small chance of possible future benefit. However, pregnancy may be one area of practice where this would happen, and the risk of harm appears significantly smaller than the chance of benefit.

- *The likelihood of the expected benefit being realised for an individual patient should be made more explicit in the ACD. The number needed to treat to prevent one foetal loss is 5,790.*

Cost Effectiveness
While the analysis in the evaluation is generally handled on a population basis there is one significant area, as indicated in the sensitivity analysis, that is calculated on individual events and this inconsistency feeds through into the conclusions in the ACD.

Specifically, the years of life lost (YLL) for each foetal loss are calculated on an individual basis, at 79 (average life expectancy). However, most couples will have further pregnancies until the planned family size is achieved and there will therefore be no overall years of life lost to the population.

While desired family size may unfortunately not be fully obtainable for an individual mother following foetal loss due to haemolytic disease, for RhD negative mothers overall the average family size should not be significantly affected by this intervention given the small absolute risk of foetal loss due to haemolytic disease prevented. This does not detract from the intense grief and devastating effect on families having a late foetal loss, but there is an attempt in the supporting evaluation to account for this elsewhere.

In all official national statistics of years of life lost, deaths in children under the age of one are specifically excluded. While the current explanation in the definition is that the causes of death under one are unique to that age group, this is true at other ages also and previous definitions have included the consideration that planned family size tends to be maintained after an infant death.

Given the general exclusion of infant deaths in the calculation of years of life lost, it is difficult to see why foetal loss due to Rhesus disease should contribute to years of life lost in the supporting evaluation. There is also no other situation in which years of life lost are attributed to foetal loss at any stage of pregnancy, and it appears inappropriate that Rhesus disease should be such a special case. This contradicts the last bullet point (page 109 of the evaluation) which asserts otherwise.

Internationally, the World Health Organisation, which arguably has a particular focus on infant mortality, also gives reduced weights to YLL in childhood and additionally discounts subsequent YLL to give a total of 33 YLL for an infant death. No YLL are included for foetal loss in their statistics. This would also suggest that attributing 79 YLL gained for a foetal loss prevented by this intervention is questionable.

- *The cost per QALY in section 4.2.1 to prevent HDN associated foetal loss appears to be to low because 79 YLL have been allocated for a foetal loss. This appears to be inconsistent with national and international approaches.*

iii) Do you consider the recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

- *The response for question ii) on cost effectiveness would produce a different assessment of cost effectiveness for the intervention and would probably result in a different conclusion if this was taken into account.*

There are two other areas on which we would wish to comment.

Service Delivery
The assessment concludes that there is a lack of evidence to support either a single dose or dual dose regimen for Anti-D in RhD negative mothers-to-be and makes no recommendation as to which should be implemented. This is unhelpful operationally and the appraisal may consequently add little to practice.

While accepting the lack of evidence, a decision on which regimen to implement does have to be made. A consistent national approach would be beneficial, particularly considering the likelihood of systems failure when pregnant women or clinicians move between areas that use different regimens. Where there is no evidence on which to base a preference, either regimen could be recommended on other grounds until there is sufficient evidence from research.

In this instance, the balance of comments made in the report and received from consultees would suggest the two dose regimen was to be preferred because of a wider period of protection. However, the cost effectiveness acceptability curve (page 121 of the evaluation) would suggest that a single dose regimen for all RhD negative pregnancies is most cost effective.

- *The recommendations would be more useful operationally if it were specified which of two possible regimens should be implemented.*

Reassurance and Multigravidae
Paragraph 4.3.2 indicates that one of the benefits to pregnant women is reassurance and 4.3.5 suggests that it would be difficult not give an intervention in a subsequent pregnancy if it had been given in the first. This is a difficult consideration as the grounds for reassurance may be known to be either misplaced or limited.

Generally, it is more appropriate to provide unbiased information to individual patients on the evidence based balance of risks and benefits so that they (with their clinicians) may make informed choices. An obvious example of this issue would be antibiotics for sore throats which historically have provided misplaced reassurance.

Also, the ICER associated with the intervention in multigravidae is considerably above the upper threshold usually used for NICE. NICE routinely makes decisions on the use of interventions in subgroups and the following of previous clinical practice would not normally be sufficient reason to disregard NICE's usual approach.

- *Reassurance and existing practice seems to be given as the reason in the ACD for recommending the intervention to multigravidae where the ICER is between £46,000 and £52,000. This is appears to be inconsistent with NICE's general attempt at following an evidence based approach and an upper threshold of £30,000 for ICER, and may have significant resource implications if applied to future technology appraisals.*

iv) Are there equality related issues that may need special consideration?

Paragraph 2.5 of the appraisal consultation document would suggest that the recommendation was largely based on the effect on the white population. In fact, the evaluation report indicates that benefits are greater to the non white population (page 110 of the evaluation) because if fathers are from the same ethnic group more pregnancies in RhD negative mothers are likely to be affected.

- *The implication of implementation is one of a reduction in inequalities because of a disproportionate benefit for pregnancies in non-white mothers, and it would be helpful to acknowledge this in the ACD*

This completes our comments on the ACD

Yours sincerely