Title of the project

High-throughput, non-invasive prenatal testing for fetal rhesus D status in RhD-negative women not known to be sensitised to the RhD antigen: a systematic review and economic evaluation

Name of External Assessment Group (EAG) and project lead

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Plain English Summary

Rhesus disease is a condition where antibodies in a pregnant woman's blood destroy her baby's blood cells. Rhesus disease does not harm the mother, but it can cause the baby to become anaemic and develop jaundice. If rhesus disease is left untreated, severe cases can lead to stillbirth. In some cases, it can lead to brain damage, learning difficulties, deafness and blindness.

Rhesus disease only happens when the mother has rhesus negative blood (RhD negative) and the baby in her womb has rhesus positive blood (RhD positive). The mother must have also been previously sensitised to RhD positive blood. Sensitisation happens when a woman with RhD negative blood is exposed to RhD positive blood, usually during a previous pregnancy with an RhD positive baby. The woman's body responds to the RhD positive blood by producing antibodies that destroy the foreign blood cells.

If sensitisation occurs, the next time the woman is exposed to RhD positive blood, her body produces antibodies immediately. If she's pregnant with an RhD positive baby, the antibodies can cross the placenta, causing rhesus disease in the unborn baby. The antibodies can continue attacking the baby's red blood cells for a few months after birth.

Rhesus disease is uncommon in the UK because it can usually be prevented using injections of anti-D immunoglobulin. NICE recommends that all women are offered blood tests early in pregnancy to determine whether their blood is RhD negative or positive. All people identified as RhD negative would be tested for the presence of antibodies that may harm the baby. If the mother is RhD negative, she will be offered injections of anti-D immunoglobulin at certain points in her pregnancy regardless of whether the fetus is RhD positive or negative. This anti-D immunoglobulin helps to remove the RhD fetal blood cells before they can cause sensitisation.

Currently all RhD negative mothers are offered anti-D immunoglobulin injections, rather than only those who have an RhD positive fetus. Therefore a large number of RhD negative pregnant women receive anti-RhD immunoglobulin even though they do not need it (about 39,000 per year). High-throughput non-invasive prenatal testing (NIPT) is a technology that can identify the rhesus status of a fetus using a sample of the mother's blood. NIPT could allow anti-D immunoglobulin to be withheld from women who are RhD negative and carry an RhD negative fetus. These women could avoid unnecessary treatment with anti-D immunoglobulin, which can have side effects and carry a risk of transmitting prion disease and blood-borne viruses. High-throughput NIPT may also lead to savings for the NHS. The purpose of this project is to assess the clinical effectiveness and cost effectiveness of high-throughput NIPT testing for fetal RhD status in RhD-negative women not known to be sensitised to the RhD antigen.

Decision problem

The purpose of this appraisal is to assess whether high-throughput, non-invasive prenatal testing (NIPT) for fetal RhD status in RhD-negative women not known to be sensitised to the RhD antigen presents a clinical- and cost-effective use of NHS resources.

Population

Human red blood cells carry antigens on their surfaces. People with the RhD antigen are described as being RhD positive, and those without the antigen as RhD negative. A baby inherits its blood type from both parents, therefore a pregnant woman who is RhD negative may carry a baby who is RhD positive.

The presence of fetal RhD-positive cells in the maternal circulation can cause a mother who is RhD negative to produce antibodies against the RhD antigen (anti-D antibodies). This process is called sensitisation, and can happen at any time during pregnancy, although it is most common in the third trimester and during childbirth. Sensitisation can follow events in pregnancy known to be linked with feto-maternal haemorrhage, such as medical interventions (chorionic villus sampling, amniocentesis or external cephalic version), terminations, late miscarriages, antepartum haemorrhage and abdominal trauma. These are called potentially sensitising events.

The process of sensitisation has no adverse health effects for the mother and usually does not affect the pregnancy during which it occurs. In women who are RhD negative and have been sensitised to the RhD antigen, a subsequent pregnancy with an RhD positive fetus can cause an immune response in the mother. The anti-D antibodies produced by the mother cross the placenta and bind to RhD antigen on the surface of fetal red blood cells. These antibody-coated fetal red blood cells are removed from the fetal circulation and fetal anaemia results if the red blood cells are removed faster than they are produced. Severe anaemia can lead to fetal heart failure, fluid retention and swelling (hydrops), and intrauterine death. This is known as haemolytic disease of the fetus and newborn.

There were 646,904 births in England from April 2013 to March 2014, of which approximately 15% (97,036) were to women who are RhD negative.[1] About 40% of these women carry an RhD negative fetus (around 39,000 per year), and therefore do not need treatment with anti-D immunoglobulin. White populations of European descent have approximately a 15% incidence of RhD negativity, while in African American it is 3% to 5% and is very rare in those of Eastern Asian origin.[2] Despite mixing of the genes, in Caucasians, the majority of RhD- negative individuals are a result of gene deletion, and RHD gene variants are relatively rare in white people (less than 1% of all RhD negative people). In Africans, however, Rh-negative phenotype is mostly the result of genes that contain RhD sequences but do not produce D antigen, these are the RHD-pseudogene and RHD-CE-Ds. In people of African and Caribbean family origin, an inactive RHD gene, called the RHD pseudogene, is present in 66% of RhD negative individuals. These gene distributions are present but different between black Africans, African Americans and black South Africans.[3]

Care pathway

The NICE guideline on antenatal care (2008) recommends that women should be offered testing for blood group and rhesus D status in early pregnancy.[4] All women identified as RhD negative would be tested for the presence of RhD antibodies, regardless of whether they are known to be sensitised or not. In women identified as RhD negative anti-D immunoglobulin is recommended, both as prophylaxis and following potential sensitising events, to prevent sensitisation occurring. Routine antenatal anti-D prophylaxis can be given as 2 doses at weeks 28 and 34 of pregnancy, or as a single dose between 28 and 30 weeks.

Anti-D immunoglobulin is produced from pooled plasma from large numbers of RhD negative donors who have been transfused with RhD positive red cells to stimulate the production of RhD antibodies. Therefore it carries a risk of transmission of human blood-borne viral and prion diseases. The National Comparative Audit of Blood Transfusion from 2013 indicates that of the women eligible for anti-D immunoglobulin, 99.0% had anti-D immunoglobulin.

Before anti-D immunoglobulin was available, the incidence of RhD sensitisations in women who are RhD negative following the birth of two RhD positive babies was approximately 16%. Haemolytic disease of the fetus and newborn was a significant cause of morbidity and mortality, occurring in approximately 1% of all births. Since the introduction of routine post-partum administration of anti-D

immunoglobulin, the rate of sensitisations has dropped to approximately 2%. A further decrease in the sensitisation rate ranging from 0.17% to 0.28% was achieved after the introduction of routine antenatal prophylaxis during the third trimester of pregnancy. This led to a reduction in mortality associated with haemolytic disease of the fetus and newborn, from 46 in 100,000 births before 1969 to 1.6 in 100,000 births by 1991.

For pregnant women who are RhD negative and are sensitised to RhD antigen, the Royal College of Obstetricians and Gynaecologists have published guidance on the management of women with red cell antibodies during pregnancy.[5] This guideline recommends that all women who are RhD negative and are sensitised to RhD antigen should attend for pre-pregnancy counselling with a clinician with knowledge and expertise of this condition; have their blood group and antibody status determined at the booking appointment (ideally by 10 weeks of gestation) and at 28 weeks of gestation; be offered non-invasive fetal RhD genotyping using maternal blood if maternal RhD antibodies are present. Once an RhD positive fetus is identified, additional monitoring and treatment are required during the pregnancy.

Intervention technology

The intervention technology of this assessment is high-throughput NIPT for fetal Rhesus D status (International Blood Group Reference Laboratory, Bristol). High-throughput NIPT of fetal RhD status uses a real time quantitative polymerase chain reaction method for predicting fetal RhD genotype from fetal DNA in the plasma of RhD negative women. The test principle is based on analysis of cell-free fetal DNA - small fragments of fetal extracellular DNA shed from the placenta circulating freely in the maternal plasma.

High-throughput NIPT for fetal RhD status may enable anti-D immunoglobulin to be withheld from women who are RhD negative and carrying an RhD negative fetus. These women could avoid unnecessary treatment with routine anti-D immunoglobulin, along with the potential risk associated with blood products. In addition, these women may not need testing and provision of anti-D immunoglobulin following potentially sensitising events, and there may no longer be a need for serologic cord testing at birth.

Despite mixing of the genes, in people of European ethnicity, the majority of RhD-negative individuals are a result of gene deletion. In people of African ethnicity, however, Rh-negative phenotype is mostly the result of genes that contain RhD sequences but do not produce D antigen, these are the RHD-pseudogene and RhD-CE-Ds.[3] It is, therefore, important to know the background ethnicity of the population when performing NIPT. In the presence of pseudogene, prenatal determination of fetal Rh type from maternal blood will reveal an RhD-positive type in a mother tested as Rh-negative by serology because of the abundant maternal D gene sequences that are not expressed but are amplified. This may pose specific challenges for pre-natal RhD testing in this population, and may lead to higher rates of false positives results. There is a diverse array of Rh variant genes and it is generally accepted that at least two exons of RHD should be targeted for accurate RhD status prediction. Targeting exon 7 (or exon 10) only would not detect presence of RHD pseudogene and other variants; targeting exon 10 only would not detect presence of RHD pseudogene or the hybrid RHD-CE-D(s) gene, also common in black people, but which does not express RhD antigen.

There is evidence suggesting that the diagnostic accuracy of NIPT testing may vary according to gestational age at time of sampling. Two meta-analyses found that diagnostic accuracy of NIPT was higher in the first trimester compared with the second and third trimester.[6, 7] However, a recent UK cohort study found that testing was more sensitive (i.e. had a higher proportion of RhD positive fetuses identified correctly) if performed from 11 weeks' gestation than before this time.[8]

Patient issues and preferences

According to a 2013 audit of anti-D immunoglobulin prophylaxis, 131 of 5972 pregnant women who are RhD negative declined anti-D immunoglobulin.[9] If NIPT for fetal RhD status is performed, pregnant women who are RhD negative and are identified as having an RhD positive fetus through NIPT would be able to make a more informed choice about whether or not to have anti-D immunoglobulin. Pregnant women who are RhD negative and are identified as having an RhD negative fetus through NIPT would gain the knowledge that the mother is not at risk of sensitisation. This may reduce anxiety for the family and the mother could avoid having unnecessary anti-D immunoglobulin.

Rationale

The clinical and cost effectiveness of high-throughput NIPT for fetal Rhesus D status in RhD-negative women not known to be sensitised to the RhD antigen for the NHS is uncertain. High-throughput NIPT for fetal RhD status may enable anti-D immunoglobulin to be withheld from women who are RhD negative and carrying an RhD negative fetus. This subgroup of women could therefore avoid unnecessary prophylaxis with anti-D immunoglobulin during pregnancy, along with the risks associated with exposure to blood products, and this may have resource and cost implications for the NHS.

Objectives

This project will assess the clinical and cost effectiveness of using high-throughput NIPT to identify fetal Rhesus D status with any consequent changes in treatment management. To achieve this, the following key objectives are proposed:

Clinical effectiveness

- To perform a systematic review and meta-analysis of the diagnostic accuracy of high-throughput NIPT testing for fetal RhD status.
- To perform a systematic review of the clinical impacts of high-throughput NIPT testing, including sensitisation events, and adverse effects to the mother and fetus.

Cost effectiveness

- To systematically review the cost-effectiveness evidence on high-throughput NIPT testing and its impact on management of pregnant women
- To produce a de-novo cost-effectiveness model assessing the cost effectiveness of high-throughput NIPT to identify fetal RhD status in RhD-negative women not known to be sensitised to the RhD antigen.
- To assess the impact of alternative scenarios related to the timing of the test and the impact of the test on the use of antenatal anti-D prophylaxis for sensitising events and post-delivery testing.

Reviews of clinical effectiveness

The inclusion criteria for clinical effectiveness reviews are as follows:

Types of studies

Diagnostic accuracy

Prospective cohort studies in which index test (high-throughput NIPT testing) and reference standard test are done independently in the same group of people, and that report sufficient data to construct a two-by-two contingency table such that the cells in the table can be labelled as true positive, false positive, true negative, and false negative.

Clinical effectiveness outcomes

Any experimental or observational study in which high-throughput NIPT testing is used to determine fetal RhD status, where anti-D prophylaxis is given as required, and that reports relevant clinical outcomes as listed below. Ideally this will include studies that included a control group that did not undergo NIPT testing (including randomised trials). If no comparative studies are identified for all eligible outcomes, studies that only recruit women who have received NIPT testing will be included, providing they report relevant clinical outcomes for this appraisal.

We will also include relevant publications reporting issues related to implementation of, or practical advice relating to, high-throughput NIPT testing as a screening tool to guide use of anti-D prophylaxis. This may include publications with no numerical data, but which inform research recommendations.

The following types of report will be excluded: editorials and opinions; case reports; reports focusing only on technical aspects of the NIPT technology (such as technical descriptions of the testing process or specifications of machinery). Studies with a sample size of 10 or less will be excluded. We will select the most recent or most complete report in cases of multiple reports for a given study or when we cannot exclude the possibility of overlapping populations.

Population

Pregnant women who are RhD negative and not known to be sensitised to RhD antigen.

Index tests

High-throughput, NIPT free-cell fetal DNA tests of maternal plasma used to determine fetal RhD status will be eligible for inclusion. We will consider as high-throughput any NIPT tests which are conducted using an automated robotic platform (including automated DNA extraction and liquid handling) and are able to process large numbers of samples rapidly. The test should be intended for large scale screening purposes to determine fetal RhD status in women not known to be sensitised to RhD antigen. Studies where this test is used for diagnostic (rather than screening) analysis of sensitised women will be excluded. Studies where other DNA sources (such as maternal blood or serum) are used will be included if separate diagnostics accuracy data are provided for test of maternal plasma.

Reference standard

Serologic cord blood testing at birth, or any other suitable post-natal blood test of the infant.

Outcomes

The following outcomes will be included:

- Test accuracy, including sensitivity and specificity
- Number of inconclusive results, with reasons (e.g. no DNA detected)
- Number of pregnant women who are RhD negative and not sensitised who accept the test
- Number of doses of anti-D immunoglobulin given (routine antenatal, following potentially sensitising events and postnatal)
- Compliance with anti-D (antenatal and postnatal) immunoglobulin

Clinical outcomes

- Number of infections from anti-D immunoglobulin
- Number of sensitisations
- Number of cases of haemolytic disease of the fetus and newborn in subsequent pregnancies
- Adverse effects of testing

Patient related outcomes

- Health related quality of life including anxiety

Search strategy

Both published and unpublished literature will be identified from systematic searches of electronic sources, consultation with experts in the field, and reference checking of relevant systematic reviews and included studies.

The following databases will be searched: MEDLINE, MEDLINE In-Process, EMBASE, CINAHL, Maternity and Infant Care, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, Cochrane Central Register of Controlled Trials (CENTRAL).

In addition, information on studies in progress, unpublished research or research reported in the grey literature will be sought by searching a range of relevant databases including Conference Proceedings Citation Index: Science, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform portal, EU Clinical Trials Register and PROSPERO. Key conference proceedings relevant to non-invasive prenatal testing (NIPT) will be identified and searched.

A search for relevant guidelines will be carried out on the following resources: NICE guidelines website, Royal College of Obstetricians and Gynaecologists website, UK National Screening Committee, National Guidelines Clearinghouse, TRIP database and NHS Evidence. We will also check other relevant guideline developers, in particular those from the Netherlands, Denmark and Germany. Reference lists of relevant reviews and included studies will be checked in order to identify additional potentially relevant reports.

Study data from the UK will be of most relevance to this review. We will therefore contact clinical experts from the Diagnostics Advisory Committee assessment sub-group who will be asked to provide details of any additional potentially relevant studies, and to provide data from these studies if this is feasible. In particular, we may request relevant unpublished data from the International Blood Group Reference Laboratory, NHS Blood and Transplant, Bristol. If time allows we will contact other clinical experts as needed.

A draft search strategy has been developed on Ovid MEDLINE which can be found in appendix 1. This strategy will be further developed and converted to run appropriately on other databases. The

strategy combines terms for Rhesus D status in pregnancy (including associated conditions e.g. rhesus disease, rhesus alloimmunisation) with terms for NIPT. Only reports published in English will be sought. No date limits will be applied to the search strategy and study design search filters will not be used. EndNote X7 software will be used to manage the references for the project.

Study selection strategy

Two reviewers will screen independently the titles and abstracts (if available) of all reports identified by the search strategy. Full text copies of all studies deemed to be potentially relevant will be obtained and two reviewers will independently assess them for inclusion. Any disagreements will be resolved by consensus or by a third party.

We will select the most recent or most complete report in cases of multiple reports for a given study or when we cannot exclude the possibility of overlapping populations.

Data extraction strategy

A data extraction form will be developed and piloted. One reviewer will independently extract details from full text studies of study design, participants, index, comparator and reference standard tests and outcome data. The data extraction will be checked by another reviewer. Any disagreements will be resolved by consensus or arbitration by a third party.

For studies reporting diagnostic data, we will extract the number of true positives, true negatives, false positives and false negatives for each index test evaluated in each study to construct 2 x 2 tables. If such data are not provided by the trial authors, we will attempt to contact them to construct the 2 x 2 table for the study population or the pre-specified subgroups. Otherwise, we will calculate the number of true positives, true negatives, false positives and false negatives from the summary estimates of sensitivity and specificity of the index test, if available. If reported, we will extract data on the number of undetermined or uninterpretable results. For studies for which only a subgroup of patients will be included in the review, we will extract, analyse and present data for this subgroup only. If some data are unclear or missing, we will attempt to contact study authors to obtain additional data.

For studies reporting clinical outcomes we will extract data on these as numbers of women or fetuses experiencing the specified outcome. Mean differences, relative risks or odds ratios (with 95% confidence intervals) will be extracted from comparative studies, where reported. Results adjusted for potential confounding factors will be preferentially extracted.

Where original data are made available, data from these studies will be summarised in a similar fashion to the published data, as described above.

Quality assessment strategy

One reviewer will independently assess the quality of all included studies in terms of risk of bias. Risk of bias from diagnostic accuracy studies will be assessed using the quality assessment of diagnostic accuracy studies (QUADAS-2) checklist. The QUADAS-2 tool will be adapted to ensure it is applicable to assessing the quality of studies of non-invasive prenatal tests for detecting Rhesus D status. The Cochrane risk of bias tool for randomised studies and the Cochrane ACROBAT-NSRI tool for non-randomised studies will be used and adapted as appropriate for studies reporting other eligible clinical outcomes. The quality assessment will be checked by another reviewer. Any disagreements will be resolved by consensus or by a third party.

Statistical analysis and data synthesis

Using extracted diagnostic accuracy data from the 2 x 2 tables, estimates of sensitivity and specificity will be calculated and presented on forest plots and in the receiver operating characteristic (ROC) space to examine the variability in diagnostic test accuracy within and between studies. In the primary analysis undetermined or uninterpretable results will be counted as being test positive, in accordance with current practice.

The hierarchical bivariate model described by Reitsma et al.[10] will be fitted which calculates summary estimates of sensitivity and specificity and the associated 95% confidence intervals (CIs). The hierarchical summary ROC (HSROC) model will also be fitted to produce summary ROC curves.[11] Results of both models will be presented in ROC plots. Positive and negative likelihood ratios will be calculated based on sensitivity and specificity estimates, and positive and negative predictive values will be calculated using relevant fetal rhesus status prevalence data from the UK.

Other eligible clinical outcomes will be pooled if at least two studies report on the same outcome, and if data are reported consistently enough for analysis to be feasible. Otherwise, results will be synthesised narratively. Where meta-analyses are performed, data will be pooled using standard random-effects DerSimonian-Laird meta-analyses.

Analyses will be conducted in R and/or Stata software, as appropriate. Groups that include 100 patients or less will be excluded from the analyses.

Investigation of heterogeneity

For diagnostic accuracy data, we will initially visually inspect the forest plots and ROC space to check for heterogeneity between study results. To investigate sources of heterogeneity, we will incorporate relevant covariates in the bivariate and HSROC models. Subgroup analyses will be conducted, by performing separate bivariate and HSROC models in defined subgroups of studies.

If sufficient studies are available, we will consider the following factors as potential sources of heterogeneity:

- Gestational age at time of NIPT
- Type of NIPT (e.g. Bristol test vs. other)
- Ethnicity (e.g. European vs. African)

For other clinical outcomes, where possible, heterogeneity will be assessed using I^2 and visual inspection of forest plots. Subgroup analyses and meta-regression will be used where feasible. Possible sources of heterogeneity will be discussed and accounted for in the interpretation of the results.

Sensitivity analyses

We will carry out sensitivity analyses to explore the robustness of the results according to study quality based on QUADAS domain results (for example, by excluding studies with verification bias) for diagnostic accuracy studies, and based on results from the Cochrane risk of bias tool and ACROBAT-NRSI, study date (to reflect improvements in technology), by excluding small studies (<100 patients) and by excluding samples for absence of DNA or lack of Rhesus confirmation.

We will conduct additional sensitivity analyses to explore:

- the impact of including and excluding undetermined or uninterpretable NIPT test results on the pooled test accuracy estimates.
- the impact of targeting at least two exons (exons 5, 7 and/or 10) versus only one exon (e.g. exon 10 only) on the pooled test accuracy estimates.

Where participants from several studies are recruited from the same cohorts and significant overlap is suspected, data from only one study with the most reliable reporting will be included in the main analyses. The impact of studies where substantial overlap is suspected, or where only a composite outcome is reported, will be explored by including/excluding them from the main analyses (sensitivity analyses).

Additional clinical evidence to inform the economic model

As the diagnostic test of interest is used to inform the use of anti-D prophylaxis and treatment it will be necessary to identify up-to-date evidence on the clinical and cost-effectiveness of anti-D treatment in current UK practice. This will inform both the clinical effectiveness analysis, by identifying how use of fetal free-DNA testing might alter clinical outcomes; and the cost effectiveness analysis. To achieve this, in the first instance, relevant evidence from existing NICE guidance of antenatal and post-natal management will be consulted to identify best-quality evidence of relevance to the NHS. Where gaps in the evidence are identified, clinical experts from the Diagnostics Advisory Committee assessment sub-group may be contacted to provide any additional potentially relevant data. Where necessary, we will conduct additional targeted searches of the relevant published and unpublished literature to identify additional evidence on clinical effectiveness and safety. A pragmatic approach will be adopted to identify the most relevant and best available evidence to inform the model within the time constraints of the project.

Methods for synthesising evidence of cost-effectiveness

Relevant economic evidence on high-throughput NIPT to identify fetal RhD status in RhD-negative women not known to be sensitised to the RhD antigen will be systematically identified, appraised for quality, and summarised.

Identifying and systematically reviewing published cost-effectiveness studies

The results of the searches carried out for the systematic review of diagnostic accuracy will be used to inform the assessment of cost-effectiveness of high-throughput NIPT for fetal Rhesus D status. In addition the following databases will be searched: NHS Economic Evaluation Database (NHS EED), EconLit and Research Papers in Economics (RePec) using the search strategy in Appendix 1 as a basis for these searches.

A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature.

The main findings of existing economic evaluations will be narratively summarised and tabulated for comparison. In particular, information will be extracted on the comparators, study population, main analytic approaches (e.g. patient-level analysis/decision-analytic modelling), primary outcome

specified for the economic analysis, details of adjustment for quality-of life, direct costs and indirect costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis).

The review will examine existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. This review will be used to identify the central issues associated with adapting existing decision models to address the specific research question posed and to assist in the development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review.

The presence of any additional data gaps that may need to be filled during the development of the model will be identified and additional targeted searches to inform the model will be developed as necessary. We will also work with relevant experts at the start of the project to identify relevant UK data sources and will make contact with investigators with a view to securing access to this data should this be required.

Evaluation of costs and cost effectiveness

Following the review of existing cost-effectiveness, a de-novo economic model will be developed to assess the cost-effectiveness of high-throughput NIPT to identify fetal Rhesus D status in women who are RhD negative and not known to be sensitised to the RhD antigen compared to a strategy of no testing. The model will be populated using results from the systematic clinical effectiveness review, other focused reviews to inform key parameters (e.g. utilities), routine sources of cost data, and if necessary additional study specific cost estimates provided by experts and/or relevant investigators.

Costs will be considered from an NHS and Personal Social Services perspective and depending on data availability will include:

- Cost of high-throughput NIPT for fetal RhD status
- Cost of testing following potentially sensitising events
- Anti-D immunoglobulin, associated administration costs and treatment of any adverse effects
- Costs of postnatal testing
- Cost of hospital stay following birth (length of stay)
- Costs of managing future pregnancies when sensitisation has occurred
- Costs associated with treatment of haemolytic disease of the fetus and newborn.

If an RhD negative fetus is identified through high-throughput NIPT, both routine antenatal anti-D prophylaxis and anti-D immunoglobulin following potentially sensitising events and birth could be avoided by women who are RhD negative and who are not known to be sensitised to the RhD antigen. Alternatively, only routine antenatal anti-D prophylaxis could be avoided, but anti-D immunoglobulin following potentially sensitising events and birth could be administered according to current clinical guidelines. These alternative scenarios will be investigated in the model.

In addition, high-throughput NIPT for fetal RhD status determination could also impact post-delivery testing in one of four ways:

- Post-delivery cord blood typing and feto-maternal haemorrhage testing would continue to be performed as per current guidelines in all women who are RhD negative, regardless of the fetal RhD status identified through NIPT.

- Post-delivery cord blood typing and feto-maternal haemorrhage testing would be withheld if NIPT of fetal RhD status had identified an RhD negative fetus, but would continue to be performed in women who are RhD negative if NIPT had identified an RhD positive fetus.

- Post-delivery cord blood typing would be performed if NIPT of fetal RhD status had identified an RhD negative fetus. Feto-maternal haemorrhage testing and post-delivery anti-D immunoglobulin would be administered to women who are RhD negative if NIPT had identified an RhD positive fetus.

- Post-delivery cord blood typing would not be performed in any women who are RhD negative. Feto-maternal haemorrhage testing and post-delivery anti-D immunoglobulin would be administered to women who are RhD negative if NIPT had identified an RhD positive fetus.

The impact that post-delivery testing may have on the cost-effectiveness results will be explored using separate scenarios in the model.

The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise existing care pathways and the subsequent impact of using high-throughput NIPT for fetal RhD status determination on the use of antenatal anti-D prophylaxis (routine and for sensitising events) and post-delivery testing.

- To incorporate sufficient flexibility within the model structure to incorporate different timings of the test (and impact on parameter estimates and assumptions), recognising that the preferred timing of NIPT for fetal RhD status may differ in different maternity services.

- To incorporate sufficient flexibility within the model structure to enable alternative assumptions to be made concerning the impact of NIPT testing on use of antenatal anti-D prophylaxis for sensitising events and post-delivery testing.

- To populate this model using the most appropriate data. This is likely to be identified systematically from published literature, routine data sources and potentially using data elicited from relevant clinical experts.

- To relate short-term outcomes, such as test results and use of antenatal anti-D prophylaxis, to intermediate and final health outcomes including: number of infections and adverse events from anti-D, number of sensitisations and cases of haemolytic disease of the fetus and newborn (HDFN) in subsequent pregnancies. Final health outcomes will be expressed in terms of QALYs. This is necessary in order to provide decision makers with an indication of the health gain achieved by NIPT, relative to its additional cost, in units which permit comparison with other uses of health service resources.

- To estimate the mean cost-effectiveness of high-throughput NIPT testing based on an assessment of long-term NHS and Personal Social Service costs and quality-adjusted survival. The time horizon of the model will be sufficient to capture both the short-term and longer-term outcomes arising from HDFN. The final specification of the time horizon and the structural implications for the model will be determined during the review and model conceptualisation stage. The model

used for the NICE technology appraisal of routine antenatal anti-D prophylaxis for women who are rhesus D negative (2008; NICE technology appraisal guidance 156) will also be used to inform the development of the de novo model. This will ensure consistency between the modelling approaches used in the technology appraisal and the diagnostics assessment of high-throughput NIPT for fetal Rhesus D status. Should possible data gaps be identified requiring modification to the model, these will be discussed with members of the Assessment subgroup.

- To characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision makers. A probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this parameter uncertainty, is translated into uncertainty in the overall results. This ultimately helps decision makers understand the probability that, in choosing to fund an intervention, they are making the wrong decision – that is, decision uncertainty. This is presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.

- To use sensitivity and scenario analysis to explore the sensitivity of the cost-effectiveness results to changes in the structural assumptions of the model.

The base-case model will be based on the testing service provided by the International Blood Group Reference Laboratory in Bristol and will be compared to a no testing strategy. However, it is possible that over time other laboratories may set up testing services for high-throughput NIPT for fetal RhD status. The test accuracy and test costs at these laboratories may differ from the test accuracy and test costs at Bristol. Sensitivity analyses involving different test accuracy and increased test costs will be included in the economic analysis.

Handling of information from researchers

Where original data are provided from relevant studies, these will be transferred to the EAG using a suitable secure method (such as encrypted email). Data will be anonymised and stored on a secure server at York, accessible only to the EAG members. Results from analyses of these data will be considered as confidential in the report if they have not been published, or as requested. If confidential information is included in economic models then a version using dummy data or publically available data in place of confidential data will be provided.

Any such ‘commercial in confidence’ or ‘academic in confidence’ data provided by members of the assessment sub-group, and specified as such, will be highlighted as appropriate in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

Competing interests of authors

None

Timetable/milestones

Milestones	**Completion time**
Draft protocol	19/10/2015
Final protocol	12/11/2015

Progress report	12/02/2015
Draft assessment report	12/04/2015
Final assessment report	11/05/2015
Final executable economic model	13/05/2015

References

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Appendix 1:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
30 October 2015
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1 Rh-Hr Blood-Group System/ (10005)
2 (RhD or "rhesus D" or "Rh(D)" or "Rh-(D)" or Rh D).ti,ab. (3320)
3 (Rh-negative or Rh-positive).ti,ab. (897)
4 (Rhesus negative or Rhesus positive).ti,ab. (228)
5 ((rh or rhesus) adj2 (factor or factors or antigen$ or system or group)).ti,ab. (3435)
6 or/1-5 (13808)
7 Rh Isoimmunization/ (1505)
8 ((isoimmuni$ or iso-immuni$ or isoimmune or iso-immune) adj6 (rh or rhesus or maternal or pregnan$)).ti,ab. (1164)
9 ((alloimmuni$ or allo-immuni$ or alloimmune or allo-immune) adj6 (rh or rhesus or maternal or pregnan$)).ti,ab. (867)
10 ((unsensiti#ed or un-sensiti#ed or non-sensiti#ed) adj6 (rh or rhesus or maternal or pregnan$)).ti,ab. (25)
11 ((sensiti#ation$ or sensiti#ed) adj6 (rh or rhesus or maternal or pregnan$)).ti,ab. (1071)
12 ((fetomaternal or feto-maternal or foetomaternal or foeto-maternal) adj2 immuni#ation).ti,ab. (80)
13 ((rh or rhesus) adj2 (immuni#ation or autoimmuni#ation)).ti,ab. (695)
14 or/7-13 (4422)
15 exp Erythroblastosis, Fetal/ (11004)
16 ((hemolytic or haemolytic) adj2 (disease$ or disorder$)).ti,ab. (4460)
17 HDFN.ti,ab. (95)
18 ((rhesus or rh) adj2 (disease$ or disorder$)).ti,ab. (742)
19 ((rhesus or rh or RhD) adj2 (incompatib$ or antagonism)).ti,ab. (750)
20 ((erythroblastoses or erythroblastosis) adj2 f?etal$).ti,ab. (760)
21 or/15-20 (13544)
22 6 or 14 or 21 (25707)
23 Prenatal Diagnosis/ (33262)
24 Maternal Serum Screening Tests/ (152)
25 Hematologic Tests/ (5557)
26 ((prenatal or pre-natal or antenatal or ante-natal) adj3 (test$ or screen$ or diagnos$ or determin$ or detect$)).ti,ab. (32905)
27 ((fetal or foetal or fetus$ or foetus$) adj3 (test$ or screen$ or diagnos$ or determin$ or detect$)).ti,ab. (20021)
28 (NIPD or NIPT).ti,ab. (328)
29 or/23-28 (69936)
30 Genotyping Techniques/ (2739)
31 ((genotype$ or genotyping) adj2 (fetal or foetal or fetus$ or foetus$ or prenatal or pre-natal or antenatal or ante-natal)).ti,ab. (604)
32 ((genotype$ or genotyping) adj2 (maternal or pregnan$)).ti,ab. (787)
33 ((genotype$ or genotyping) adj2 (noninvasive or non-invasive)).ti,ab. (69)
34 cell-free f?etal DNA.ti,ab. (487)
35 cffDNA.ti,ab. (86)
36 or/30-35 (4456)
37 22 and 29 (1791)
38 22 and 36 (274)
39 37 or 38 (1865)
40 (letter or editorial or comment).pt. (1513152)
41 39 not 40 (1778)

42 exp animals/ not humans/ (4135218)
43 41 not 42 (1769)