**High-throughput, non-invasive prenatal testing for fetal RHD genotype to guide antenatal prophylaxis with anti‑D immunoglobulin: a cost-effectiveness analysis**

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**Running title:** Cost-effectiveness of NIPT to guide prophylaxis with anti-D

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**Abstract**

**Objective**

To evaluate the cost-effectiveness of high-throughput, non-invasive prenatal testing (HT-NIPT) for fetal RhD genotype to guide antenatal prophylaxis with anti‑D immunoglobulin compared to routine antenatal anti-D immunoglobulin prophylaxis (RAADP).

**Design**

Cost-effectiveness decision-analytic modelling.

**Setting**

Primary care.

**Participants**

A simulated population of 100,000 RhD negative women not known to be sensitised to the RhD antigen.

**Methods**

A decision tree model was used to characterise the antenatal care pathway in England and the long-term consequences of sensitisation events. The diagnostic accuracy of HT-NIPT was derived from a systematic review and bivariate meta-analysis; estimates of other inputs were derived from relevant literature sources and databases. Women in whom the HT-NIPT was positive or inconclusive continued to receive RAADP, while women with a negative result received none. Five alternative strategies in which the use of HT-NIPT may affect the existing post-partum care pathway were considered.

**Main outcome measures**

Costs expressed in 2015GBP and impact on health outcomes expressed in terms of quality adjusted life years (QALYs) over a lifetime.

**Results**

The results suggested that HT-NIPT appears cost saving but also less effective than current practice, irrespective of the post-partum strategy evaluated. A post-partum strategy in which inconclusive test results are distinguished from positive results performed best. HT-NIPT is only cost-effective when the overall test cost is £26.60 or less.

**Conclusions**

HT-NIPT would reduce unnecessary treatment with routine anti-D immunoglobulin and is cost saving when compared to current practice. The extent of any savings and cost-effectiveness is sensitive to the overall test cost.

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**Keywords:**

Cell-free fetal DNA; non-invasive prenatal screening; rhesus; cost-effectiveness analysis; economic evaluation

**Tweetable abstract:**

HT-NIPT is cost saving compared to providing anti-D to all RhD negative pregnant women

# Introduction

Approximately 15% of women giving birth in England and Wales are RhD negative.(1) A fetus can inherit RhD positive blood type from a RhD positive father. If fetal RhD positive cells enter the circulation of a mother who is RhD negative she may become sensitised and produce antibodies against the RhD antigen.

Sensitisation may cause haemolytic disease of the fetus and newborn, which can result in fetal morbidity or mortality. Following the introduction of routine antenatal administration of anti-D immunoglobulin for all unsensitised RhD negative women, the incidence of RhD sensitisation dropped from 16% to approximately 0.2%. This led to a decrease 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.(2)

Treatment with routine anti-D immunoglobulin is unnecessary with an RhD-negative fetus. The potential risks and ethics of giving a blood product pooled from multiple donors as unnecessary treatment to healthy pregnant women have been questioned.(3)

The development of high-throughput non-invasive prenatal testing (HT-NIPT) allows fetal RhD status to be assessed, and a policy of targeted anti-D immunoglobulin. Test results may be positive, negative or inconclusive (e.g. when no DNA detected), although some studies treat inconclusive test results as positive. Women in whom the test identifies an RhD negative fetus could avoid unnecessary treatment prophylactically and following potentially sensitising events (PSEs), and there may no longer be a need for serologic cord and/or fetal-maternal haemorrhage (FMH) testing at birth. However, the potential for false negative results may increase the risk of sensitisations.

The cost effectiveness of HT-NIPT for fetal RhD status in RhD negative women not known to be sensitised for the UK is uncertain. Two studies (4, 5) reported that HT-NIPT for fetal RHD genotype was cost saving in the absence of routine antenatal anti-D immunoglobulin prophylaxis, while another three (6-8) reported that HT-NIPT for fetal RhD genotype was not of no economic benefit. Of these, the only UK study by Szczepura et al (6), did not include costs relating to PSEs and did not consider the impacts of HT-NIPT on post-partum care nor subsequent pregnancies.

Uncertainties remain as to whether health benefits and cost savings from avoiding unnecessary use of blood product could outweigh the additional cost of introducing HT-NIPT to the antenatal care pathway and any health lost from increased sensitisations. This cost-effectiveness analysis was developed to inform recommendations from the National Institute for Health and Care Excellence (NICE). We aimed to assess the value of HT-NIPT as a diagnostic test for RhD status and the cost implications of implementing a HT-NIPT screening programme.

# Methods

### Decision analytic model

We built a decision tree to simulate the experience of RhD negative pregnant women not known to be sensitised to the RhD antigen (Figure 1). The model was informed by a previous NICE appraisal of the cost-effectiveness of routine antenatal anti-D prophylaxis (RAADP).(9)

A pregnant woman enters the current antenatal care pathway after having been identified as RhD negative and not yet sensitised based on the results of tests from bloods drawn at first contact with the doctor or midwife. All further contacts between the woman and the health service are informed by the recorded test results. At the routine 16 week visit the woman is informed about her RhD status, whether or not she is sensitised, and how these results impact on further management. If the woman contacts the health service following any PSEs she may be offered anti-D immunoglobulin and, if after 20 weeks’ gestation, FMH test to determine the dosage. Women provided with RAADP receive it at either or both of the routine visits at 28 and 34 weeks’ gestation. At delivery, a sample of cord blood is taken and the baby's RhD status established to guide the use of FMH tests and the administration of post-partum anti-D immunoglobulin.

HT-NIPT is assumed to be introduced early enough in the care pathway to guide the use of RAADP at 28 weeks’ gestation (e.g. at the routine 16 week visit). Once the results of the HT-NIPT are known they will be communicated to the woman at future antenatal visits and used to inform all further contacts and decisions regarding testing and treatment. We assumed that RAADP and management for PSEs would only be subsequently offered to women in whom the test result indicates that their fetus is RhD positive and in whom the test result is inconclusive.

All pregnancies and the long-term consequences of sensitisations are evaluated, in terms of costs and health-related quality of life, with a lifetime horizon. This lifetime horizon includes the full life expectancy of any fetus lost as a consequence of sensitisation in any subsequent pregnancy. The decision model follows a UK NHS perspective and all costs and effects are discounted at a rate of 3.5% each year. The main outcomes of interest are the total lifetime costs and total lifetime QALYs for each of the alternative pathways. Cost-effectiveness threshold values of £20,000 and £30,000 per QALY gained are used in line with those specified by NICE. Other outcomes recorded in the model include: the number of sensitisations and the associated costs; the number of affected fetuses following sensitisation; and the number of fetuses lost and associated QALY loss.

<< Figure 1 here >>

Five alternative strategies for how HT-NIPT may affect the existing post-partum care pathway were considered (Table 1):

(1) Post-partum strategy 1 (HT-NIPT PP1): post-partum cord serology and FMH testing would continue to be performed, as per current guidelines, in all women regardless of the fetal RhD status identified through HT-NIPT;

(2) Post-partum strategy 2 (HT-NIPT PP2): post-partum cord serology and FMH testing (and by implication anti-D immunoglobulin) would be withheld if HT-NIPT identifies a RhD negative fetus, but would continue to be performed if HT-NIPT was inconclusive or had identified a RhD positive fetus;

(3) Post-partum strategy 3 (HT-NIPT PP3): post-partum cord serology would be performed if HT-NIPT of fetal RhD status identifies a RhD negative fetus. FMH testing and post-delivery anti-D immunoglobulin would be administered if HT-NIPT is inconclusive or identified a RhD positive fetus;

(4) Post-partum strategy 4 (HT-NIPT PP4): post-partum cord serology not performed in any women. FMH testing and post-delivery anti-D immunoglobulin administered if HT-NIPT is inconclusive or has identified a RhD positive fetus; and

(5) Post-partum strategy 5 (HT-NIPT PP5): post-partum cord serology would be performed if HT-NIPT identifies a RhD negative fetus or if test result is inconclusive. FMH testing and post-partum anti-D immunoglobulin administered irrespective of the result of HT-NIPT and guided by either FMH or FMH and cord serology.

These were compared against each other, and current practice (i.e. no use of HT-NIPT) comprising: (i) RAADP and supplementary anti-D immunoglobulin (as required based on PSEs) offered to all RhD negative pregnant women; (ii) further post-partum anti-D immunoglobulin offered to all RhD negative women whose baby’ RhD status is confirmed to be positive after cord serology.

<< Table 1 here >>

The last column of Table 1 highlights the HT-NIPT type I/II identification issues that cord blood testing at birth could expose. For instance, in strategy HT-NIPT PP5, all HT-NIPT negative and inconclusive cases will undergo post-partum cord serology, which will correct any HT-NIPT false negatives and false positives. Nonetheless, HT-NIPT positive cases will not undergo cord-serology or any further testing, leaving some potential false positive cases uncorrected.

### Data sources

A full list of parameters and their characteristics is shown in Table S1 in the Supporting Material.

***Patient population***

The number of pregnancies in RhD negative women in England was estimated to be of 99,225 per year (1, 10), representing a cross section of all pregnancies (first, second, third and subsequent pregnancies). The probability of having a RhD positive baby was assumed to be the same in the first and subsequent pregnancies.

***HT-NIPT accuracy and inconclusive results***

Data on the diagnostic accuracy of HT-NIPT are based on bivariate random-effects meta-analyses.(11) The base case uses the pooled results for the subgroup of UK (Bristol-based) studies, (12-14) as this technology assessment was intended to inform UK practice. Considering UK Bristol studies only, and treating inconclusive results as if testing positive, pooled sensitivity and pooled specificity were found to be 0.998 (95% CrI: 0.992-0.999) and 0.942 (95% CrI: 0.920-0.959), respectively. The results of the diagnostic accuracy studies suggest that the probability of an RhD positive baby is higher among women in whom the HT-NIPT is inconclusive (70.7%) compared to the probability across all RhD negative women. HT-NIPT inconclusive test results account for the majority of false positives results.

***Effectiveness of anti-D immunoglobulin***

RAADP efficacy was estimated based on the same set of clinical effectiveness studies that were considered most representative of the UK within NICE Technology Appraisal (TA) 156. Evidence for the clinical effectiveness of the post-partum use of anti-D immunoglobulin was sourced from a previous Cochrane review.(15) No evidence was found that supported the existence of adverse effects associated with anti-D immunoglobulin, and so, as in previous appraisals (9), the model includes no adverse health consequences. For women with false negative HT-NIPT results who receive only post-partum anti-D immunoglobulin, the model assumes a rate of sensitisation of 0.95%.(2)

***Potentially sensitising events***

The number of PSEs was taken from the recent audit on anti-D immunoglobulin prophylaxis.(16) We assumed that PSEs involving fetal death were not a consequence of sensitisation, but incorporated them in the model to adjust the amount of post-partum health resource consumption following delivery.

***Compliance with RAADP and post-partum anti-D immunoglobulin***

We assume compliance with HT-NIPT will be high (17), but this does not impact on cost-effectiveness beyond throughput and its impact on unit cost. Also, we assumed women will comply with a HT-NIPT negative result and will not request anti-D immunoglobulin.

***Sensitisation outcomes***

The fetal loss rate per RhD negative women at risk (i.e. carrying a RhD positive baby) was taken from Finning et al.(13) The long-term consequences were accounted for by considering the proportion of babies affected by haemolytic disease which resulted in minor or major developmental problems, together with the average duration of development problems and individual’s life expectancy. In the absence of more recent or relevant data, the health related quality of life evidence relating to minor and major development problems in children and the associated uncertainty was the same as used in NICE TA 156.(9)

### Costs

For the base case analysis, the cost of HT-NIPT per sample was taken from Szczepura et al.(6) The unit cost per sample may fluctuate, as it is a function of machine capacity and predicted level of usage of each testing machine annually (i.e. the level of throughput, the total number of samples). We assumed sufficient machines to process all pregnancies in England in a given year.

The cost of anti-D immunoglobulin was taken from the British National Formulary.(18) The market prices of anti-D immunoglobulin may vary with supply and demand. Regional and local price negotiations exist which may make the cost anti-D immunoglobulin lower than the values indicated below. The cost of anti-D immunoglobulin for a PSE was estimated to be £31.69, based on a recent audit.(16) The cost of RAADP was estimated to be £41.58, representing a weighted average of single (1500 IU) and two (2x 500 IU) dose regimens and the proportions in which these are used in current practice.(16) Similarly, the cost of anti-D immunoglobulin administered post-partum was estimated to be £35.69, which reflects the expected utilisation of ‘standard’ doses, 500 IU (66.3%) and 1500 IU (33.7%).(16) As in the previous NICE TA 156 (9), an administration cost of anti-D immunoglobulin was set to £5. The costs for post-partum serology and associated phlebotomy were obtained from Szczepura et al.(6) The cost of (flow cytometry) FMH testing was provided by personal communication with clinical experts. The list of relevant interventions in the management of maternal and neonatal sensitisation was taken from the previous NICE TA 156.(9) Health resource utilisation was validated by clinical experts, who highlighted that no significant changes in clinical practice have occurred since 2009. Costs refer to 2015 prices, and were discounted according to the timing of the pregnancy in which the resources were consumed.

### Sensitivity Analysis

A series of scenario and sensitivity analysis were conducted to assess the impact on the estimated costs and QALYs. We assessed the impact of basing HT-NIPT accuracy on all available studies rather than UK Bristol studies only, which provided a sensitivity of 0.996 and a specificity of 0.987.(11) We used recent evidence from a UK study to determine sensitivity to providing HT-NIPT at different gestation periods(12). To perform a sensitivity analysis around the rate of HT-NIPT inconclusive results we replaced the pooled estimates for the sensitivity and specificity with the individual study results from the bivariate random-effects meta-analyses performed in Saramago et al.(11) We also assessed the impact of reducing compliance with RAADP and post-partum anti-D immunoglobulin, to about 90% based on estimates obtained from a recent anti-D immunoglobulin audit.(16) The impact of altering the cost per diagnostic test, which could be via test price or other additional costs imposed by introduction of test, (between £16.00 to £25.00) and the cost of anti-D immunoglobulin treatment (±20%) was analysed. Finally, we evaluated the impact of reducing the cost of the FMH test from £128.10 (for test by flow cytometry, NHS Blood and Transport Red Cell Immunohaemotology) to £3.17 (for a Kleihauer test, updated to 2015 prices, in Szczepura et al (6)).

### Economic modelling framework and assumptions

The main economic modelling assumptions are:

(a) all HT-NIPT are assumed to be performed early enough to guide the use of RAADP at 28 weeks’ gestation;

(b) antenatal prophylactic anti-D immunoglobulin is only offered to women in whom the HT-NIPT result indicates that their fetus is RhD positive or in whom the results are inconclusive;

(c) no adverse health impacts from use of a blood based product such as anti-D immunoglobulin are assumed (5, 6, 8, 9);

(d) PSEs that involve fetal death were assumed independent of sensitisation within the same pregnancy; and

(e) provision of HT-NIPT can be incorporated into routine antenatal care without requiring additional visits.

The decision-analytic model was evaluated using 10,000 Monte Carlo simulations to reflect the joint uncertainty across all of the inputs according to the probability distributions assigned to each, as shown in Table S1 in the Supporting Material. Simulations were used to estimate mean costs and QALYs and assess the probability that the technology is cost-effective.(19)

# Results

All results are based on the probabilistic analysis and expressed per 100,000 pregnancies.

### Base case

The model estimates that for each additional sensitisation there is a loss of approximately 0.9 QALYs. Any difference in QALYs between strategies is attributable wholly to the difference in the number of sensitisations. In the model, the health gains for the post-partum strategies are determined by the management of HT-NIPT false negative test results.

Table 2 presents the cost-effectiveness results for each post-partum testing strategy and current practice of ‘No test and RAADP’. All post-partum strategies are cost saving but also less effective than current practice of ‘No test and RAADP’. Hence where the ICER is *above* the cost-effectiveness threshold this would support the use of HT-NIPT (e.g. No test and RAADP *vs* HT-NIPT PP5, ICER approximately £1,660,000 per QALY gained). The least effective strategies are those that omit blood cord serology for women who test negative on the HT-NIPT. Without cord serology false negatives are not picked up at delivery and are not provided with post-partum anti-D immunoglobulin. All HT-NIPT post-partum strategies have an expected net health benefit (NHB) higher than ‘No test and RAADP’, at a threshold of £20,000 per QALY gained. HT-NIPT PP5 obtains the highest probability of being cost-effective, at a threshold of £20,000 per QALY gained.

<< Table 2 here >>

Regarding those with HT-NIPT inconclusive results as distinct from those on whom the HT-NIPT indicates an RhD positive fetus (HT-NIPT PP5) allows blood cord serology to be provided to women with negative results in order to identify false negatives and to women with inconclusive results in order to identify false positives. However cord serology is withheld in women in whom the HT-NIPT indicates a RhD positive fetus. This approach is estimated to be the cheapest of strategies and of highest NHB. Compared to HT-NIPT PP5, current practice leads to an additional 0.5 QALYs per 100,000 pregnancies, however at an additional cost of approximately £762,000.

Using the HT-NIPT negative results to rule out post-partum cord serology, FMH test and anti-D immunoglobulin (HT-NIPT PP2 and HT-NIPT PP4) has lower QALYs compared to ‘No test and RAADP’, HT-NIPT PP1, HT-NIPT PP3 and HT-NIPT PP5. While there are further cost savings from avoiding post-partum blood cord serology and anti-D immunoglobulin, the majority of sensitisations occur and can be prevented by the administration of anti-D immunoglobulin at delivery.

Providing blood cord serology to all women, as with HT-NIPT PP1, will identify both the false positive (the small number of false positives and the proportion of women with inconclusive results who are carrying RhD negative babies) and false negative results. While HT-NIPT PP1 has higher costs compared to HT-NIPT PP2 due to the additional cord serology tests, these are offset somewhat by cost savings from avoiding sensitisations in false negatives.

HT-NIPT PP5 and HT-NIPT PP3 have the same QALY gain as the model assumes no adverse health benefits from unnecessary use of anti-D immunoglobulin. HT-NIPT PP3 is more costly than HT-NIPT PP5 due to the use of FMH testing on false positives, and, thus, is dominated by HT-NIPT PP5.

Clinical outcomes for each strategy, including number of sensitisations and fetus lost are shown in Table S2 in the Supplementary Material.

### Sensitivity Analysis

The majority of sensitivity analyses showed that base case results were robust to changes to model parameters. Compared to all other strategies, HT-NIPT PP5 was still found to provide higher NHBs when: using different HT-NIPT performance values; providing HT-NIPT at different gestation; changing anti-D immunoglobulin effectiveness; considering different uptake levels of antenatal and/or post-partum anti-D immunoglobulin; and when using a reduced cost for FMH testing (Table S3 in the Supporting Material).

Figure S1 (in the Supporting Material) shows how population NHBs for HT-NIPT PP5 varies with the rate of HT-NIPT inconclusive results. NHBs associated with HT-NIPT PP5 increase with the rate of inconclusive results and do not fall below those offered with No test and RAADP.

An increase of 20% in the cost of anti-D immunoglobulin represents a cost of £39.50\*0.2 = £7.90. At a cost-effectiveness threshold of £20,000 per QALY gained, this is equivalent to assuming a health cost of 7.9/20,000 = 0.0004 QALYs per administration, or a loss of 3.5 hours of full lifetime health per dose of anti-D immunoglobulin.

The results of a two-way analysis around these unit costs show that the base case is sensitive to both the price of HT-NIPT and the price of anti-D immunoglobulin (Figure 2).

<< Figure 2 here >>

The threshold cost for HT-NIPT PP5 is £26.60. That is, raising the cost per HT-NIPT test to £26.60 implies that HT-NIPT PP5 is no longer cost-effective and the best strategy reverts to ‘No test and RAADP’.

# Discussion

* 1. **Main findings**

The decision model suggested that HT-NIPT appears cost saving but also less effective at preventing sensitisation than current practice, irrespective of the post-partum strategy evaluated. However, the magnitude of the potential cost-savings appeared sufficient to outweigh the small increase in sensitisations and the associated small QALY loss. Based on a cross section of 100,000 pregnancies, the likely magnitude of cost savings ranged between £493,000 and £762,000 across the separate post-partum strategies. The strategy in which the HT-NIPT inconclusive results are differentiated in post-partum care from those on whom an RhD positive fetus is indicated is considered the best strategy.

The results indicate that the timing of the test does not appear influential in determining the cost-effectiveness results either in terms of diagnostic accuracy or in terms of the extent of management costs for PSEs that can be avoided. Findings demonstrate that even with a HT-NIPT inconclusive result rate close to 15%, the introduction of HT-NIPT compares favourably to current practice. The ability of HT-NIPT to avoid unnecessary use of anti-D immunoglobulin varies systematically according to ethnicity, as some ethnic groups (e.g. African ancestry) would have proportionately higher rates of inconclusive test results. We conclude that the identification of the false positive results is key to the estimation of the cost-effectiveness outcomes, negatively influencing the results if this rate is higher, and altering the post-partum strategy that would offer the highest NHB.

There exists uncertainty regarding the cost of introducing the HT-NIPT. The unit cost will vary with throughput, and may be subject to an additional royalty fee. Unless the HT-NIPT can be incorporated seamlessly into routine antenatal care, it may result in additional costs for blood draw, transport of samples, and antenatal care visits to administer the test and deliver counselling and results. Extensive sensitivity analysis was conducted to address this uncertainty and to identify the threshold cost per HT-NIPT. The cost per HT-NIPT needs to go above £26.60 for No test and RAADP to be the preferred strategy. The total testing cost of HT-NIPT to the UK NHS is the most important parameter in determining the cost-effectiveness.

### Strengths and limitations

Due to the limited evidence, the potential clinical impact of HT-NIPT on the care pathway remains unclear. No studies were identified reporting comparative data relating to patient-related outcomes such as health related quality of life. Whether the diagnostic performance of HT-NIPT differs between different ethnic groups remains unclear.

Evidence on the diagnostic accuracy of HT-NIPT in women of non-white ethnicity is needed, for which large prospective cohort studies collecting diagnostic accuracy data will be required. This is of particular concern, as non-white women may be more likely to have inconclusive test results.(20, 21) Due to a lack of UK-based evidence, the generalisability of studies reporting compliance rates to antenatal anti-D immunoglobulin treatment to the UK setting remains uncertain. Key issues around implementation include ensuring anti-D immunoglobulin prophylaxis compliance, effective management of transporting samples, and greater knowledge of HT-NIPT among physicians, midwives and pregnant women.

### Interpretation of findings in light of other evidence

Our findings are in line with two economic studies that reported HT-NIPT to be cost saving compared with non-targeted RAADP. However, these studies estimated a similar or lower risk of sensitisation if HT-NIPT were to be used compared to non-targeted RAADP, which disagrees with our findings. Our results are also in line with Hawk et al.(8) and Szczepura et al.(6) studies which reported that the main factor driving their findings was the cost of the test itself. We note that the findings from our study are UK specific.

# Conclusions

HT-NIPT is highly accurate for the detection of fetal Rhesus D status in RhD negative women. The use of HT-NIPT can largely remove unnecessary exposure to prophylactic anti-D immunoglobulin treatment, without substantially altering the rate of sensitisations. Targeted provision of anti-D immunoglobulin prophylaxis using HT-NIPT is estimated to be cost saving compared to current practice of providing prophylactic pre-natal anti-D immunoglobulin to all women who are RhD negative. A post-partum strategy that distinguishes between inconclusive results and positive results (HT-NIPT PP5) offers the greatest cost-savings. Further evidence on the clinical impact of HT-NIPT testing is needed. Appropriate auditing of HT-NIPT and anti-D immunoglobulin administration process should be considered, if it is implemented, recording clinical outcomes, such as sensitisation rates, HT-NIPT and anti-D immunoglobulin compliance, together with health-related quality of life. Further clarifications over the potential additional costs for blood drawing, transporting of samples, and antenatal care visits to administer the test and deliver counselling and results, is needed. Further research to comprehensively appreciate the full impact of sensitisations over mothers and children is warranted. Although well-conducted cohort studies that comprehensively assess the full impact of sensitisations over mothers and children would be ideal, the complexity and cost associated with such studies means that promoting more systematic reporting and good quality national audit data collection may be preferred.

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# Disclosure of interests

None

# Contribution to Authorship

Pedro Saramago (Research Fellow) was responsible for the cost-effectiveness analysis, development of the economic model and writing of the manuscript.

Huiqin Yang (Research Fellow) contributed to the clinical interpretation of results and commented on drafts of the manuscript.

Alexis Llewellyn (Research Fellow) contributed to the clinical interpretation of results and commented on drafts of the manuscript.

Stephen Palmer (Professor of Health Economics) provided project management and commented on drafts of the manuscript.

Mark Simmonds (Research Fellow) contributed to the clinical interpretation of results and commented on drafts of the manuscript.

Susan Griffin (Senior Research Fellow) contributed to the cost-effectiveness analysis, to the development of the economic model and writing the manuscript and had overall responsibility of the project.

# Details of ethical approval

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