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Benefits and harms of antenatal and newborn screening programmes in health economic assessments: the VALENTIA systematic review and qualitative investigation

Oliver Rivero-Arias, May Ee Png, Ashley White, Miaoqing Yang, Sian Taylor-Phillips, Lisa Hinton, Felicity Boardman, Abigail McNiven, Jane Fisher, Baskaran Thilaganathan, Sam Oddie, Anne-Marie Slowther, Svetlana Ratushnyak, Nia Roberts, Jenny Shilton Osborne and Stavros Petrou

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Benefits and harms of antenatal and newborn screening programmes in health economic assessments: the VALENTIA systematic review and qualitative investigation

Oliver Rivero-Arias,[1†*] May Ee Png,[2] Ashley White,[2] Miaoqing Yang,[1] Sian Taylor-Phillips,[3] Lisa Hinton,[2,4] Felicity Boardman,[3] Abigail McNiven,[2] Jane Fisher,[5] Baskaran Thilaganathan,[6] Sam Oddie,[7] Anne-Marie Slowther,[3] Svetlana Ratushnyak,[1] Nia Roberts,[8] Jenny Shilton Osborne[1] and Stavros Petrou[2†]

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This article

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Abstract

Benefits and harms of antenatal and newborn screening programmes in health economic assessments: the VALENTIA systematic review and qualitative investigation

Oliver Rivero-Arias[1†*] May Ee Png[2] Ashley White[2] Miaoqing Yang[1] Sian Taylor-Phillips[3] Lisa Hinton[2,4] Felicity Boardman[3] Abigail McNiven[2] Jane Fisher[5] Baskaran Thilaganathan[6] Sam Oddie[7] Anne-Marie Slowther[3] Svetlana Ratushnyak[1] Nia Roberts[8] Jenny Shilton Osborne[1] and Stavros Petrou[2†]

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Background: Health economic assessments are used to determine whether the resources needed to generate net benefit from an antenatal or newborn screening programme, driven by multiple benefits and harms, are justifiable. It is not known what benefits and harms have been adopted by economic evaluations assessing these programmes and whether they omit benefits and harms considered important to relevant stakeholders.

Objectives: (1) To identify the benefits and harms adopted by health economic assessments in this area, and to assess how they have been measured and valued; (2) to identify attributes or relevance to stakeholders that ought to be considered in future economic assessments; and (3) to make recommendations about the benefits and harms that should be considered by these studies.

Design: Mixed methods combining systematic review and qualitative work.

Systematic review methods: We searched the published and grey literature from January 2000 to January 2021 using all major electronic databases. Economic evaluations of an antenatal or newborn screening programme in one or more Organisation for Economic Co-operation and Development countries were considered eligible. Reporting quality was assessed using the Consolidated Health Economic Evaluation Reporting Standards checklist. We identified benefits and harms using an integrative descriptive analysis and constructed a thematic framework.

Qualitative methods: We conducted a meta-ethnography of the existing literature on newborn screening experiences, a secondary analysis of existing individual interviews related to antenatal or newborn screening or living with screened-for conditions, and a thematic analysis of primary data collected with stakeholders about their experiences with screening.

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Results: The literature searches identified 52,244 articles and reports, and 336 unique studies were included. Thematic framework resulted in seven themes: (1) diagnosis of screened for condition, (2) life-years and health status adjustments, (3) treatment, (4) long-term costs, (5) overdiagnosis, (6) pregnancy loss and (7) spillover effects on family members. Diagnosis of screened-for condition (115, 47.5%), life-years and health status adjustments (90, 37.2%) and treatment (88, 36.4%) accounted for most of the benefits and harms evaluating antenatal screening. The same themes accounted for most of the benefits and harms included in studies assessing newborn screening. Long-term costs, overdiagnosis and spillover effects tended to be ignored. The wide-reaching family implications of screening were considered important to stakeholders. We observed good overlap between the thematic framework and the qualitative evidence.

Limitations: Dual data extraction within the systematic literature review was not feasible due to the large number of studies included. It was difficult to recruit healthcare professionals in the stakeholder's interviews.

Conclusions: There is no consistency in the selection of benefits and harms used in health economic assessments in this area, suggesting that additional methods guidance is needed. Our proposed thematic framework can be used to guide the development of future health economic assessments evaluating antenatal and newborn screening programmes.

Study registration: This study is registered as PROSPERO CRD42020165236.

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List of supplementary material

Report Supplementary Material 1	List of studies excluded at full-text screening stage, with brief reasons
Report Supplementary Material 2	Results of thematic framework analysis
Report Supplementary Material 3	Additional results from Chapter 7

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/PYTK6591).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

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List of abbreviations

16D	16-Dimension
ALD-DRS	Adrenoleukodystrophy-Disability rating scale
ARC	Antenatal Results and Choices
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CVS	chorionic villus sampling
DALY	disability-adjusted life-year
EQ-5D	EuroQol-5 Dimensions
EQ-5D-Y	EuroQol-5 Dimensions-Youth
HCP	healthcare providers
HIV	human immunodeficiency virus
HTA	Health Technology Assessment
HUI	Health Utilities Index
IQI	Infant health-related Quality of Life Instrument
MP	member of parliament
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NIPT	non-invasive prenatal testing
NPEU	National Perinatal Epidemiology Unit
NSC	National Screening Committee
OECD	Organisation for Economic Co-operation and Development
PICOS	Population, Intervention, Comparator, Outcome and Study design
PKU	phenylketonuria
PPI	parent and public involvement
PROM	patient-reported outcome measure
QALY	quality-adjusted life-year
QWB	Quality of Well-Being Scale
SCBU	special care baby unit
SF-6D	Short Form 6-dimension
TANDI	Toddler and Infant health-related Quality of Life Instrument
WP	work package

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Plain language summary

Every year the NHS offers pregnant women screening tests to assess the chances of them or their unborn baby having or developing a health condition. It also offers screening tests for newborn babies to look for a range of health conditions. The implementation of screening programmes and the care for women and babies require many resources and funding for the NHS, so it is important that screening programmes represent good value for money. This means that the amount of money the NHS spends on a programme is justified by the amount of benefit that the programme gives. We wanted to see whether researchers consider all the important benefits and harms associated with screening of pregnant women and newborn babies when calculating value for money. To do this, we searched all studies available in developed countries to identify what benefits and harms they considered. We also considered the views of parents and healthcare professionals on the benefits and harms screening that creates for families and wider society.

We found that the identification of benefits and harms of screening is complex because screening results affect a range of people (mother–baby, parents, extended family and wider society). Researchers calculating the value for money of screening programmes have, to date, concentrated on a narrow range of benefits and harms and ignored many factors that are important to people affected by screening results. From our discussions with parents and healthcare professionals, we found that wider impacts on families are an important consideration. Only one study we looked at considered wider impacts on families. Our work also found that parent's ability to recognise, absorb and apply new information to understand their child's screening results or condition is important. Healthcare professionals involve in screening should consider this when supporting families of children with a condition.

We have created a list for researchers to identify the benefits and harms that are important to include in future studies. We have also identified different ways researchers can value these benefits and harms, so they are incorporated into their studies in a meaningful way.

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Scientific summary

Background

National population screening programmes are implemented in the NHS on the advice of the United Kingdom National Screening Committee (UK NSC), which makes independent, evidence-based recommendations to ministers in the four countries of the UK. The recommendation to adopt a screening programme on a national scale is based on the premise that the benefits associated with the programme outweigh the harms to all relevant stakeholders. Screening committees require up-to-date evidence of these benefits and harms, as well as data demonstrating that the screening programme represents value for money. The latter is determined using a health economic assessment confirming that the additional costs to the NHS of implementing the programme and any unavoidable harms associated with it are justified by the benefits achieved, which are usually evaluated through outcome measures such as the incremental cost per quality-adjusted life-year (QALY) gained metric. Although there is established guidance on best practice for economic assessments of screening programmes in general (such as economic modelling), such guidance does not address the challenge of how the full range of potentially relevant benefits and harms can be incorporated into a single assessment, nor does it specifically focus on antenatal and newborn screening. Guidance in this area, therefore, remains limited.

Objectives

The overall objectives of this programme of work were to:

1. enhance knowledge about methods for the identification and valuation of benefits and harms within economic assessments of antenatal and newborn screening
2. identify attributes of relevance to stakeholders (parents/carers, health professionals, other relevant stakeholders) that should be considered for incorporation into future economic assessments using a range of qualitative research methods
3. make recommendations about the benefits and harms that should be considered by economic evaluations and the health economic tools that could be employed for this purpose.

Methods

Systematic review and development of thematic framework of benefits and harms to use in future health economic assessments

A systematic review of the published and grey literature of articles and reports published after January 2000 was conducted to identify health economic assessments evaluating antenatal and newborn screening programmes in one or more of the Organisation for Economic Co-operation and Development (OECD) countries (see *Chapter 3*). A protocol for this review was registered with PROSPERO (CRD42020165236) and published in January 2020. The Population, Intervention, Comparator, Outcome and Study design (PICOS) framework was used to develop the study eligibility criteria and applied to the literature searches. No language restrictions were imposed. The published literature was searched using a comprehensive selection of electronic bibliographic databases. The academic electronic database search was supplemented by manual reference searching of bibliographies, contacts with experts in the field and author searching. The list of sources of grey literature searched was informed by a recent systematic review of national policy recommendations on newborn screening. Two independent reviewers assessed the suitability for inclusion of outputs identified in the published and grey literature.

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A data extraction sheet was created including: (1) items from the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, and (2) a bespoke form created by the research team to extract benefits and harms adopted by economic assessments evaluating antenatal and newborn screening programmes.

The information captured in the bespoke form was used to develop a framework of benefits and harms adopted by health economic assessments using a number of themes grouped into categories based on an integrative descriptive analysis (see *Chapter 4*). Benefits and harms reported by articles and reports were categorised into themes and subtheme(s) according to the condition and screening type, using this thematic framework.

Qualitative component

We conducted a qualitative study using multiple methods to capture stakeholders' views about the benefits and harms of antenatal and newborn screening that should be incorporated into future economic assessments. The qualitative study included:

1. a meta-ethnography of the existing literature on newborn screening experiences (see *Chapter 5*)
2. secondary analysis of existing individual interviews related to antenatal screening, newborn screening and living with screened-for conditions (see *Chapter 6*)
3. thematic analysis of primary data collected with stakeholders about their experiences with antenatal and newborn screening (see *Chapter 7*).

We conducted a meta-ethnography to better understand what was known about the experiences of newborn bloodspot screening. The experiences of antenatal screening have been extensively investigated, but newborn screening experiences remained underexplored. In our secondary analysis, the goal was to bring together, examine and interpret the findings from disparate qualitative research studies and produce a richer and broader understanding than would be possible by looking at the studies individually. We drew on a large body of existing interview data reflecting a range of screening experiences, to better understand how individuals affected by screening discussed their experiences. What emerged was a complex web of individuals, organisations, technologies and discourses that shape the screening landscape. Finally, we conducted a thematic analysis of evidence generated from primary research with three groups of stakeholders (individuals, charity and policy professionals, and healthcare providers) to understand how these groups conceptualised the benefits and harms of screening. This primary data collection amplified concepts from our meta-ethnography and secondary analysis. By using a range of qualitative methods, we identified well-informed conclusions about not only the benefits and harms of screening as understood by a variety of stakeholders, but also concepts which do not fit neatly into that framework. We present the methods and findings for each of these pieces of work in individual chapters before summarising critical findings from across components of the qualitative study (see *Chapter 8*).

Blending benefits and harms taxonomy with qualitative evidence

A mapping exercise was carried out to identify levels of overlap between the outcomes of the systematic review and the qualitative component of the study. The aim of this exercise was to identify whether health economics assessments miss the adoption of key benefits and harms when evaluating antenatal and newborn screening programmes. We mapped the qualitative data (see *Chapters 5–7*) onto the completed thematic framework. In some cases, the qualitative data collected did not cover subcategories of the framework, and we noted the absence. There were also themes from the qualitative data that could not be easily mapped onto the thematic framework.

Stakeholder workshops

A scoping review of alternative methods to value benefits and harms associated with screening scenarios was conducted. The aim of this exercise was to clarify which valuation methods should be implemented to value antenatal and newborn benefits and harms in future studies. The final selected

alternatives were presented to our parent and public involvement (PPI) members to understand the feasibility of administering these valuation methods to relevant participants in future studies. This was supplemented by a separate workshop held with a broad set of stakeholders to review the findings of the VALENTIA research programme and contribute to a set of recommendations about approaches for the measurement and valuation of outcomes that should be considered by future economic assessments of antenatal and newborn screening, and to highlight areas for future methodological enquiry. The session was attended by healthcare professionals, representatives from relevant academic disciplines, representatives from charities, outreach services and support groups, and representatives from policy-making bodies.

Results

Systematic review and development of taxonomy of benefits and harms to use in future health economic assessments

We identified 52,244 articles and reports from the searches of the published and grey literature and included 336 records in the data extraction. The majority of the records were journal articles, with almost half conducted in the USA or UK. Genetic conditions and infectious diseases were the main areas covered by the articles and reports assessing antenatal screening, while metabolic and structural conditions were the main areas covered in the evaluations of newborn screening programmes. Decision-analytical models were employed in 272 (81.0%) of the articles and reports, while 117 (43.0%) used a lifetime time horizon. Almost half of the studies conducted a cost–utility analysis reporting incremental cost per QALY values (167, 49.4%). The costing perspective adopted was not stated in 117 (33.7%) articles and reports. Reporting quality assessed using the CHEERS checklist was heterogeneous. The top five items not satisfied among the studies for antenatal screening programmes were 'Abstract' (160, 88.4%), 'Time horizon' (153, 84.5%), 'Choice of model' (153, 84.5%), 'Discount rate' (130, 71.8%) and 'Study funding, limitation, generalisability and current knowledge' (123, 68.0%). The top six items not satisfied among newborn screening programme studies were 'Abstract' (69, 83.1%), 'Time horizon' (67, 80.7%), 'Study funding, limitation, generalisability and current knowledge' (59, 71.1%), 'Choice of model' (55, 66.3%), 'Discount rate' (53, 63.9%) and 'Setting and location' (53, 63.9%). The top five items satisfied among the studies for both antenatal and newborn screening programmes were 'Background and objectives' (264, 100%), 'Target population and subgroups' (264, 100%), 'Choice of health outcomes' (263, 99.6%), 'Measurement of effectiveness' (260, 98.5%) and 'Estimate resources and cost' (247, 93.6%).

We identified 86 unique descriptions of consequences associated with benefits and harms across all articles and reports. Our thematic analysis resulted in seven core themes of benefits and harms: (1) diagnosis of screened for condition, (2) life-years and health status adjustments, (3) treatment, (4) long-term costs, (5) overdiagnosis, (6) pregnancy loss and (7) spillover effects on family members. Diagnosis of screened-for condition (115, 47.5%), life-years and health status adjustments (90, 37.2%) and treatment (88, 36.4%) accounted for most of the benefits and harms evaluating antenatal screening. The same themes accounted for most of the benefits and harms included in studies assessing newborn screening. Overdiagnosis and spillover effects tended to be ignored. Only 10 out of the 242 (4.1%) antenatal screening evaluations adopted benefits and harms from all of themes 1–4, whereas only 9 out of the 95 (9.5%) newborn screening evaluations adopted benefits and harms from all of themes 1–4.

Qualitative component

By looking across a range of moments, outcomes and conditions across international contexts, our meta-ethnography identified that newborn screening experiences vary widely across families. We developed the concept of absorptive capacity – the ability to recognise, assimilate and apply new information – to capture the abilities of parents, and crucially also the limits of those abilities, to comprehend their child's screening results or condition. We explain the various ways that parents experience the expansion and

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compression of time throughout and beyond the screening pathway, demonstrating the far-reaching implications of screening across time, as well as to wider family and kin.

Our secondary analysis brought together a large, rich data set and yielded a situational map. This map demonstrates that conversations about antenatal and newborn screening involve a complicated weaving of individuals, organisations, materials and discourses. We identified elements that may (or may not) be involved in an individual's situation and consider implicated environments that shape the landscape of screening. We generated a list of stakeholders that are central to screening conversations and uncovered temporal, spatial, economic and societal issues shaping screening experiences and debates.

We conducted in-depth interviews and focus groups with people who had recently made decisions about screening, charity and professional stakeholders and healthcare providers. While different stakeholders named different benefits and harms, there was a substantial amount of overlap between groups. Consistently named benefits included screening's ability to get information, prevent harm and provide reassurance. Consistently named harms included possible pressure to have termination of pregnancy, lack of preparation for unexpected results, emotional distress and a lack of understanding of the purposes and potential implications of screening tests.

Blending benefits and harms from the thematic framework with qualitative evidence

Our mapping exercise resulted in an overall good overlap between the quantitative and qualitative evidence, with elements of the qualitative evidence relevant to specific themes on the thematic framework identified. There was no suggestion that our thematic framework of benefits and harms excluded any important themes. Elements of the qualitative evidence not present in the thematic framework were also identified. For most of these elements, it was clear that they were not relevant for the development of health economic assessments (e.g. challenge of information provision to make sure choice is 'informed'). However, the area of wide-reaching family implications of screening was considered important to our stakeholders in the qualitative work but often overlooked by developers of health economic assessments evaluating antenatal and newborn screening programmes.

Stakeholder workshops

In the first workshop, concerns around the practicality of the number of valuation techniques that could be applied within the online workshops led to a focus on best–worst scaling and discrete choice experiments as the primary valuation techniques. The workshops highlighted a number of factors that can inform the design of future preference elicitation studies in this area. In the second workshop, we reviewed the findings of the VALENTIA research programme and informed the final set of recommendations about approaches for the measurement and valuation of outcomes that should be considered by future economic assessments of antenatal and newborn screening, and highlighted areas for future methodological enquiry.

Conclusions

Benefits and harms of antenatal and newborn screening are complex and multidimensional, and they have generally been incorporated in a haphazard manner into economic evaluations. Our work suggests that there is an immediate need to provide methods guidance for researchers conducting these types of studies in future work. Our proposed framework of benefits and harms can be used as a starting point to guide the development of health economic assessments evaluating antenatal and newborn screening for specific conditions and to prevent exclusion of important harms. It is important that future economic evaluations in this area incorporate benefits and harms of spillover effects to family members, as this was considered very important to the stakeholders consulted during the study. The QALY remains a common approach for capturing the benefits and harms associated with antenatal and newborn screening programmes. This study identifies a range of benefits and harms that should be considered for

inclusion within future economic assessments and provides preliminary evidence of the feasibility of applying alternative economic valuation methods in this area.

Study registration

This study is registered as PROSPERO CRD42020165236.

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Chapter 1 Introduction

Background

National population screening programmes are implemented in health systems on the advice of screening committees such as the United Kingdom National Screening Committee (UK NSC), which makes independent, evidence-based recommendations to ministers in the four countries of the UK. Antenatal and newborn screening are covered by 6 of the 11 NHS screening programmes, namely fetal anomaly screening, infectious diseases in pregnancy screening, the newborn and infant physical examination, newborn blood spot screening, newborn hearing screening and sickle cell and thalassaemia screening. The recommendation to adopt a screening programme on a national scale is based on the premise that the benefits associated with screening outweigh the harms to all relevant stakeholders once implemented.[1] Harms of screening associated with false-positive and false-negative results include unnecessary additional resources to conduct further investigations, adverse psychological effects and legal claims, as well as decreased trust and confidence in the healthcare system.[2] In antenatal screening, when a decision to continue a pregnancy is made after a true-positive result, a clear screening benefit is the time it offers expectant parents to prepare for the care of a child with a clinical condition. An informed decision to terminate a pregnancy can also follow after a true-positive result. Both outcomes can sometimes lead to long-lasting psychosocial sequelae for women and their partners, affecting their quality of life and their future pregnancy choices.[3–9] The use of whole genome sequencing for newborn screening presents an opportunity to identify and treat or prevent severe health conditions, thus maximising survival and quality of life of the newborn, but is subject to overdiagnosis and over-treatment that need careful evaluation.[10,11]

Screening committees require up-to-date evidence of these benefits and harms as well as data demonstrating that the screening programmes represent value for money.[12] The latter is determined using a health economic assessment confirming that the additional costs of implementing a screening programme are justified by the additional benefits achieved, usually through outcome measures such as the incremental cost per quality-adjusted life-year (QALY) gained, where the QALY combines preference-based health-related quality-of-life weights (health utilities) with data on length of time in the health states of interest.[13] This approach to cost-effectiveness assessment mirrors those recommended more broadly by Health Technology Assessment (HTA) agencies in the UK, such as the National Institute of Health and Care Excellence (NICE) in England and the Scottish Medicines Consortium in Scotland.[14,15] It also mirrors the preferred form of cost-effectiveness assessment adopted by HTA, pricing and reimbursement authorities in several other industrialised countries.[16–18] Although there is established guidance on best practices for economic assessment for screening programmes in general, such as in the area of economic modelling,[19] such guidance does not address the challenges of how to incorporate the breadth of potentially relevant benefits and harms into a single assessment, and does not specifically focus on antenatal and newborn screening. Guidance in this area, therefore, remains limited.[20]

Furthermore, several methodological factors have constrained capacity to evaluate antenatal and newborn screening programmes using the standard incremental cost per QALY gained metric. These include challenges surrounding the valuation of prenatal life when decisions following antenatal screening and diagnostic testing result in the termination of the fetus or unborn child,[21,22] the absence of a multi-attribute utility measure validated for use in infancy and through early childhood[23] and the challenges surrounding QALY aggregation across the mother, child and potentially other family members.[24] Attributes of relevance to parents, such as the utility derived from information per se or reassurance following a screen-negative test result, and the disutility associated with anxiety from a false-positive test result or over-diagnosis of disease, are likely to be missed, or at least inadequately covered, by standard approaches to health utility measurement, such as available multi-attribute utility

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measures [e.g. EuroQol-5 Dimensions (EQ-5D), Short Form 6-Dimension (SF-6D), Health Utilities Index Mark 3].[25,26] In addition, numerous ethical challenges also compound the technical complexities surrounding economic assessments of antenatal and newborn screening programmes. These emanate from differences in moral perspectives on the status of the fetus or unborn child[22] and how society should value disability,[27] and differing perspectives on the ownership of genetic information[28] and the potential harms of inadequately informed consent processes on parental autonomy.[29] Failure to incorporate all relevant benefits and harms when assessing the cost effectiveness of antenatal and newborn screening programmes may lead screening committees to make decisions based on suboptimal levels of evidence, resulting in a suboptimal allocation of resources.

Previous work has focused on the identification of methodological challenges and the development of good practice guidelines for the purpose of health economic assessments of antenatal and newborn screening programmes.[20,30,31] However, none has specifically focused on the range of benefits and harms incorporated into health economic assessments of antenatal and newborn screening programmes, or the methodological issues surrounding their identification, measurement and valuation.

Objectives

The overall aim of the proposed programme of work was to enhance knowledge about methods for valuing benefits and harms within economic assessments of antenatal and newborn screening and make recommendations about the benefits and harms that should be considered by economic evaluations and the health economic tools that could be employed for this purpose. Our specific objectives were:

1. to systematically identify the benefits and harms adopted by health economic assessments evaluating antenatal and newborn screening programmes, and to assess how they have been measured and valued
2. to identify attributes of relevance to stakeholders (parents/carers, health professionals, other relevant stakeholders) that should be considered for incorporation into future economic assessments using a range of qualitative research methods
3. to make recommendations about approaches for the measurement and valuation of outcomes that should be considered by future economic assessments in these contexts.

A brief explanation of the foundations of health economic assessments for non-health economists.

A note about benefits and harms of screening

The aim of a screening programme is to identify asymptomatic people who may be developing or at a greater risk of developing a condition and offer further investigations and/or treatment. The objective is then to allow individuals to make informed choices and reduce complications in the future. Screening programmes run on a national population scale and every year millions of people in countries with established screening organisations benefit from these programmes. However, no screening test is perfect and when false-negative result (individual with a negative screening result with the target condition) and false-positive result (individual with a positive screening result without the target condition) happen, there is potential to generate harm to the people the programme is intended to help. Consequently, screening programmes are subject to benefits as well as harms. In the UK, the NSC makes recommendations about adding new conditions to the current antenatal and newborn screening programmes based on the premise that the benefits associated with screening outweigh its harms at a population level. Essentially, screening agencies evaluate available evidence about benefits and harms of the screening programme in an attempt to understand whether it does more good than harm to the population.

The benefits of screening are diverse and include better future health for individuals who are identified asymptomatically or at an early onset of the disease, more effective treatment for individuals who are true screen positive, reassurance of women and their families, informed decisions about continuation or end a pregnancy and justifiable allocation of NHS resources to implement the programme. Harms of screening are also diverse and encompass incorrect results and associated anxiety or false reassurance, difficult decisions about continuing or ending a pregnancy, risks associated with treatment or the screening test and over-treatment (people identify with a condition that would never develop into a serious condition over the life course). If harms of screening are not quantified correctly, screening agencies risk that many people could be harmed instead of benefiting from screening.

How these benefits and harms are included in health economic assessments is currently not known and VALENTIA aims to clarify this. In the previous section, we introduce the QALY as an outcome measure widely used in economic evaluation to evaluate the health benefits of screening. We hypothesise in this study that QALYs are a good outcome measure to capture functional and psychological impacts of screening test results for women and their babies in newborn screening, but that present challenges in antenatal screening test results leading ending a pregnancy. Moreover, we also hypothesise that a particular screening result may be seen as a benefit for a group of women and seen as a harm for another group. Whether researchers have attempted to estimate QALYs capturing all these complexities is currently not known.

Organisation of the VALENTIA study

To achieve the objectives set out in *Objectives*, VALENTIA was organised into four linked work packages (WPs) as described in *Figure 1*.

In the first WP1, a systematic review of the published and grey literature identified all health economic assessments evaluating antenatal and newborn screening programmes in Organisation for Economic Co-operation and Development (OECD) countries. Information relevant to the screening programmes, complemented by the reporting items contained within the Consolidated Health Economic Evaluation Reporting Standards (CHEERS), was extracted. This exercise provided a complete picture of the cost-effectiveness evidence assessing antenatal and newborn screening programmes in terms of the clinical areas and the reporting quality of the articles and reports. *Chapter 3* describes the methodology of the systematic review with associated results and interpretation. Detailed information about the types of benefits and harms included in each of the studies was also extracted. Using an integrative

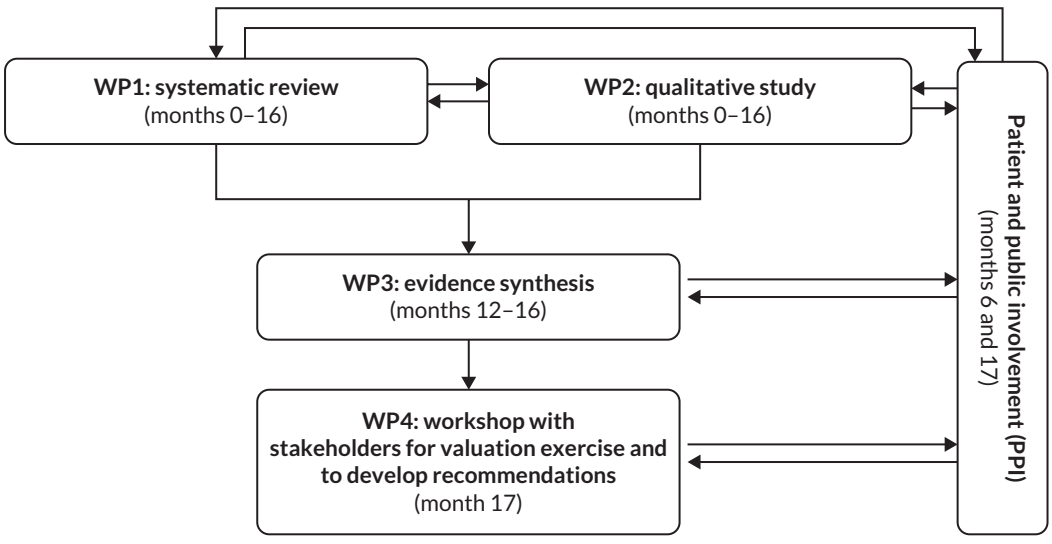

FIGURE 1 Flow diagram of the four linked WPs of the VALENTIA study.

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descriptive analysis, we developed a thematic framework of benefits and harms used in health economic assessments in this area. We applied this thematic framework to the literature identified and discovered that economic evaluations assessing antenatal and newborn screening programmes have generally adopted a narrow range of benefits and harms or ignored important benefits and harms in their evaluations. Our work suggests that there is an immediate need to provide guidance for researchers conducting economic evaluations of antenatal and newborn screening. Our proposed thematic framework of benefits and harms can be used to guide the development of future health economic assessments evaluating antenatal and newborn screening programmes, to prevent exclusion of important potential harms. The development of this framework and its application is presented in *Chapter 4*.

Work package 2 was a qualitative study conducted using multiple methods to capture stakeholders' views about the benefits and harms of antenatal and newborn screening that should be incorporated into future economic assessments. The qualitative component of VALENTIA is presented in three separate chapters in this report. Experiences of antenatal screening have been extensively investigated, but newborn screening experiences remained underexplored. Therefore, a meta-ethnography was conducted to better understand what was known about the experiences of newborn bloodspot screening (see *Chapter 5*). This was followed by secondary analysis of existing individual interviews related to antenatal screening, newborn screening and living with screened-for conditions (see *Chapter 6*). In this exercise, the goal was to bring together, examine and interpret the findings from disparate qualitative research studies and produce a richer and broader understanding than would be possible by looking at the studies individually. A large body of existing interview data was drawn upon to reflect a range of screening experiences and to better understand how individuals affected by screening discussed their experiences. What emerged was a complex web of individuals, organisations, technologies and discourses that shape the screening landscape. In *Chapter 7*, a thematic analysis of primary data collected with stakeholders about their experiences with antenatal and newborn screening was carried out. This analysis was conducted with three groups of stakeholders (individuals, charities, professionals working in the field of policy and healthcare professionals) to understand how these groups conceptualised the benefits and harms of screening. This primary data collection further developed the concepts derived from our meta-ethnography and secondary analysis, which developed an understanding of the landscape in which benefits and harms might be conceptualised. By using a range of qualitative methods, the benefits and harms of screening as experienced and perceived by a variety of stakeholders were identified, as well as concepts which did not map neatly onto the harms and benefits identified within existing economic assessments from WP1. The methods and results for each of these pieces of work in individual chapters are presented before summarising critical findings from across components of the qualitative study at the end of *Chapter 7*.

Work package 3 compared the benefits and harms identified in the quantitative health economics literature (WP1) and the qualitative literature (WP2) using a narrative synthesis exercise. The aim was to understand whether benefits and harms relevant to stakeholders were missing in the health economic assessment conducted in antenatal and newborn screening. In general, we observed good overlap between both types of data, but some gaps were also found. We present this in *Chapter 8* and provide a discussion about potential alternatives to incorporate some of the missing benefits and harms in future work.

The final WP4 involved meeting with key stakeholders to discuss potential valuation techniques to value antenatal and newborn screening scenarios following the results from previous WPs and a final meeting to present the results of the study and our recommendations for future work. Although originally planned as face-to-face meetings over 2–3 days with different stakeholders' groups, this was not possible due to pandemic restrictions at the time of the study. Given this change in format and the challenges of keeping audiences engaged in online settings, we instead conducted two online workshops with participants from our patient and public involvement group where we discussed potential

alternative valuation techniques, and a large virtual workshop with the remaining stakeholders to discuss our final results and recommendations. Full details are presented in *Chapter 9*.

A final set of recommendations for the conduct of economic evaluations assessing antenatal and newborn screening programmes arising from the study is presented in *Chapter 10*.

An important aspect of the VALENTIA study was our approach to parent and public involvement (PPI). From the design of the study through to delivery, we placed PPI at the centre of our programme of work. Our strategy involved working with our PPI co-investigator to create a group of PPI members at the beginning of the study with different antenatal and newborn screening experiences to support the work carried out in the WPs. We explain this strategy and the areas where we have benefited from input from our PPI members in the next chapter (see *Chapter 2*).

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Chapter 2 Parent and public involvement

Background

The inclusion of the public and patient voice is now widely regarded as an important element of research, ensuring that research is both relevant to the people affected by it and written in a way that is easily understood by the general public.[32] For VALENTIA, it was clear from the conceptualisation of the study that PPI would be fundamental to the identification and interpretation of benefits and harms of screening, since this calls for first-hand experience of antenatal and newborn screening.

There were several key considerations which steered the development of the PPI strategy for the study. Firstly, the many kinds of experiences that a woman and/or her partner may have during their interactions with a screening programme would need to be reviewed to determine how to put together a representative group for the PPI. Secondly, an engagement strategy would be needed since the PPI members would be engaged over a considerable period of time (24 months) and across several of the WPs. Finally, it was crucial that the PPI members were treated sensitively and respectfully, given the potential for traumatic experiences related to screening outcomes. There was particular concern to ensure the emotional well-being of all PPI members, avoiding harm through interactions with other PPI members who may hold different views or have had very different screening experiences.

This chapter describes the development of the PPI strategy, the 'recruitment' and characteristics of the group, and reflects on the successes and challenges of the PPI element of the study. Where our PPI members provided input into the specific workstreams, this is expanded in the PPI sections in the relevant chapters. We have reported the methodology and results according to the GRIPP2 guidelines.[33] The GRIPP2 short form table (*Table 1*) identifies the area(s) in the report where each reporting element can be found.

Objective

The aim of our PPI was to create a representative group of members of the public with direct experience of the antenatal and newborn screening programmes in the UK. The group was established to help clarify and interpret the study results, the sampling and data collection methods, analysis and synthesis of the results and conclusions of the study. The PPI group was an integral part of the research process, being involved at several stages for input and guidance, and receiving regular study updates.

TABLE 1 GRIPP2 short form

Section and topic	Item	Reported on
1: Aim	Report the aim of PPI in the study	*Chapter 2*
2: Methods	Provide a clear description of the methods used for PPI in the study	*Chapter 2*
3: Study results	Outcomes – report the results of PPI in the study, including both positive and negative outcomes	*Chapters 2*, *6*, *7*, *9*
4: Discussion and conclusions	Outcomes – comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	*Chapters 6*, *7*, *9*
5: Reflections/critical perspective	Comment critically on PPI input in the study, reflecting on the things that went well and those that did not, so others can learn from this experience	*Chapter 2*

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Methods

In a first step, in collaboration with our PPI co-investigator (JF), the research team mapped out the broad categories of possible antenatal and newborn screening experiences, resulting in 14 different 'groups' of experience (*Figure 2*).

These groups were shaped and refined according to several factors: whether parents consented or not to the screening, whether the results of the screening tests were positive or negative and whether a condition was diagnosed or not ('true-' or 'false-' positive or -negative results). Depending on which categories parents' experiences fall into, their perceptions of the benefits and harms of screening vary. As a result, it was decided that representation across as many of the groups as possible in *Figure 2* was needed. We aimed to recruit several members from each category, with the goal of including a minimum number of two members from each experience group, representing 28 potential PPI members. We were also cognisant to include seldom-heard voices within the screening process, including fathers, people with disabilities and those from ethnic minority groups.[34–36] Engaging such a large and diverse group would be a significant undertaking, so early in the study a PPI Coordinator (JSO) joined the study team.

The creation of the PPI group coincided with the start of the global pandemic and affected the PPI element in two ways. Firstly, resources: access to recruitment avenues, and then the available time and energy that potential PPI members had for a study such as this were drastically reduced. Charities with whom we engaged were under resourced and many were not able to support reaching out to their communities in a way we had hoped. Potential PPI members were likely to be parents of young children, some with additional support needs, with dual working from home and child-care responsibilities, which significantly impacted the likelihood of being able to participate. Secondly, restrictions in the UK meant that the planned face-to-face interactions had to take place online, which caused concern over the development of rapport and group cohesion. However, we found that regular communication by e-mail and holding discussions online still provided the depth of response and input we had hoped for.

To begin engaging possible PPI members, we contacted relevant organisations as well as contacts linked to pregnancy, parenting, screened-for conditions and parental support following the diagnosis of a condition, drawing on the networks of our co-investigators. The National Perinatal Epidemiology

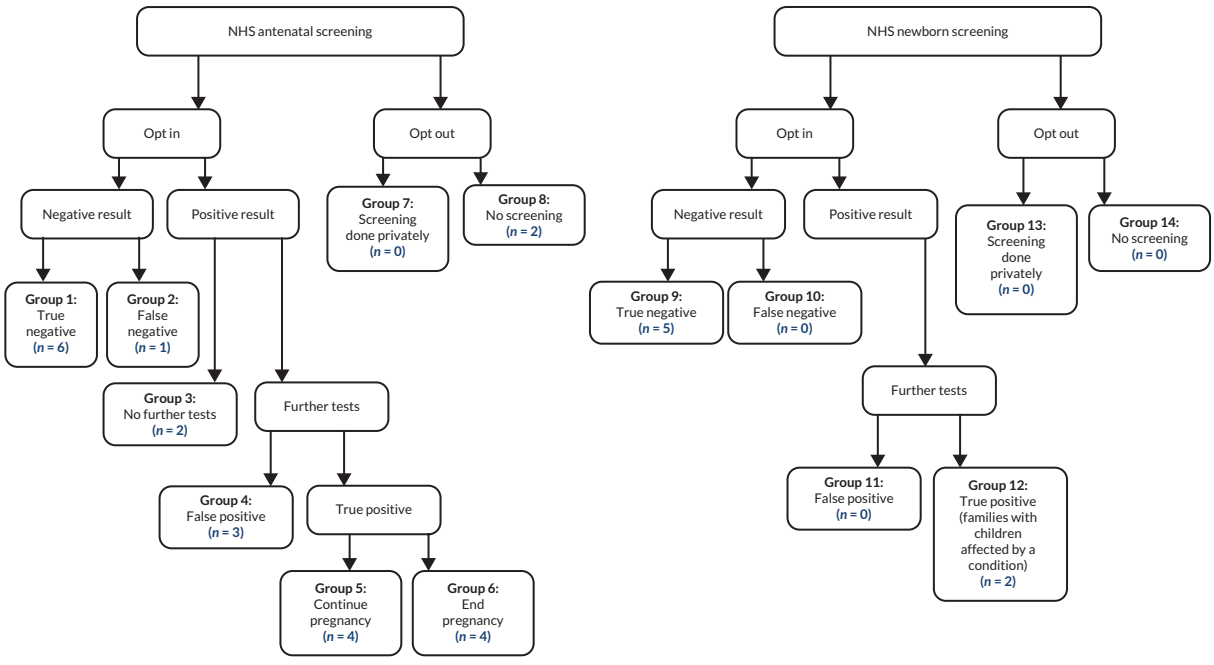

FIGURE 2 Flow chart of the categories of experience of newborn and antenatal screening.

Unit (NPEU), where several of the research team were based, has long-standing relationships with such organisations. Twenty-eight organisations were identified through these sources and contacted, including several that support parents in socially deprived areas such as Maternity Mates (based in Tower Hamlets). Eleven of the organisations responded to the team's request to advertise the opportunity to their members. Alongside this, VALENTIA co-investigator JF, who is Director of Antenatal Results and Choices (ARC), a charity that supports parents following the diagnosis of a genetic or physical condition, shared the project with service users, and co-investigator FB identified parents and people with disabilities who had been involved in earlier research relating to screening and who had consented to participate in future research.

These 'trusted intermediaries' enabled the team to undertake wide-reaching advertising, which, along with other avenues such as social media posts and snowballing, resulted in 30 PPI members across 9 of the experience groups in *Figure 2* volunteering to participate as PPI members. Groups 7, 10, 12, 14 and 15 including those who opted out of NHS screening and either undertook private screening or no screening at all proved more difficult to engage with. Several clinics and privately practising clinicians were contacted for support with reaching those parents who opted for private screening but declined to engage with the study. It was expected that parents opting out of screening would be a harder population to reach,[37] given that only a very small number of parents do not have tests. In 2018–9, the NHS reported that 99.1% of eligible parents in England had a fetal anomaly screening test result documented. Of the nine groups that were represented most had between two and four representatives, but it should also be acknowledged that, while parents were 'assigned' to a group based on their most recent or prominent experience, many parents had multiple experiences of screening over one or more pregnancies, and therefore members provided a broad and rich depth of perspectives.

To maintain engagement and reflect the value they added to the study, we ensured that all our PPI members were remunerated at a rate consistent with National Institute for Health and Care Research (NIHR) Centre for Engagement and Dissemination guidelines. We maintained regular e-mail communication throughout the project, providing updates on progress and signposting when further input may be needed. We also produced training videos to explain the roles of PPI in research, an overview of the study and an overview of qualitative research. There was concern that not being able to hold face-to-face PPI focus groups would be detrimental to the members' engagement with the project. Careful thought was given to how to recreate the level of interaction and rapport gained through face-to-face discussions using online communication tools. We chose the platform 'SLACK' which allowed PPI members to have own anonymised communication though an individual 'channel' where a researcher could ask their input, share resources such as training videos or written material, and to respond to questions and discussion points that were posted by the research team either in their own time or over a specified window. This feature was crucial for the accessibility of the PPI strategy, given the competing demands on members' time, and our desire not to exclude those with limited availability, for example, due to caring responsibilities. In some ways, it was an advantage over face-to-face discussion groups. Towards the end of the study, we also facilitated two smaller online focus group discussions using Zoom conference facilities, which enabled the researchers and PPI members to interact in real time and enabled more free-flowing discussions (see *Chapter 9*).

Demographics

It took a significant amount of time and resources, from April to September 2020, to reach sufficient numbers of representatives for the group. Thirty members, representing 10 of the 14 experience groups, ultimately consented to take part; however, 1 member withdrew prior to the first interaction session due to personal reasons, resulting in a final group of 29 members. Their characteristics are shown in *Table 2*.

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TABLE 2 Characteristics of PPI members

Woman, ***n*** (%)	27 (93.1)
Mean age, years	34.8
Range of age, years	23–41
Disability, *n* (%)	
No	27 (93.1)
Yes	1 (3.4)
Prefer not to say	1 (3.4)
Religious beliefs, *n* (%)	
Christian	7 (24.1)
Hindu	1 (3.4)
None	20 (69.0)
Other/prefer not to say	1 (3.4)
Nationality, *n* (%)	
British	22 (75.9)
Scottish	1 (3.4)
British and American	1 (3.4)
Other/prefer not to say	5 (17.2)
Ethnicity, *n* (%)	
White	20 (69.0)
Other white background	4 (13.8)
Black	1 (3.4)
Asian/British Asian	2 (6.9)
Mixed/multiple ethnic background	2 (6.9)
Employment status, *n* (%)	
Full-time	8 (27.6)
Part-time	10 (34.5)
Self-employed	4 (13.8)
Furloughed	1 (3.4)
Unemployed/working with your family/caring	5 (17.2)
Other/prefer not to say	1 (3.4)

Despite the unprecedented burdens of child care on this group, we managed to build up the PPI group over several months. The PPI group was demographically diverse, although we acknowledge not nationally representative. The group characteristics included a range of age and socioeconomic status, but it was not as diverse as we had hoped for in terms of ethnicity, religion or disability. Efforts were made to engage with people from minority ethnic backgrounds, such as engaging with 'Maternity Mates', sharing widely through charities and social media and using wording which encouraged men and lesser heard voices to participate. With the limited resources available and the pressures on this particular

population, it was not possible to achieve representativeness in the group. Perhaps if the timing of the study had been different, it might have been easier to obtain a more representative PPI group, and this is acknowledged as a significant challenge and limitation.

Results

The PPI members provided input at several points over the duration of the project, feeding significantly into WP2 and WP4. They reviewed the sampling strategy of the qualitative WP, and identified additional participant groups to include. They also provided feedback on the wording and screening scenarios that would be used as tools to prompt discussions during focus groups and interviews with participants in the qualitative research, and supported the recruitment of participants to the qualitative WP.

We tracked how many PPI members took part in the interactions over the duration of the study to give us a sense of engagement levels with the study. Ninety-seven per cent (28/29) of PPI members responded to the first task and 76% (22/29) to the second task a few weeks later. By the end of the study, around 15 months after the first task, 41% (12/29) of PPI members were still actively involved with the study and responding to communications. Thirty-five per cent (10/29) participated in the last online focus groups. They represented the following categories: one in group 3 (positive antenatal screening and no further tests); two in group 4 (false-positive antenatal screening); one in group 5 (positive antenatal screening and continue pregnancy); three in group 6 (positive antenatal screening and pregnancy termination); two in group 9 (true-negative newborn screening); and one in group 13 (true-positive newborn screening), representing six of the experience groups. Given the global pandemic, the duration of the study and the fact that PPI members had caring responsibilities, the rate of attrition was unsurprising. However, the focus groups did benefit from the breadth of experiences represented by the PPI members.

Discussion and reflections

Despite the limitation of the representativeness of the PPI group, the study benefitted significantly from its input based on their experiences of screening over the perinatal period. Their input included advising on appropriate language for research participants; reviewing and adding to the list of stakeholders; supporting recruitment of participants into the primary research; and ultimately advising on the appropriateness of employing different health economic methods to value antenatal and newborn screening scenarios. Their input shaped the success of the study by not only enhancing the engagement the research team had with the study participants, but also advising on the feasibility of the recommendations to move forward. Specific examples of PPI input that were taken forward and led to an amendment in the methodology or improvement in interpretation are expanded upon in *Chapters 6*, *7* and *9*.

Having a PPI co-ordinator to manage the group proved crucial due to the numbers involved, the extraordinary circumstances of the pandemic and the length of time members needed to be involved. Some aspects of the engagement strategy were labour-intensive, for example, recruitment, creating the online platform; producing information videos to explain the role of PPI in research and another to explain qualitative research; and producing study progress communications. Another aspect was the involvement of JF as a co-investigator, who was able to provide contacts, champion the involvement of the PPI at the regular project meetings and advice on ways that their input could be helpful. PPI engagement was well-maintained for a significant duration, and the quality of the input was high, with the members providing very insightful and thoughtful input throughout, shaping the progress and recommendations of the study.

Our final interaction with the PPI members involved two smaller online group discussions with the health economics researchers (see *Chapter 9*). The research team gained very useful input on some of

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the proposed recommendations of methods for valuing benefits and harms of antenatal and newborn screening. The PPI group and the research team did not get to meet other than these final interactions, due to COVID-19 restrictions. Our experience demonstrates that engaging a large PPI group such as this is possible, that it greatly improves the quality of the research. It also demonstrates that group cohesion does not necessarily rely on face-to-face interactions. However, it does require significant resource commitment, thought and effort on behalf of both the research team and PPI group members.

Chapter 3 Work package 1: systematic review of health economic assessments evaluating antenatal and newborn screening

Sections of this chapter have been previously reported in Png *et al*. (2021).[38]

Introduction

In this chapter, we report our systematic review of health economic assessments evaluating antenatal and newborn screening programmes in developed countries. The systematic review had two distinct purposes. The first was to identify all available evidence in the published and grey literature over the last two decades and understand its main characteristics, the clinical areas and conditions covered and the reporting quality of the contributing studies. The second objective was to extract detailed information about the benefits and harms incorporated into these health economic assessments. This chapter covers the first aim and reports a comprehensive overview, whereas the second aim is presented in *Chapter 4*.

Methods

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist[39] when reporting the methods and results of the systematic review. The review protocol has been registered with PROSPERO (CRD42020165236) and published on 13 January 2020. This review is based on data available from secondary sources and published materials with no primary data collection required, so ethics committee approval or written informed consent was not required.

Eligibility criteria

The Population, Intervention, Comparator, Outcome and Study design (PICOS) framework was used to develop the study eligibility criteria (*Table 3*) and applied to the literature searches. Searches were limited to studies published after 1 January 2000. Studies reporting health economic assessments, such as economic evaluations and studies that use economic frameworks of cost-effectiveness evidence or economic notions of value (e.g. multi-criteria decision analyses, programme budgeting and marginal analyses) of antenatal or newborn screening programmes, were included. Non-English language studies were included, but studies were limited to those conducted in developed countries (defined, for the purposes of this review, as a member of the OECD[40]).

Information sources

Systematic searches of both published and grey literature, including peer-reviewed journal articles controlled by commercial publishers and documents produced by all levels of government, academia, business and industry, were conducted. The following electronic bibliographic databases were searched: MEDLINE (OvidSP) (1946–present), EMBASE (OvidSP) (1974–present), NHS Economic Evaluation Database (via CRDWeb www.crd.york.ac.uk/CRDWeb/) (inception to 31 March 2015), EconLit (Proquest) (1969–present), Science Citation Index, Social Science Citation Index and Conference Proceedings Citation Index – Science (Web of Science Core Collection) (1945–present), CINAHL (EBSCO*host*) (1982–present) and PsycINFO (OvidSP) (1806–present). SCOPUS (Elsevier) was used to run forward and backward citation searches once relevant studies were identified. The academic electronic database searches were supplemented by manual reference searching of bibliographies from studies that were included, contacts with experts in the field and author searching based on experts' opinion. The first full search of published literature was conducted on 24 April 2020 with a top-up

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TABLE 3 Inclusion and exclusion criteria for identification of relevant studies

Characteristics	Inclusion criteria	Exclusion criteria
Population	Pregnant women Newborns	Anyone other than pregnant women or newborns Studies on animals Not conducted in an OECD member country[a]
Intervention	Antenatal or newborn screening programme[b]	Pre-conception screening No screening programme
Comparator	No screening or specific form(s) of screening other than experimental intervention(s), as defined by specific conditions	
Outcome	Benefits and harms of antenatal or newborn screening that have been identified, measured and valued by economic assessments	
Study design	Economic evaluation design: • Cost-effectiveness analysis • Cost–utility analysis • Cost–benefit analysis • Cost–consequences analysis • Cost-minimisation analysis Economic framework that incorporates cost-effectiveness evidence or economic notion of value (e.g. multi-criteria decision analysis, programme budgeting and marginal analysis)	Descriptive cost analysis Budget impact analysis Not an economic evaluation Other report types: • Editorial • Letter • Methodological research without applied evidence • Perspective, opinion or commentary • Protocol • Review

a Studies from countries that become OECD members after the title/abstract screening process was completed were not included in our review (last OECD member included was Colombia).[40]
b This included actual and proposed, for example hypothetical screening programmes as well as any aspect of a screening programme (defined as a whole system of activities needed to deliver high-quality screening), for example, the performance of screening test.

search conducted on 2 July 2020 to include the 'perinatal' search term while a refresh search was conducted on 22 January 2021.

The list of grey literature searched was derived from a pool of relevant websites that was informed by a recent systematic review of national policy recommendations on newborn screening that identified websites of national and regional screening organisations with documentation about antenatal and/or newborn screening recommendations.[41] This was widened to cover websites reported by the Health Grey Matters checklist and those for national and regional screening organisations, HTA agencies, paediatrics organisations, and obstetrics and gynaecology societies in OECD countries, as well as international decision-making bodies, such as the World Health Organization, the European Council, European Commission and the European Observer.[41,42] A customised web scraping tool that used the Google search engine was built using Python to directly query the stated websites (see *Appendix 1*) from 18 to 27 January 2021 using English search terms and from 14 to 17 February 2021 using translated search terms for non-English websites, as well as to automate the data extraction processes.

Search strategy

The search strategies applied to the published literature (see *Appendix 2*, *Tables 21–26*) were developed using a combination of medical subject headings (MeSH) and free-text keywords related to health economic assessments of antenatal and newborn screening programmes in collaboration with an information specialist (NR) with expertise in conducting systematic literature reviews in the health sciences. A simplified search strategy derived based on the Cochrane guidelines was applied to the grey

literature search.[43] Translation of the simplified search terms for non-English websites was performed by professional translators.

Data management

The results of the literature searches were uploaded into the Endnote software package X9 (Clarivate, Philadelphia, PA, USA, 2019), a reference management system specifically designed for managing bibliographies and citations, to remove duplicates. Unique records were subsequently imported into Covidence,[44] an online software program that facilitates collaboration among reviewers during the screening and data extraction stages. This software allows importation of references and files to be screened and information can be entered into a pre-created data extraction form after removing duplicates. Screening criteria based on the inclusion and exclusion criteria specified in *Table 3* were developed and tested. A calibration exercise was undertaken to pilot and refine the screening criteria before the formal screening process started. For non-English language papers, Google Translate (Google, Mountain View, CA, USA) was used to translate relevant documents.

Selection process

For the published literature, two reviewers (MEP and MY) independently screened the titles and abstracts of all retrieved articles and documented the reasons for study exclusion according to the criteria specified in *Table 3*. Full texts of potentially relevant articles were reviewed independently by the same reviewers (MEP and MY), and study eligibility based on the inclusion and exclusion criteria was assessed. At each stage of the selection process, any disagreement was resolved by discussion and consensus between the two reviewers. When consensus could not be reached, input from the rest of the review team (ORA and SP) was obtained. For the grey literature, only one reviewer (MEP) did the title/abstract and full-text screening of all the retrieved articles, while another reviewer (SR) screened the titles/abstracts of a random sample of at least 10% (13%) of the retrieved articles due to a change and shortage in work force and limited time.

Data collection process

A data extraction form, which was piloted and refined using 10 randomly selected studies identified in the academic electronic databases, was created using Microsoft Excel following recommendations from the Cochrane Handbook for Systematic Reviews of Interventions.[43] As we had anticipated a large number of articles to data extract, after consulting our Independent Oversight Committee members and Information Specialist (NR), a selection of 10% of the articles/reports was extracted independently by two health economists (MEP and MY), followed by a reconciliation process. During this reconciliation process, MEP and MY had to extract the same key information from a random set of conference abstracts, journal articles and reports before they proceeded to extract the other studies independently and this was observed after assessing around 10% of the papers/reports. The rest of the published literature was subsequently divided between the two reviewers (MEP and MY), while data from the grey literature were extracted by one reviewer (MEP) only. Furthermore, any uncertainties related to data extracted by the two independent reviewers (MEP and MY) was discussed with the two senior investigators (ORA and SP) at weekly meetings. The list of variables extracted from each report included at the final stage of the review process was finalised following the piloting and refinement of the data extraction sheet.

The data extraction form consisted of two parts: (1) a section that contained items from the CHEERS checklist,[45] modified where applicable to align with our research focus (i.e. benefits and harms within economic assessments) (see *Appendix 3*). This included bibliographic details; condition(s) screened; approaches for measuring and valuing health outcome measures; the journal impact factor quartile during the year that the article was published, obtained from Clarivate Analytics and SCImago; whether the authors made any policy recommendation based on their economic evaluation evidence; and whether the authors might have had any potential conflicts of interest in promoting their screening programme or mechanism (defined as a study that was funded by an industry sponsor, unless it was an unrestricted grant, and at least one of the authors being clearly employed by the industry sponsor);

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and (2) a bespoke form (see *Appendix 4*) created by the research team to extract benefits and harms adopted by economic assessments evaluating antenatal or newborn screening programmes. This form was created de novo as we could not find any previous examples in the published literature. A detailed description of the process to create the bespoke form is described in *Chapter 4*. This bespoke form contained consequences as reported by authors by screening test outcome (i.e. true positives, false positives, true negatives and false negatives) and type of data (i.e. probability, cost or outcome), which were captured and categorised as either a benefit or a harm. We also recorded the stage of the disease pathway at which the screening test was administered and the phase(s) of the screening programme using categorisations from recent guidance,[1] as well as recorded whether the structure of decision-analytical models had been reported, and the consequences associated with treatment where applicable.

Data items

In order to reduce bias from including data from multiple reports of the same study, multiple articles published by the same authors with similar titles and abstracts were treated as linked companion studies (i.e. multiple reports from a single study) and only the most detailed publication was included in our final outputs. Similarly, if conference abstract(s) and a journal article by a similar group of authors had been published on the same topic, only the journal article was included at the full-text screening stage. Since we were interested in the methodological approaches to the measurement and valuation of benefits and harms and how the results were reported, if the article/report title suggested that an economic evaluation was conducted but neither the methods nor the results were presented in the abstract or full text, the article/report was excluded at the screening stage(s). Articles/reports that did not focus specifically on pregnant women or newborns but reported separate results of screening of pregnant women or newborns within broader populations were still included. In addition, authors were not contacted for missing data on individual data items included in our data extraction sheet, which were instead recorded as 'not stated'.

Assessment of reporting quality of individual studies

Since only aggregated data and no effect sizes were sought, we did not assess the risk of bias or conduct a formal meta-analysis. Instead, the reporting quality of articles and reports (excluding conference abstracts) was assessed using the CHEERS reporting statement.[45] The items were considered as 'satisfied' if reported in full or 'not satisfied' if not reported or partially reported. The items were not scored as per the guidance in the CHEERS reporting statement.[45]

Deviations from protocol

There were a few of deviations from the protocol. First, we used Endnote and Covidence for different components of the systematic review. Endnote was used to record all the studies identified as part of our searches and employed to identify and remove duplicates. Covidence was used as it can better facilitate collaboration among reviewers during the screening and data extraction stages than Endnote. Second, we did not use any risk of bias tools such as Cochrane ROBEQ tool and Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) for different study designs because the aim of the systematic review was to understand the benefits and harms of antenatal and newborn screening and not to extract any quantitative information from the papers. Therefore, we excluded any reference to risk of bias assessment from the final published protocol for the systematic review. For the same reason, we did not explore further the external validity of any of the cost-effectiveness results published in the studies. We have used the CHEERS statement to evaluate the reporting quality of the studies since understanding the reporting quality of these studies was a primary aim of our systematic review as it was good indicator of whether a particular study was going to provide all the information in our bespoke form. Last, data extraction was not conducted independently by the two reviewers and a 10% sample was used because the former was not feasible as we ended up including 336 articles and reports and it was decided given our timelines to change the strategy for the data extraction. All deviations were discussed and approved by our Independent Oversight Committee.

Results

Search results

We identified 52,244 articles and reports from the searches of the published and grey literature. Among the 16,052 records that were sought for retrieval based on identification of records via other methods (i.e. grey literature), 7464 records were non-English (46.5%). Thirty-nine studies of the non-English records were assessed for eligibility with five subsequently included in the data extraction phase. A total of 336 records, 310 articles (1.4% of databases) and 26 reports (0.08% of websites), were included in the systematic review. One HTA report included two separate economic evaluations that were separated into two different reports, resulting in 337 outputs. Study selection and reasons for exclusion as well as data extraction of the bespoke form are summarised in the modified PRISMA diagram (*Figure 3*). The list of studies excluded is summarised in *Report Supplementary Material 1*.

There was no trend in the publication year of the articles and reports (*Figure 4*). Characteristics of the included articles and reports are presented in *Table 4*. The majority of the articles and reports included were journal articles (228, 67.7%) and almost half of the studies were conducted in the USA (109, 32.2%) and the UK (43, 12.7%). The majority of the articles and reports also required further information to determine if the authors had potential conflicts of interests (221, 65.6%). Furthermore, the authors did not make any recommendation about the adoption of the screening programme based on the

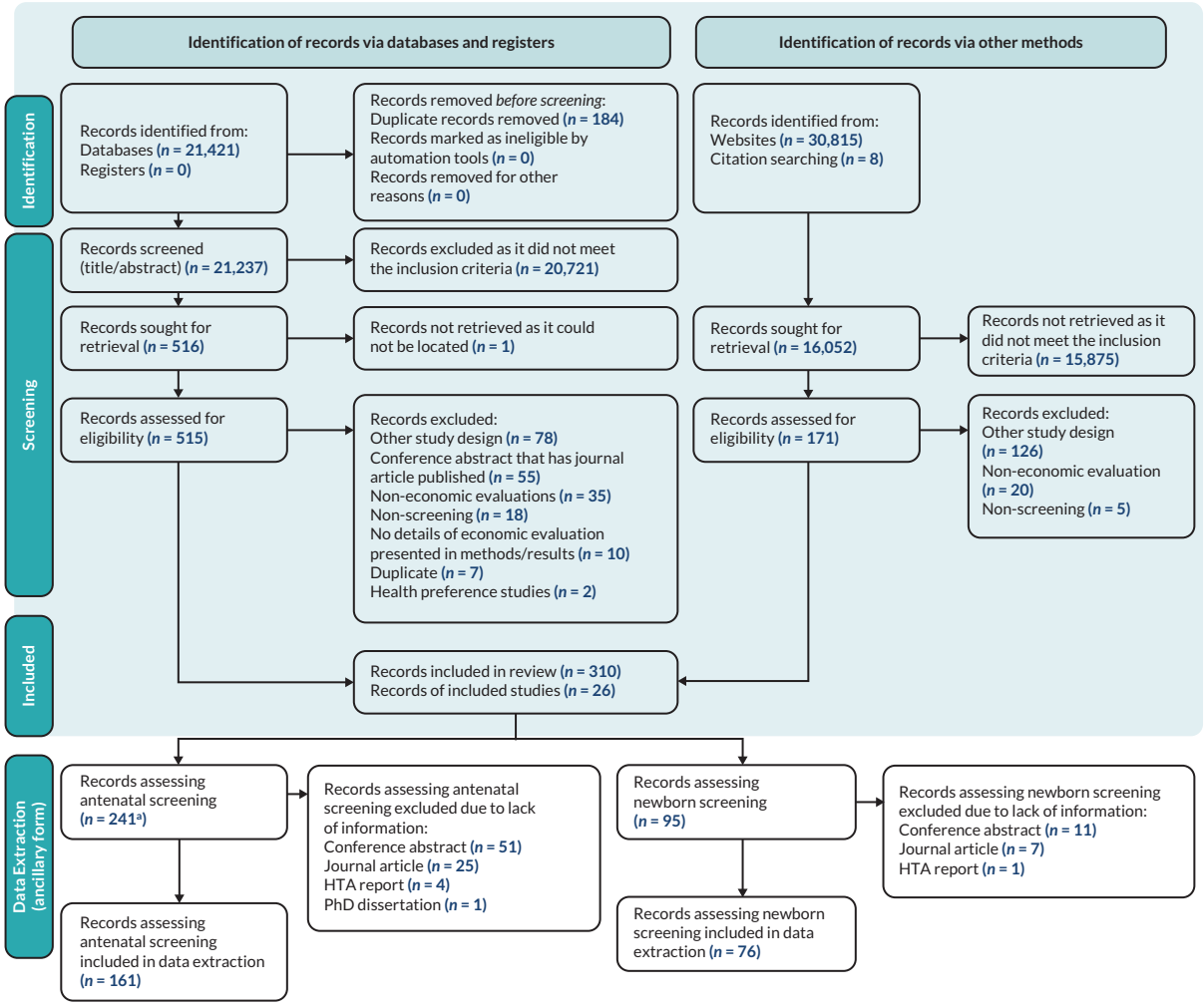

FIGURE 3 Modified PRISMA flow diagram. a, One HTA report included two separate economic evaluations that were separated into two different reports, resulting in 242 outputs from the 241 records.

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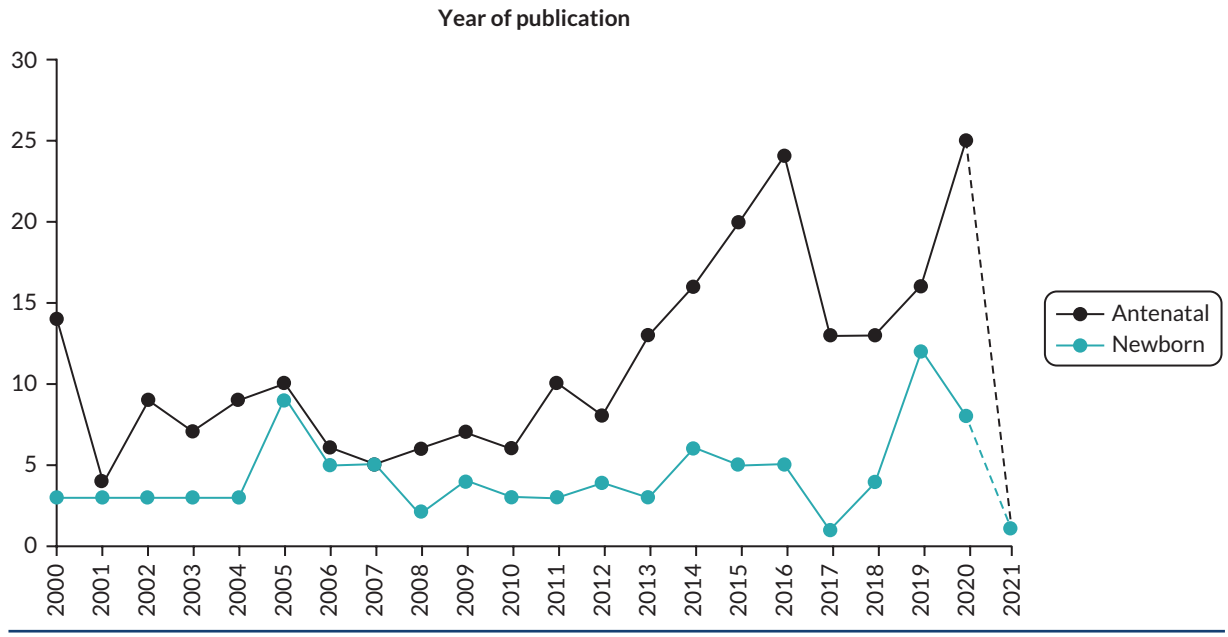

FIGURE 4 Number of articles and reports published from 2000 to January 2021. Note: Dotted lines were used to indicate that only January 2021 was included in this chart.

TABLE 4 Characteristics of articles and reports

	Articles and reports assessing antenatal screening (%) (*n* = 242)	Articles and reports assessing newborn screening (%) (*n* = 95)	Articles and reports assessing either screening type (%) (*n* = 337)
Publication type			
Journal article	156 (64.5)	72 (75.8)	228 (67.7)
Conference abstract	61 (25.2)	12 (12.6)	73 (21.7)
HTA report	24 (9.9)	11 (11.6)	35 (10.4)
PhD dissertation	1 (0.4)	0 (0)	1 (0.3)
Country of screening programme[a]			
USA	82 (33.7)	27 (28.4)	109 (32.2)
UK	32 (13.2)	11 (11.6)	43 (12.7)
Canada	17 (7)	15 (15.8)	32 (9.5)
The Netherlands	12 (4.9)	9 (9.5)	21 (6.2)
France	8 (3.3)	4 (4.2)	12 (3.6)
Australia	9 (3.7)	3 (3.2)	12 (3.6)
Spain	6 (2.5)	4 (4.2)	10 (3.0)
Colombia	3 (1.2)	3 (3.2)	6 (1.8)
Austria	3 (1.2)	1 (1.1)	4 (1.2)
Israel	4 (1.6)	0 (0)	4 (1.2)
Italy	3 (1.2)	1 (1.1)	4 (1.2)
Germany	1 (0.4)	2 (2.1)	3 (0.9)
Belgium	1 (0.4)	2 (2.1)	3 (0.9)
Finland	1 (0.4)	1 (1.1)	2 (0.6)

TABLE 4 Characteristics of articles and reports (*continued*)

	Articles and reports assessing antenatal screening (%) (*n* = 242)	Articles and reports assessing newborn screening (%) (*n* = 95)	Articles and reports assessing either screening type (%) (*n* = 337)
Sweden	1 (0.4)	3 (3.2)	4 (1.2)
Chile	1 (0.4)	0 (0)	1 (0.3)
Czech Republic	1 (0.4)	0 (0)	1 (0.3)
Denmark	1 (0.4)	0 (0)	1 (0.3)
Ireland	2 (0.8)	0 (0)	2 (0.6)
Japan	0 (0)	1 (1.1)	1 (0.3)
New Zealand	1 (0.4)	1 (1.1)	2 (0.6)
Norway	2 (0.8)	0 (0)	2 (0.6)
Switzerland	1 (0.4)	0 (0)	1 (0.3)
Not stated	51 (21)	7 (7.4)	58 (17.2)
Potential conflicts of interest			
No	70 (28.9)	38 (40)	108 (32.0)
Yes	7 (2.9)	1 (1.1)	8 (2.4)
More information needed to classify	165 (68.2)	56 (58.9)	221 (65.6)
Policy recommendation			
No	194 (80.2)	79 (83.2)	273 (81.0)
Yes	48 (19.8)	16 (16.8)	64 (19.0)
Journal impact factor quartile (articles only)			
First quartile of medical journals	36 (10.7)	93 (27.6)	129 (38.3)
Second quartile of medical journals	17 (5)	26 (7.7)	43 (12.8)
Third quartile of medical journals	11 (3.3)	27 (8)	38 (11.3)
Fourth quartile of medical journals	3 (0.9)	7 (2.1)	10 (3)
Not available	5 (1.5)	3 (0.9)	8 (2.4)

a Does not add up to the total *n* or 100% as some articles and reports included more than one country. HTA (refers to reports generated by screening and HTA organisations).

economic evidence generated for the majority of the articles and reports (273, 81.0%). The majority of the articles were published in top quartile medical journals (i.e. quartile one; 129, 38.3%).

Target population and setting

The characteristics of screening programmes and populations in the included articles and reports are summarised in *Table 5*. There were 173 (71.5%) studies on antenatal screening and 63 (66.3%) studies on newborn screening that did not state the setting of the screening (236, 70.0%) or the women's gestational stage at the time of screening (168, 65.4% of the antenatal screening studies). The majority of the studies were targeted at the general population of pregnant women (197, 57.1%) or infants (91, 26.4%). Many studies were investigations at the symptomless stage with pathologically definable change present (303, 89.9%) or involved all phases of the screening programmes (162, 48.1%).

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TABLE 5 Characteristics of screening programmes and population in the articles and reports

	Articles and reports assessing antenatal screening (%) (*n* = 242)	Articles and reports assessing newborn screening (%) (*n* = 95)	Articles and reports assessing either screening type (%) (*n* = 337)
Setting of screening[a]			
Home	0 (0)	3 (3.2)	3 (0.9)
Primary care	6 (2.5)	3 (3.2)	9 (2.7)
Secondary care	58 (24.0)	22 (23.2)	80 (23.7)
Primary and secondary care	5 (2.1)	4 (4.2)	9 (2.7)
Not stated	173 (71.5)	63 (66.3)	236 (70.0)
Population[a]			
Healthy pregnancy	196 (79.0)	1 (1.0)	197 (57.1)
Pregnant women and their partner/relative	8 (3.2)	0 (0)	8 (2.3)
Pregnancy at risk	37 (14.9)	1 (1.0)	38 (11.0)
Healthy infant	7 (2.8)	84 (86.6)	91 (26.4)
Infant at risk	0 (0)	11 (11.3)	11 (3.2)
Gestation stage of pregnant women			
First trimester	25 (9.7)	0 (0)	25 (7.2)
First or second trimester	3 (1.2)	0 (0)	3 (0.9)
First and second trimesters	6 (2.3)	0 (0)	6 (1.7)
First and third trimesters	1 (0.4)	0 (0)	1 (0.3)
Second trimester	25 (9.7)	0 (0)	25 (7.2)
Second and third trimesters	10 (3.9)	0 (0)	10 (2.9)
Third trimester	19 (7.4)	0 (0)	19 (5.5)
Not stated	168 (65.4)	2 (2.2)	170 (49.0)
Not applicable	0 (0)	88 (97.8)	88 (25.4)
Stage of disease pathway			
Person at risk but no pathological changes present	24 (9.9)	6 (6.3)	30 (8.9)
Symptomless stage with pathologically definable change present	217 (89.7)	86 (90.5)	303 (89.9)
Signs and/or symptoms exist but condition undiagnosed	1 (0.4)	2 (2.1)	3 (0.9)
Clinical phase	0 (0)	1 (1.1)	1 (0.3)
Phase(s) of screening programme			
Screening and diagnostic	60 (24.8)	16 (16.8)	76 (22.6)
Screening and intervention	59 (24.4)	10 (10.5)	69 (20.5)
Screening, diagnostic and intervention	103 (42.6)	59 (62.1)	162 (48.1)
Not clear	20 (8.3)	10 (10.5)	30 (8.9)

a Does not add up to the total *n* or 100% as some articles and reports presented more than one category.

Medical conditions investigated are summarised in *Table 6*. Genetic conditions and infectious diseases (153, 63.2%) were the main areas covered by the articles and reports assessing antenatal screening. Metabolic and structural conditions (57, 60.0%) were the main areas covered by health economic assessments evaluating newborn screening programmes.

The key methodological characteristics of the health economic assessments from the CHEERS checklist are summarised in *Table 7* and in the following subsections.

Choice and time horizon of model

The most common type of economic evaluation used was 'cost–utility analysis', which reports outcomes in terms of QALYS or disability-adjusted life-years (DALYs), for antenatal screening (129, 53.3%), and cost-effectiveness analysis for newborn screening (47, 50.0%). Decision-analytical models were employed in 272 (81.0%) of the articles and reports for the economic evaluations – 200 (82.6%) in antenatal screening and 72 (76.6%) in newborn screening. Among these studies, the majority either employed a lifetime horizon (82, 41.0% for antenatal screening and 37, 51.4% in newborn screening) or did not state the time horizon (75, 37.5% for antenatal screening and 14, 19.4% for newborn screening).

Cost perspective

The costing perspective adopted was not stated in 117 (33.7%) articles and reports. Among those that stated a costing perspective, the majority adopted a health system or payer perspective (107, 43.5% for antenatal screening and 53, 52.5% for newborn screening).

Main outcome measures used in the economic evaluations

The source to inform the main outcome measures in the economic evaluations came predominantly from evidence synthesis of secondary data for both antenatal (167, 77.3%) and newborn (62, 67.4%)

TABLE 6 Medical conditions investigated

Conditions	Articles and reports assessing antenatal screening (%)[a] (*n* = 242)	Articles and reports assessing newborn screening (%)[a] (*n* = 95)
Developmental	0 (0)	6 (6.3)
Endocrinology	24 (9.9)	4 (4.2)
Genetic	77 (31.8)	12 (12.6)
Gestational cardiorenal	5 (2.1)	0 (0)
Haematology	18 (7.4)	12 (12.6)
Infection	76 (31.4)	3 (3.2)
Intrauterine fetal demise/ sudden infant death syndrome	1 (0.4)	1 (1.1)
Maternal mental health	1 (0.4)	6 (6.3)
Metabolic	0 (0)	32 (33.7)
Neurodevelopment	1 (0.4)	3 (3.2)
Neurological	0 (0)	1 (1.1)
Nutrition	4 (1.7)	0 (0)
Structural	36 (14.9)	25 (26.3)
Urology	1 (0.4)	0 (0)

a The sum of the individual conditions is not equivalent to the total value across all conditions because there are five articles and reports that investigated more than one condition.

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TABLE 7 Health economic assessment characteristics of the articles and reports

	Articles and reports assessing antenatal screening (%) (*n* = 242)	Articles and reports assessing newborn screening (%) (*n* = 95)
Study design		
Individual patient-level data analysis	12 (5.0)	6 (6.4)
Cohort	10 (4.1)	5 (5.3)
Cross-sectional	0 (0)	1 (1.1)
Randomised controlled trial	2 (0.8)	0 (0)
Decision-analytical model	200 (82.6)	72 (76.6)
Decision tree	90 (37.2)	39 (41.5)
Decision tree and Markov model	9 (3.7)	6 (6.4)
Discrete event simulation model	1 (0.4)	1 (1.1)
Markov model	10 (4.1)	15 (16.0)
Model type not specified	83 (34.3)	8 (8.5)
Patient-level simulation model	7 (2.9)	3 (3.2)
Other	2 (0.8)	3 (3.2)
Not stated	28 (11.6)	13 (13.8)
Type of economic evaluation[a]		
Cost–benefit analysis	18 (7.4)	5 (5.3)
Cost–consequences analysis	6 (2.5)	3 (3.2)
Cost-effectiveness analysis	87 (36.0)	47 (50.0)
Cost-minimisation analysis	2 (0.8)	3 (3.2)
Cost–utility analysis	129 (53.3)	38 (40.4)
Perspective of costs[a]		
Health system or payer	107 (43.5)	53 (52.5)
Societal	44 (17.9)	25 (24.8)
Not applicable[b]	0 (0)	1 (1.0)
Not stated	95 (38.6)	22 (21.8)
Time horizon of decision-analytical model		
Up to delivery	9 (4.5)	0 (0)
From delivery to 1 year from delivery	26 (13.0)	7 (9.7)
Between 1 year to specific time horizon excluding lifetime	8 (4.0)	14 (19.4)
Lifetime: infant	52 (26.0)	37 (51.4)
Lifetime: mother	16 (8.0)	0 (0)
Lifetime: mother and infant	12 (6.0)	0 (0)
Not stated	77 (38.5)	14 (19.4)
Sources to inform health benefits		
Primary data collection	21 (9.7)	13 (14.1)
Evidence synthesis of secondary data	167 (77.3)	62 (67.4)

TABLE 7 Health economic assessment characteristics of the articles and reports (*continued*)

	Articles and reports assessing antenatal screening (%) (*n* = 242)	Articles and reports assessing newborn screening (%) (*n* = 95)
Combination of primary and secondary data	28 (13.0)	16 (17.4)
Expert opinion only	0 (0)	1 (1.1)
Main outcome measure used in the economic evaluation[a]		
Natural units	187 (59.2)	73 (65.2)
QALYs	126 (39.9)	36 (32.1)
DALYs	3 (0.9)	2 (1.8)
Not applicable[b]	0 (0)	1 (0.9)
Reporting of preference-based outcomes in cost–utility analysis		
Maternal QALYs/DALYs	94 (72.9)	4 (10.5)
Infant QALYs/DALYs	19 (14.7)	34 (89.5)
Maternal and infant QALYs/DALYs	16 (12.4)	0 (0)

a Does not add up to the total *n* or 100% as some articles and reports reported more than one category.
b This is a multiple-criteria decision analysis.

screening. Natural units such as number of cases averted and number of cases detected were the more commonly reported outcome measure in both antenatal (187, 59.2%) and newborn (73, 65.2%) screening studies. QALYs were used as the main outcome measure in 129 (39.9%) of antenatal screening and 36 (32.1%) of newborn screening studies. The DALY metric (an outcome measure that combines years of life lost due to premature mortality and years lived with a disability) was used in five studies across both types of screening programmes. Maternal preference-based outcomes (QALYs/DALYs) were reported in 94 (72.9%) of the antenatal screening evaluations, whereas infant preference-based outcomes were reported in 34 (89.5%) of the newborn screening evaluations.

Preference-elicitation methods for valuation of outcomes

Thirty out of 162 studies generated QALYs based on preferences for relevant health states using direct valuation exercises or preference-based instruments based on individual patient-level data. Thirteen out of the 65 studies (20%) reported that they had used a standard gamble and/or time trade-off method to obtain preferences directly from individuals within their studies; of which, 10/47 (21.3%) were antenatal screening programme assessments and 3/18 (16.7%) newborn screening programme evaluations. The use of preference-based instrument to describe health-related quality of life outcomes was limited with only 9/47 studies (19.1%) that investigated antenatal screening programmes and 7/18 (38.9%) that investigated newborn screening programmes stating clearly the instrument used and included the EQ-5D, Health Utilities Index 2 (HUI2), HUI3, 16-Dimension (16D) or the Quality of Well-Being Scale (QWB). There were two studies (one each for antenatal and newborn screening programmes) that used mapping of a non-preference-based survey [i.e. Edinburgh Postnatal Depression Scale and Adrenoleukodystrophy-Disability rating scale (ALD-DRS)] onto a generic preference-based measure.

Assessment of reporting quality

Reporting quality assessed using the CHEERS checklist was heterogeneous among the 264 full-length articles and reports (as summarised in *Appendix 5*). The top five items not satisfied among the studies for antenatal screening programmes were 'Abstract' (160, 88.4%), 'Time horizon' (153, 84.5%), 'Choice of model' (153, 84.5%), 'Discount rate' (130, 71.8%) and 'Study funding, limitation, generalisability, and current knowledge' (123, 68.0%). Similar results were found among studies assessing newborn

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screening programmes. The top five items not satisfied among these studies were 'Abstract' (69, 83.1%), 'Time horizon' (67, 80.7%), 'Study funding, limitation, generalisability, and current knowledge' (59, 71.1%), 'Choice of model' (55, 66.3%), 'Discount rate' (53, 63.9%) and 'Setting and location' (53, 63.9%). The majority of these items were partially satisfied as authors failed to justify the rationale of their methodology as required by the CHEERS checklist.

Discussion

This is the first systematic review to synthesise the evidence surrounding the benefits and harms adopted by health economic assessments evaluating antenatal and newborn screening programmes in OECD countries. Almost half of the articles were published in first-quartile journals, indicating interest in the topic by high-impact journals. Most of the economic evidence of antenatal screening programmes focused on screening for genetic conditions or infectious diseases, while that surrounding newborn screening programmes primarily focused on screening for metabolic or structural conditions.

We found clear evidence that decision-analytic models represent the main vehicle for the conduct of these studies, unsurprisingly given the nature of the evidence synthesis needed. Almost half of the articles and reports used standard health economic measures of QALYs or DALYs to measure the health benefits of the screening programmes. Only 30 of the studies using QALYs attempted to estimate preferences for relevant health states using valuation exercises or employing a preference-based instruments or mapping exercise on participant-level data sets. Therefore, the main source of information to inform utility values used in QALY estimations was the published literature.

A key strength of this review includes the focus on a comprehensive set of antenatal and newborn screening programmes across OECD countries. We did not restrict our search to English-only records to avoid language bias and did not restrict to the published literature only to avoid publication bias. However, this study has its limitations. We did not perform dual extraction of data, as currently recommended,[43] due to the large amount of information to extract from the final included articles and reports and the timelines to complete the project. For practical purposes and quality assurance, dual data extraction was performed for 10% of the papers after consulting our Independent Oversight Committee and information specialist (NR) using a reconciliation process that ended in a high-level agreement between reviewers. Furthermore, reporting quality was assessed using the original CHEERS checklist and not the CHEERS 2022 checklist that was published after the completion of the systematic review.[46] Arguably, application of the CHEERS 2022 checklist, which includes requirements to report on the use of health economic analysis plans, the contributions of patients and members of the public to study design and reporting, and trade-offs between efficiency and equity concerns, would have led to different assessments of reporting quality.

We found that many of these studies did not adhere to recent reporting guidance for health economic evaluations. Time horizon, choice of model and discount rates were poorly reported in general. Related to time horizon, we observed that authors employed longer time horizons to estimate health benefits than their associated costs counterparts. It was common to observe studies that used a lifetime horizon for the estimation of QALYs but a shorter time frame (e.g. up to delivery or when a case was detected) for the costs included in the model. Current lack of long-term data to inform accurate costs of living with a condition over time partly explains this result,[11] but it highlights a serious limitation of these studies. It also indicates that these studies did not adhere to recognised methods guidelines for the conduct of economic evaluations for the purposes of assessing the value for money of screening programmes.[14] This suggests that policy-makers using cost-effectiveness information from these studies to inform local decision-making should read these reports with caution.

Chapter 4 Work package 1: developing a thematic framework of benefits and harms to use in health economics assessments evaluating antenatal and newborn screening programmes

Introduction

The systematic review presented in the previous chapter identified all the health economic assessments evaluating antenatal and newborn screening programmes over the last two decades and described their characteristics and reporting quality. This chapter presents the methodology used to understand the benefits and harms adopted in these studies.

Methods

Development of bespoke form

A rapid review was conducted to identify previous checklists in the area of identification of benefits and harms associated with screening programmes. We evaluated checklists for the conduct of economic evaluations of screening programmes [i.e. Consensus Health Economic Criteria for trial-based studies and International Society of Pharmacoeconomics and Outcomes Research (ISPOR) checklist for model-based studies], and report of harms in clinical studies [i.e. PRISMA-Harms, PRIO-Harms, McHarm and Consolidated Standards of Reporting Trials (CONSORT)-Harm checklists]. This review suggested that no previous checklist was fit-for-purpose to identify benefits and harms associated with screening and adopted by economic evaluations. We therefore developed a de novo bespoke form for this purpose. Our starting point was that benefits and harms can manifest across the screening pathway and that ideally studies should report the following: the stage of the screening pathway; information on different phases of the screening programme such as the screening test, confirmatory diagnosis (if needed) and treatment; and description of consequences included, depending on the outcomes of the screening test (i.e. true positives, false positives, true negatives, false negatives as well as inconsequential conditions that will remain without symptoms during lifetime among the 'true positives' and 'false negatives') as set out in recent guidance.[1] Therefore, a bespoke form based on the aforementioned was created (see *Appendix 3*).

Development of the thematic framework

For all the studies included in the systematic review, we attempted to complete the bespoke form. The information captured in the bespoke form was used to create a framework of benefits and harms adopted by health economic assessments using a process of grouping themes derived from the data collected in the bespoke form.[47] An integrative descriptive analysis[48] of the collated themes within each category was then conducted, resulting in a taxonomy of benefits and harms consisting of a primary theme and up to four levels of subtheme(s). In the first step, the description of consequences was categorised into specific themes by ST-P. This pool of themes was the starting point of an iterative process where members of the study team (ST-P, MEP, OR-A and SP) merged, separated and refined the wording of themes and subthemes. The iterative process was maintained until consensus was reached among the study team (ST-P, MEP, OR-A and SP). Articles and reports were categorised into themes and subtheme(s) according to the condition and screening type. Bar charts were generated to illustrate the framework across and by medical condition(s).

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Results

We identified 86 unique descriptions of consequences across all articles and reports up to January 2021. Our thematic analysis resulted in seven core themes around benefits and harms with each core theme including up to four levels of subtheme(s). An update of the search strategies up to November 2021 identified an additional 18 articles but no new themes on benefits and harms emerged (see *Report Supplementary Material 2*). An abridged version of the thematic framework with a description of each theme and key examples is presented in *Table 8* with the full version up to subtheme level 4 presented in *Table 27* (see *Appendix 6*). All the themes listed are applicable to both antenatal and newborn screening except for theme 6 – pregnancy loss, which is only relevant to antenatal screening programmes.

The benefits and harms incorporated within health economic assessments are presented in *Figures 5* and *6* by screening type using the thematic framework. Limited information about benefits and harms was provided in 81 (33.5%) out of the 242 antenatal screening evaluations and 19 (20.0%) out of 95 newborn screening evaluations (e.g. conference abstracts). These included 51 (63.0%) antenatal screening evaluations and 11 (57.9%) newborn screening evaluations described in conference abstracts. Across all conditions targeted by antenatal screening, represented in *Figure 5* (n = 242), 115 (47.5%) incorporated benefits and harms related to the diagnosis of screened for condition (theme 1). Ninety (37.2%) of the evaluations included benefits and harms related to life-years and health status adjustments (theme 2). Eighty-eight (36.4%) of the antenatal screening evaluations included benefits and harms associated with treatment (theme 3). In general, for antenatal screening, benefits and harms associated with the long-term costs of screened for conditions (theme 4) were only adopted in 68 (28.1%) of the evaluations. Only 21 out of the 242 (8.7%) antenatal screening evaluations adopted benefits and harms from all of themes 1 to 4. The condition in the antenatal screening programmes which reported the widest range of themes was infectious diseases (see *Report Supplementary Material 2*). Among the 76 antenatal infectious diseases programmes, 22 (28.9%) did not have any themes and the remaining studies reported at least one theme from themes 1 to 6. However, none of them reported any spillover effects (theme 7).

In newborn screening in *Figure 6* (n = 95), 63 (66.3%) evaluations incorporated benefits and harms related to the diagnosis of screened for condition (theme 1). Fifty-one (53.7%) evaluations included life-years and health status adjustments as benefits or harms (theme 2). Forty (42.1%) of the antenatal screening evaluations included benefits and harms associated with treatment (theme 3). Benefits and harms associated with the long-term costs of screened for conditions (theme 4) were only adopted in 37 (38.9%) of the evaluations. Only 17 out of the 95 (17.9%) newborn screening evaluations adopted benefits and harms from all of themes 1 to 4. Benefits and harms related to overdiagnosis (5, 1.5%) and spillover effects (1, 0.3%) were largely absent from the studies. The condition category in the newborn screening programmes for which the widest range of themes was reported was metabolic conditions (see *Report Supplementary Material 2*). Among the 32 newborn, metabolic screening programmes, 9 (28.1%) did not have any themes and the remaining studies reported at least one theme from themes 1 to 7 (but note that theme 6 which is on pregnancy loss was not applicable to newborn screening programmes).

Table 2 in *Report Supplementary Material 2* summarises the benefits and harms adopted in the articles and reports for specific conditions. Health economic assessments evaluating antenatal screening programmes for infectious diseases adopted the broadest spectrum of benefits and harms compared to the other conditions.

Discussion

Our thematic analysis summarised a wide range of benefits and harms adopted by the studies identified in our systematic review and summarised them into seven core themes. There is no consistency on

TABLE 8 Thematic framework of benefits and harms adopted by health economic assessments evaluating antenatal and newborn screening programmes (abridged version)

Theme no.	Theme	Description	Key selected examples
1	Diagnosis of screened for condition	Related to the process of identifying a condition through screening. For example, cases diagnosed or missed, confirmatory tests (necessary and unnecessary), reduction in infants born with condition through effective treatment, or pregnancy termination	Infants born with condition Confirmatory test and additional tests to reach diagnosis of screened for condition Cases missed at screening Cases diagnosed at screening Screened for condition-related complications Additional screening of partners Additional testing to reach diagnosis in the absence of screening (links to diagnostic odyssey)
2	Life-years and health status adjustments	Impact of identifying a condition on the health of women, infants and other family members and included, for example, standard health measures such as QALYs, DALYs, life-years or impact of anxiety on parents after a false-positive result	Infant life-years post birth (including QALYs) Maternal life-years (including QALYs) Parental QALYs Psychological (anxiety/disutility from false-positive results, genetic variants of unclear penetrance, or knowledge of disease)
3	Treatment	Caused by harms of adverse reactions, unnecessary interventions and antibiotic resistance, or benefits of adverse complications averted due to timely interventions	Comparison of earlier treatment after screen detection and later after symptomatic detection Additional health care post diagnosis Hospital stay Missed due to false negative Prevention of screened for condition (infectious) Psychological (counselling about screening/confirmatory test/genetic diagnosis) Screened for condition-related treatment/management Treatment-related harm (disutility/anxiety/adverse reaction/antibiotic resistance) Unnecessary due to false positive
4	Long-term cost associated with screened for condition	Impact on long-term healthcare and non-healthcare costs related to identifying a condition through screening	Direct healthcare cost Direct non-healthcare cost (education/social care/caregiving) Productivity gains Societal cost
5	Overdiagnosis	Impact on costs and consequences of detecting a condition that would never develop into symptomatic disease	QALY decrement Unnecessary test/treatment
6	Pregnancy loss	Caused by treatment or an invasive diagnostic procedure, or an informed decision of termination after a true-positive result	Spontaneous Termination (of unaffected fetus due to false-positive test result/prevent downstream adverse maternal outcomes/psychological consequences) Treatment/test related
7	Spillover effects	Health and well-being effects to parents and other relevant stakeholders as a direct consequence of the child's diagnosis	Health impacts to parents and siblings from child's diagnosis with genetic condition, through knowledge of their own genetic status

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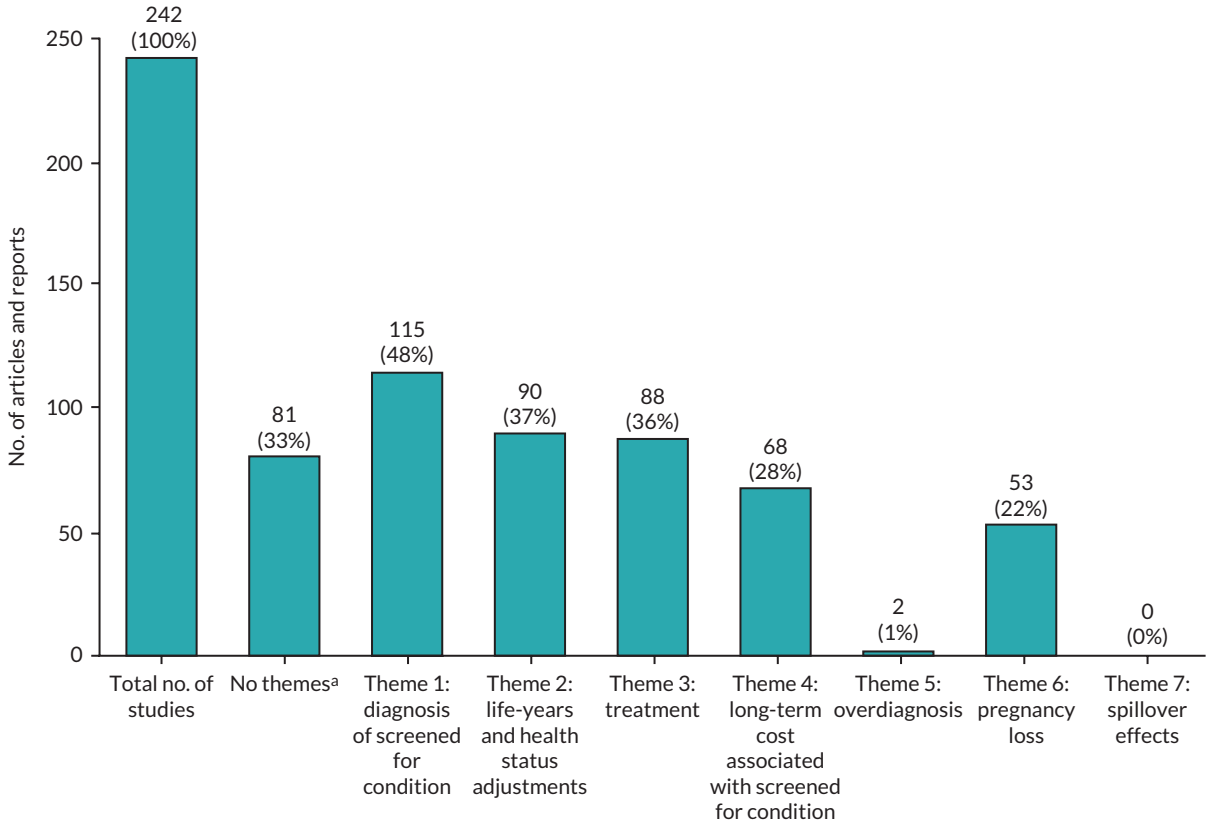

FIGURE 5 Benefits and harms adopted by health economic assessments evaluating antenatal screening programmes using thematic framework. a, Limited information about benefits and harms could be extracted from 81 (33.5%) out of the 242 antenatal screening evaluations to inform our bespoke form.

the selection of benefits and harms across and within conditions, suggesting that additional guidance is needed in this field. In general, articles and reports assessing antenatal and newborn screening programmes have considered benefits and harms that reflect the processes of identifying a condition in their health economic assessments. This includes, for example, cases correctly identified or missed or the number of unnecessary tests due to false positives. This result is not surprising because benefits and harms associated with the diagnosis of screened for conditions provide the first line of clinical evidence about these programmes and are of key interest to screening organisations. Around half of the articles and reports evaluating newborn screening programmes across all conditions did not consider benefits and harms associated with life-years and health status adjustments. Our review also found that benefits and harms identified as important by screening agencies and international health organisations, including overdiagnosis and spillover effects on family members, have rarely been adopted by these economic evaluations.[1,49] In the case of spillover effects, the only relevant subtheme identified was benefits to parents that inform future reproductive decisions from discovering carrier status as a consequence of the child's diagnosis.[50]

Our analysis of the application of the thematic framework to each study identified in the systematic review made an implicit assumption that all themes were relevant across the target condition of screening. Arguably, that may not the case. For instance, incorporating long-term costs and spillover effect for a condition, where health status is effectively restored to healthy levels after treatment for a true-positive screen result, may not be needed. However, we argue that for most of the conditions assessed by screening agencies including the UK NSC that is not the case. In general, we expect themes 1–4 to cover the main effects of screening associated with correct/incorrect results, impact on health on

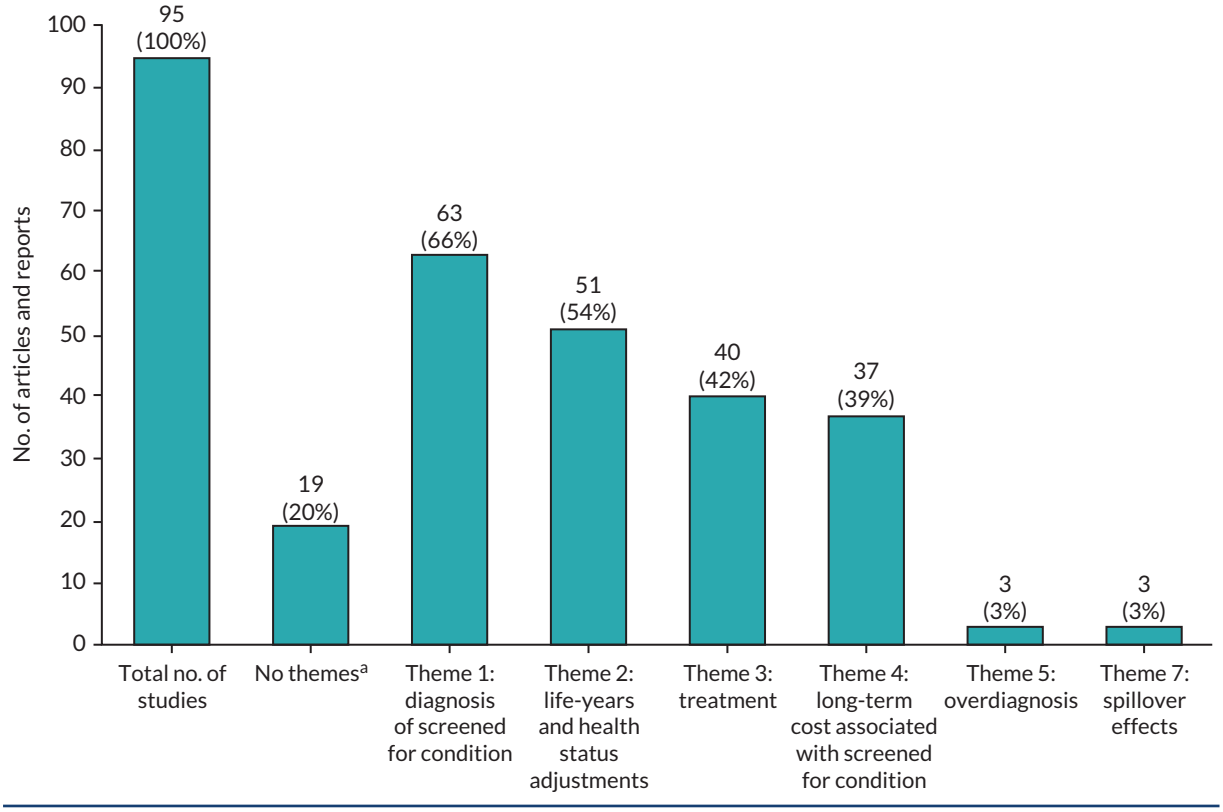

FIGURE 6 Benefits and harms adopted by health economic assessments evaluating newborn screening programmes using thematic framework. a, Limited information about benefits and harms could be extracted from 19 (20.0%) out of 95 newborn screening evaluations to inform our bespoke form.

women and their baby, consequences of treatment and implications for the healthcare system in terms on costs. All economic evaluation ought to incorporate benefits and harms associated with these themes at a minimum. Themes 5 and 7 might not be relevant to all target conditions but authors should explain their rationale to exclude these benefits and harms from their health economic assessments. Theme 6 and pregnancy loss, as already eluded in the methods, only target conditions of antenatal screening and is a key outcome of interest of the fetal anomaly scan in the UK.[51]

Authors did not generally refer to 'benefits' and 'harms' when describing the utilities and disutilities included in their evaluations. In addition, what constitutes a benefit or harm depends on the perspective of the particular stakeholder involved in the decision-making. For instance, a reduction in the number of infants born with a condition through pregnancy termination may be seen by some as a societal benefit in economic terms due to healthcare savings and reduced societal comorbidity. However, this may well be considered a devastating harm for families who value living with an infant with a condition. Therefore, we had to extract and interpret detailed information about the consequences included in the studies and reports for the thematic analysis without value judgements and recognising that the same consequence as described above could be categorised as a benefit or harm.

To our knowledge, this is the first time a detailed account of benefits and harms adopted by health economic assessments has been conducted in the literature. Previous work has focused on the identification of methodological challenges and the development of good practice guidelines in the development of health economic assessments of antenatal and newborn screening programmes.[20,30,31] Our work suggests that there is an immediate need to provide guidance for researchers conducting these types of studies in the future. This is addressed in later chapters in the report. Our proposed framework of benefits and harms can be used as a starting point to guide the development of health economic assessments evaluating antenatal and newborn screening for specific conditions.

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Chapter 5 Work package 2: systematic search and meta-ethnography of parents' experiences of newborn screening

Sections of this chapter have been previously reported in White *et al*. (2021).[52]

Introduction

This meta-ethnography[49] used a systematic review process to identify qualitative studies that focus on parents' experiences of newborn screening published in English-language academic journals from 2000 to 2019 (n = 36). The included studies represented a range of moments, outcomes, screening programmes and conditions that illuminated discrete elements of the newborn screening journey. We drew on these varied studies to construct a diagram of possible newborn screening pathways that parents may experience and identified a 'critical window' of time in parents' accounts that occurred between the signalling of a positive newborn screen and the outcome of confirmatory testing or diagnosis. During this critical window, families navigate complex emotional reactions, information, and decisions. From an in-depth analysis of this data, we developed the concept of 'absorptive capacity' as a lens through which to understand parents' experiences of, and reactions to, new and emerging information during this critical window. We also identified how the 'concertinaing of time' – the various ways that parents experience the expansion and compression of time throughout and beyond the screening pathway – directly impacts their absorptive capacities. This study underscored the need to move away from viewing newborn screening as a discrete series of clinical events, but rather a process that can have far-reaching implications across time, space and family groups. Further, it informed us of potential benefits and harms for associated with newborn screening that needed to be considered for the subsequent pieces of qualitative work.

Methods

While the larger project is solely focused on the UK, we reviewed the international literature to interpret existing findings and develop a fuller conceptual understanding of the way newborn screening is experienced. We approached the review sensitised to the possibility that different sociocultural, geographical and health system contexts will impact the screening experience but sought to identify cross-cutting themes that transcended these differences. This review did not require ethical approval since it drew on existing publications.

Deviation from protocol

As we developed our approach to reviewing the literature on experiences of newborn screening, we decided that using a meta-ethnography, rather than a scoping review, would allow give us more sophisticated purchase on the literature we sought to synthesise. The goal of this approach is to bring together, and interpret, insights from qualitative research and producing an in-depth understanding of their collective findings. This approach supported identification of the key themes of absorptive capacity, reported in the article in *Social Science and Medicine*.[52]

Approach to meta-synthesis

We opted not to conduct a meta-ethnography of experiences of antenatal screening due to the existence of several reviews, meta-syntheses and meta-ethnographies in this area,[53–56] including those published recently.[57,58] This literature highlights the sense of responsibility felt by parents to participate

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in antenatal screening,[55,56] the shock and devastation experienced when an unanticipated result was returned[54,55] as well as the significance of technology, and relationships with healthcare professionals as mediators of the antenatal screening experience.[57]

Unlike antenatal screening, parents' experiences of newborn screening have been less extensively reviewed. This is in spite of the newborn genomes programme gaining momentum[59] and increasing calls to expand the newborn bloodspot test to include more conditions (e.g. SMA Newborn Screening Alliance, 2021). As such, the scope and delivery of newborn screening is currently high on both the research and policy agenda in the UK. In light of this context, our meta-ethnography was designed to analytically interrogate parents' experiences of newborn screening to contribute to debates around expanded screening, and to interpret the findings as a contrast to the existing antenatal screening literature, where decisions, timeframes and outcomes of screening are entirely different.

The goal of a meta-synthesis is to bring together, examine and interpret findings from disparate qualitative research studies and produce a more in-depth understanding than is possible from looking at the studies individually.[50,60] It offers the opportunity to identify patterns, processes and contexts, as well as omissions from a body of work.[61] While there are multiple ways of synthesising qualitative research,[62] we followed the stages of meta-ethnography as described by Toye *et al.* (2014).[63]

Stages of meta-ethnography

We wanted to bring together qualitative studies that explored parents' experiences of newborn screening. We opted to conduct a systematic literature search to provide evidence that we sought to capture as much of the evidence within the scope of our research question as possible.[63] Recognising that it can be challenging to locate qualitative research studies, we began with a broad, systematic search strategy.[64] We searched for any instance of the terms 'newborn screen*', 'neonatal screen*' or 'newborn bloodspot' in the title or abstract of academic journals published in English from January 2000 until December 2019 across five databases accessed through the University of Oxford Libraries (*Table 9*).

After running the search, AW removed duplicate records and reviewed titles and abstracts for eligibility. If it was unclear whether or not a record should be included based on the title and abstract, it remained in the pool until the next step. Next, AW read the remaining studies in their entirety to assess eligibility. LH provided a secondary ruling for articles that AW was uncertain about. As the final step, AW hand-searched the reference lists of included studies to identify additional research not identified through the search strategy. AW maintained a database of all decisions about inclusion and exclusion (*Figure 7*).

Studies were eligible for inclusion if they focused on parental experiences of newborn bloodspot screening programmes and used qualitative methods. Non-research publications, such as commentaries or letters to editors, were excluded. Similarly, mixed-methods research was excluded, as the qualitative

TABLE 9 Search strategy based on articles published in English from January 2000 to December 2019

Search terms in title or abstract	Databases
Newborn screen[a]	CINAHL Complete
Neonatal screen[a]	JSTOR
Newborn bloodspot	PsycINFO
	Sociological Abstracts
	Web of Science

a indicates the truncation symbol used in the search strategy.

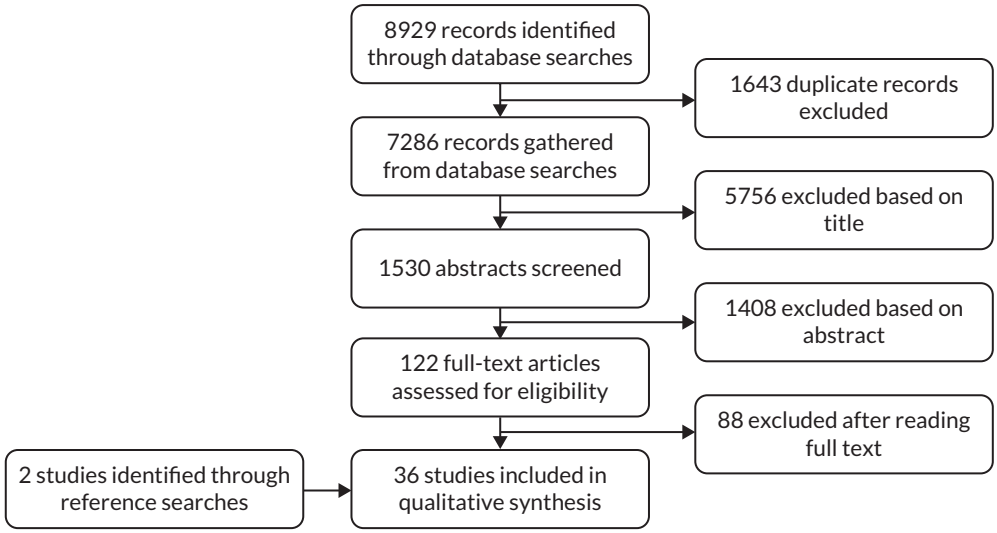

FIGURE 7 Flow diagram of included and excluded studies.

analysis was often secondary to reporting statistical findings. As we were interested in how parents experienced varying aspects of the newborn screening process, studies that included other stakeholders (e.g. genetic counsellors or midwives) alongside parents were excluded, as it was challenging to separate findings between stakeholder types. We also excluded studies that were beyond the scope of the review, including those focused on storing newborn blood spot cards, antenatal genetic counselling, being diagnosed with a screened-for condition in later life or living with a screened-for condition. We did not exclude any papers based on quality. We were aware that the authors of included papers were writing with varying aims for different audiences, and they ranged from healthcare providers to ethnographers. The papers included in this synthesis reflect the wide-ranging disciplinary backgrounds and purposes of the authors contributing to this field.

Once we had a finalised list of included studies, we divided the work of reviewing among the research team. AW read all of the studies and maintained an Excel database tracking study characteristics. We split the number of studies (n = 36) evenly among the remaining four members of the research team (AM, FB, LH, LL) so that each was responsible for focusing on nine studies. We read the included studies in their entirety, with particular attention focused on the findings and discussion sections of studies. We used a combination of computer-aided and paper-based reading and coding processes. AW uploaded PDFs for the included studies to NVivo 12 Pro (QSR International, Warrington, UK). She progressed from a line-by-line coding approach to organising codes into descriptive themes and then refining codes into conceptual categories. The remaining researchers used a paper-based approach to coding, where they read the studies and hand-coded higher-level concepts as they emerged. They made a note of these concepts and shared them with the research team during analysis meetings.

After we analysed the studies individually, we set about synthesising the literature and identifying meta-themes. This was an iterative process that took place over several months. We arranged evidence synthesis meetings to discuss our analysis and identify cross-cutting themes. We discussed overarching concepts and considered how they might apply to various other studies in the synthesis. Even though individuals were responsible for different subsets of studies, we generally found that we had developed overlapping concepts, albeit under slightly different names. As we reached consensus on the core experience dimensions drawn from the compiled literature, we synthesised these findings into higher-order interpretations across screening contexts and conditions from which substantive conclusions about the experiences and implications of newborn screening from a parental perspective could be drawn.

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Results

Mapping newborn screening pathways from included studies

Our systematic review yielded a total of 36 studies (see *Appendix 7*). Studies ranged from descriptive accounts of the newborn screening experience to theory generation about the meanings attached to those experiences. Given the complexity of newborn screening, many studies were focused on discrete points in the pathway, although collectively they covered the newborn bloodspot 'journey'. Through a cross-study analysis, a broader, richer picture takes shape compared to what can be provided in the individual papers.

Newborn screening has become an embedded part of the neonatal experience for parents. Drawing on the included studies, we mapped the various pathways that parents and babies might take when experiencing newborn screening (*Figure 8*). The consent process varies across, and even within, countries. In the USA, for example, screening is compulsory across nearly, but not, all of the 50 states. In other countries, parents are nominally required to consent to newborn screening. For example, in the UK under the NHS guidelines, healthcare providers (HCPs) should offer parents screening, and parents may verbally agree.[65] In practice, however, the extent to which parents are aware of their ability to refuse newborn screening is unclear, as a mother whose child screened negative in England reported, 'It's a very, very quick process and you're not given any option to think about it'.[66]

Regardless of the differences in the consent process, our review suggests that newborn screening is poorly understood, and its potential ramifications are not readily considered by parents. Parents frequently reported not recalling the consent process, or much about the purpose of the screen.[66–69] Parents described putting their trust in the healthcare system and medical authority, with newborn screening being largely seen as something that 'just happens' after having a baby, rather than an active choice. For these screen-negative families, newborn screening is ushered in by trusted medical authorities and is typically an experience that passes with little concern or complication.

While the majority of families exit their newborn screening journey swiftly, there is a subset of families who will receive the news that their baby screened positive, and these families are typically offered further testing or investigations. This is a moment of no return for many families, which has implications not only for the infant and parents, but also for the family writ large. Before receiving the news, parents may not have realised or appreciated how much impact the 'heel prick' test could have on their lives. Most parents – unless they are known carriers or are living with a condition – tend to have limited knowledge of the various screened-for conditions.[70] This is exacerbated by the fact that for the vast majority of conditions identified through the newborn screening 'heel prick', such as inherited metabolic diseases like phenylketonuria (PKU), the infant is typically asymptomatic at the point a positive result

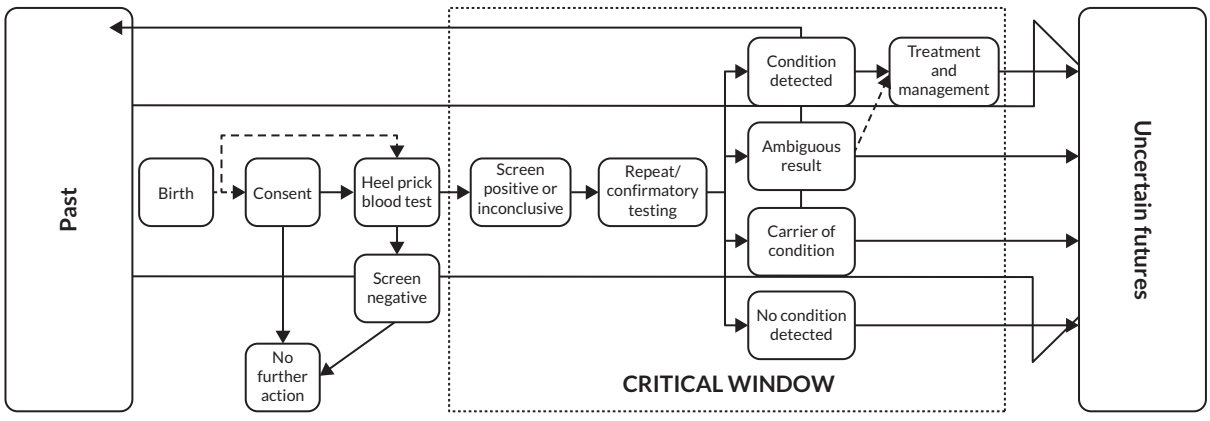

FIGURE 8 Map of newborn screening pathways.

is received. However, sometimes non-specific symptoms may have already been observed by the parent(s).[71] Regardless of context or condition, such news ushered families into a compressed, critical window of time characterised by waiting periods, strong affective responses and a need for more focused communication.[71–75]

Positive screening results are followed up by the offer of confirmatory diagnostic testing, with the nature of this testing varying by condition. From the result of the diagnostic test, the condition is either confirmed (the screening result was a 'true positive') or ruled out (the screening result was a 'false positive'). However, for a subset of families, the results of diagnostic testing are somewhat more ambiguous, indicating either a carrier status or a gene variant for which the link to phenotype is neither clear nor certain. Even in cases where a precise diagnosis is made, the broad spectrum of severities associated with the conditions screened for, combined with lack of experience with symptoms at the point of diagnosis (or potential lack of symptoms), can dramatically heighten uncertainty for parents, despite being presented with the seeming certainty of a confirmed diagnosis.

Assessing parents' absorptive capacity

Across studies, participants frequently used descriptions and metaphors of 'absorption' and 'digestion' to describe their processing of screening and testing information. For example, 'Your brain is a sponge' (mother of child with cystic fibrosis[76]) and 'There was just too much at that time to absorb' (mother of child with cystic fibrosis[77]). These metaphors and descriptions were common and prompted us to apply the concept of 'absorptive capacity' to screening contexts. 'Absorptive capacity' is a term used widely in management studies to refer to a company's ability to 'recognise the value of new, external information, assimilate it and apply it'.[78] The term is not commonly used at the level of the individual but has value as a lens through which to examine and explain parents' ability to process new diagnostic information.

For the subset of families that have a positive or inconclusive newborn 'heel prick' screen, the initial affective responses tended to be ones of shock and anxiety.[79–81] Parents were not necessarily aware of what they consented to (or did not give consent for), so hearing that their child tested positive ushered in a period of shock, confusion and fear. Before receiving the news, parents largely conceptualised their child as healthy and perfect, particularly if they had also gone through the process of antenatal screening without any positive screening results. Parents had to reconcile to the fact that their child might not be symptomatic and instead 'looked' healthy, yet still had a positive newborn screening test. In such cases, parents' distress and shock limited their ability to absorb information in the moments following the news that their child screened positive and at later points in the diagnostic process.

Absorptive capacity is also dependent on an individual's prior related knowledge, including familiarity with medical concepts and language.[78] Based on the studies in this review, we argue that even if parents remember consenting to, or being notified about, newborn screening, they do not necessarily have the tools to understand what it means. Parents' distress and subsequent inability to absorb information were augmented by their own unfamiliarity with screened-for conditions and genetics.[70,72,82] Tluczek (2006)[76] points out that even the language surrounding screening and testing can be fraught with confusion, including the counterintuitive meaning of the terms 'positive' and 'negative' when describing test results, compared to an everyday conversation where these indicate 'good' and 'bad', respectively. However, even this interpretation overlooks the complexity of ways these terms can be understood and experienced by families. There has been a more recent push from families living with a range of screened-for conditions to employ neutral language in screening contexts that do not pre-empt the parents' reception of the news as either 'good' or 'bad' which has now filtered into professional guidelines. Nevertheless, the use of inaccessible medical language to describe screening and testing results and processes was a widespread concern across the data set, which in turn impacted on parents' absorptive capacities.

Beyond parents' (un)familiarity, the format of information presentation also influenced parents' absorptive capacity. To effectively absorb information 'it is insufficient merely to expose an individual

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briefly to the relevant prior knowledge' (p. 131).[78] Consent, or lack thereof, for newborn screening is taken at a time when new parents are simultaneously exhausted, distracted and busy caring for their new child. New mothers may also be experiencing postnatal physical and mental health concerns of their own. Any information given about the screen at that point does not seem to be experienced as a choice or an active conversation, but rather a minimal (if any) conveyance of information.[66–69] For the subset of families who are notified of a positive or inconclusive screen, the limited prior communication about the potential implications of newborn screening sets the stage for what is often perceived to be a period of problematic communication.[72,75,80,83–85]

By looking across the studies, we considered how parents' information needs varied by condition detected and context. We identified a continuum of informational needs, with parents preferring different levels of information at different points in the screening process, based on their absorptive capacities at that time. Some parents wanted to dive in and 'consume' as much information as possible, while others wanted 'bite-sized' chunks. Others wanted to hold back from obtaining information until there was diagnostic clarity. Unfortunately, parents' needs were not always met. In some cases, parents reported being given a volume of information that they were ill-prepared to receive and unable to absorb. In other cases, parents reported wanting more information than was given by their HCPs. As a result, they sought other sources – primarily the internet or support organisations – in an attempt to increase their knowledge.[86–88]

Informational needs became more complicated in instances where HCPs themselves, who were looked to as the experts, did not have the expertise to provide answers to parents' questions.[81,86,89,90] HCPs may be counselling families with a rare condition for the first time, and this could undermine parents' confidence in the information provided. Although we acknowledge that there may be a discrepancy between what HCPs say and what parents hear, it seems there is room for improving communication and information provision during this critical window when absorptive capacity is in its highest state of flux.[91]

Newborn screening, uncertainty and the concertinaing of time

There is a crucial temporal component to parents' experiences of newborn screening. Throughout the critical window, time expands and contracts, generating ripple effects into the past, present, and future. During the period between a positive screen and (potentially) receiving definitive diagnostic results, families are often living through a state of ambiguity or disorientation. How people approached living in the liminal space during the critical window varied considerably.

Families who viewed ambiguity as a negative state desired definitive answers as a means of gaining control. Such families may want to find out as much as possible about a potential condition and turn to information seeking online and from those with lived experience of the condition.[82,87,92] Once these families received a diagnosis, they were more able to make sense of the condition and how to manage it in the future.[70] Even among those with an ambiguous diagnosis, there may be a drive towards labelling as an attempt to gain control and make the situation more concrete, as explored in a study of families whose children screened positive for cystic fibrosis, yet received an inconclusive diagnosis.[90] For these families, knowledge about the condition allowed them to feel prepared to manage the health and social needs of their infant moving forward. However, such families must still live with the uncertainty of how/whether the condition will manifest in their child in the future and hold out hope that they will not need to use the information in the future.

While some families sought to learn, as much as possible, other families viewed the inherent ambiguity of this liminal period in a more positive light. In such cases, families rejected in-depth information about the condition in order to retain the hope that they will never need it.[92,93] These families adopted a 'wait and see' approach to the period between screening positive and receiving a diagnosis, on the basis that 'too much information can be hurtful in a sense'.[92] If they are notified that the initial 'heel prick' result was a false positive, such families will have avoided the anxiety and stress that additional information

can bring. However, if the child is diagnosed with a condition, these families may opt for ' "easy-to digest" information and "just the facts, because you can't handle anything else" ',[83] reflecting again the concept of absorptive capacity. These families continued to look towards the future as a coping mechanism, hopeful that the condition will not manifest or will be of limited severity, or perhaps that treatments will improve over time.

While families were found to take a range of differing approaches as they moved through the critical window, they all shared a common experience that was found to have long-term ramifications for everyone involved. Indeed, for screen-positive families, the experience had ripple effects that stretched both backwards and forward in time. If an inheritable condition was detected, families found themselves looking backwards in their family tree, in an expansion of time, trying to work out where the trait might have 'come from'.[70,82,94] As families looked backwards, some grappled with shame, blame, and guilt as they considered what might have been for their child, particularly when a child inherits a condition.[77,82,86,90,94,95]

The impact of newborn screening was also found to flow forwards in time from the moment of notification of positive results, as parents found themselves reconsidering their expectations of the life they had imagined for their child and for themselves as parents. In quick succession, parents had to initiate a chain of emotional processing, discussion and medical appointments, involving not just the child but sometimes also the parents and wider family members.[73,74,94] For the parents of children who were asymptomatic at the time of the results, one particularly significant part of the screening journey was a loss of what should have been a happy time with their child – of 'blissful ignorance'. This impact was particularly pronounced when compared to the experiences of families who received a later diagnosis.[73] For some, the pre-symptomatic diagnosis ushered in by newborn screening interrupted, and limited, the joyful time families were experiencing at the birth of their child. For these families, the positive or ambiguous screening result effectively extended the length and reach of the condition earlier into the infant's life than otherwise would have been the case.

Newborn screening also has ripple effects that extended into the future, and across generations. As families moved away from receiving a diagnosis, time expands into uncertainty and the unknown. Parents of children living with conditions or ambiguous health statuses (e.g. cystic fibrosis screen positive, inconclusive diagnosis) have to consider how, when and to whom they disclose their child's condition.[90] Parents also have to consider their own future reproductive intentions, including whether or not they want further children and, if so, what role antenatal or newborn screening may play in any subsequent pregnancies.[96] Parents of children who are found to be carriers of a condition through newborn screening also need to consider if, when, and how they will tell their child about their result.[97] These planning conversations were found to take place even as children were still newborns, even though disclosure might not take place for many years to come. Looking further into the future, the child will also have to consider how they manage their condition or carrier status, how/whether to disclose it to others, as well as their own reproductive intentions.[86] The implications of newborn screening therefore play out in the months, years and even decades following diagnosis, suggesting that the aspects of screening are enduring over the life course.

Discussion

By looking across the range of moments, outcomes and conditions across international contexts, our synthesis characterised the critical features of the broader newborn screening experience from the familial perspective. Our findings demonstrate that newborn bloodspot screening is a familial experience. While currently most families will receive negative newborn 'heel prick' screening results, it is also important to consider the experiences of those who receive positive, inconclusive or ambiguous screening outcomes, particularly as we move into an era of genomic sequencing, with the potential to generate an exponential rise in the number of 'positive' and unexpected newborn screening results.

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Given the 'urgency narrative' often used to promote newborn screening programmes, it can be difficult to critique the expansion of newborn screening panels.[98] However, here we have provided evidence that the experience of screening is highly variable across families. We have identified and focused on a 'critical window' of time between being alerted to a positive or inconclusive newborn screening result and further testing wherein families must process a range of emotions, determine their informational needs, and shift through rapidly alternating periods of waiting and activity. We have developed the concept of absorptive capacity – the ability to recognise, assimilate and apply new information – to capture the abilities of parents, and crucially also the limits of those abilities, to comprehend their child's screening results or condition. We have synthesised detailed qualitative evidence to explain the various ways that parents experience the expansion and compression of time throughout and beyond the screening pathway, demonstrating the far-reaching implications of screening across time, as well as to wider family and kin. We used these findings to begin to understand possible benefits and harms of the screening experience, which we explored further in subsequent pieces of qualitative work (see *Chapters 6* and *7*).

Chapter 6 Work package 2: secondary analysis of existing interviews exploring experiences of antenatal and newborn screening

Introduction

We conducted a secondary analysis of existing qualitative interviews exploring experiences of, and attitudes towards, antenatal and newborn screening, as well as the experience of living with screened-for conditions (n = 256). Here, we present findings derived from a situational analysis mapping exercise.[99] Findings demonstrate the wide-ranging elements inherent in discussions about antenatal and newborn screening. We used this information to inform our own primary data collection (see *Chapter 7*).

Methods

Data

We conducted secondary analysis of qualitative interviews derived from previously conducted studies exploring antenatal and newborn screening experiences and attitudes (n = 256; *Table 10*). These in-depth narrative interviews were conducted over the last 13 years by FB at the University of Warwick, and LH, LL *et al.* at the Medical Sociology and Health Experience Research Group, University of Oxford. While some interviews were conducted over 10 years ago, the majority were conducted within the past 5 years. Interviews included perspectives of people with a wide range of experiences in relation to screening, testing, pregnancy termination and continuation, as well as parents and affected adults living with genetic and chromosomal conditions.

Analysis

We used a situational mapping exercise to analyse this large data set. Situational maps 'lay out the major human, non-human, discursive, and other elements in the research situation of concern and provoke analyses of relations among them' (p. 554).[99] Situational maps are a reflexive, subjective form of data interpretation which aim to capture the complexities of a situation and their relations.[99,100] They are useful for rendering large data sets manageable and identifying complexity within the data. Our aim was to understand the people, objects, places and discourses that influenced antenatal and newborn screening experiences and attitudes. AW read the interview transcripts and used concept coding to assign meanings to chunks of the data.[91] These concepts represented higher-order themes that went beyond an individual narrative, and they typically included nouns (e.g. time) or processes (e.g. conceptualising normality). Concept coding was deemed appropriate since we were interested in meta-themes across the vast data sets and progressing towards an understanding of key concepts surrounding antenatal and newborn screening.[101]

We used the concept codes to develop a situational map through an iterative, increasingly ordered representation of the elements related to antenatal and newborn screening.[99] Initially, this was a messy list of elements rooted in the empirical evidence from the conceptual codes. Over several weeks, we iteratively discussed the elements and considered the content of the data and boundaries of this project.[100] We refined the elements and organised them based on Clarke's (2003)[99] categories. Our situational map has both human elements and non-human elements. Human elements include the key individuals, groups and institutions involved in screening. Non-human elements include the technologies, materials and information that 'structurally condition the interactions within the situation through their specific properties and requirements' (p. 561).[99] We also considered the 'ideas, concepts,

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TABLE 10 Data sources for secondary analysis (*n* = 256)

Type of participant	Number of transcripts	Source of data	Year(s) of collection
Parents who have undergone antenatal or newborn screening	45 (37 women, 8 couples)	Oxford	2005
Parents whose child received a diagnosis of cystic fibrosis following newborn screening	6	Warwick	2018
Parents whose fetus received a diagnosis of thalassaemia following antenatal screening	5	Warwick	2017–8
Parents who have undergone pregnancy termination for fetal anomaly (screening or family history)	48 (40 Oxford, 12 Warwick)	Oxford, Warwick	2006–8
Parents who refused prenatal testing for condition in family	12	Warwick	2012–8
Parents who continued with a pregnancy following prenatal diagnosis	9	Warwick	2012–8
Adults living with conditions that are currently screened for	20 (10 cystic fibrosis, 10 thalassaemia)	Warwick	2017–8
Parents of children with conditions that are currently screened for	20 (7 cystic fibrosis, 7 thalassaemia, 6 Down syndrome)	Warwick	2017–8
Parents with experience of neonatal surgery	13	Oxford	2017
Participants with experience of late miscarriage	3	Oxford	2018
Families (parents and affected adults) living with genetic diseases that are not yet screened for	75 (36 spinal muscular atrophy, 22 haemophilia, 17 fragile X syndrome)	Warwick	2012–8

ideologies, discourses, symbols, sites of debate' that are involved in antenatal and newborn screening (p. 563).[99] Thus, we developed categories for economic elements (e.g. funding), sociocultural elements (e.g. gender or ethnicity), temporal elements (e.g. waiting periods), spatial elements (e.g. geographical differences) and related discourses (e.g. conceptualising quality of life).

As the situational map took shape, we conducted several rounds of revision to condense and clarify the categories. We asked PPI members to review the list of human elements (see *Human elements involved in antenatal and newborn screening*) and we also presented the entire situational map to our independent oversight committee. We used the input of these groups to make final minor adjustments to our meta-themes (e.g. naming conventions) but they deemed that no other adjustments were necessary.

Stakeholder mapping

We identified stakeholders for inclusion in our primary data collection as part of the situational analysis exercise (i.e. the individual and collective human elements). We compiled the list of stakeholders and presented it to our PPI members. We asked PPI members to review the list and brainstorm if there were any missing stakeholders based on their knowledge and/or experiences. The PPI members named different types of HCPs, but we have condensed these into broad categories in our situational analysis map (e.g. doctor, nurse). They also named different types of charities. Again, we condensed these into a broad category (i.e. 'charity organisations'); however, we did seek out the identified charities for our later primary data collection (see *Chapter 7*). We also sought approval for our stakeholder list from our independent oversight committee. Nothing further was added and the stakeholder list was approved.

Using comments submitted to the National Screening Committee

Additionally, we reviewed comments sent to the UK NSC for previous reviews of antenatal and newborn screening that went to consultation within the last 5 years. We wanted to verify that the stakeholder groups identified in our secondary analysis were reflective of the stakeholders that typically submit comments. We observed good correlation between our stakeholder list and those submitting responses to UK NSC policy reviews, and as such were satisfied with the robustness of our approach.

Results

Our situational map has 11 categories comprised of nearly 100 elements, which we describe in *Table 11*.

TABLE 11 Situational analysis map of elements involved in antenatal and newborn screening

Individual human elements	Collective human elements	Implicated actors	Discursive constructions of human elements
• Baby • Dietitian • Doctors • Employer • Extended family • Father • Fetus • Friend • Genetic counsellor • Health visitor • Midwife • Mother • Nurse • Other children • Pharmacist • Physiotherapist • Psychologist • Religious leader • Social worker	• Charity organisations • Church organisations • Online communities • People or carers of those living with condition	• Academic/scientific researchers • MP • UK NSC	• Assumptions about pregnancy or child • HCPs as (un)supportive • Living as carrier • Living with condition • Own child as special/gift/exceptional • People as unaware/uneducated about conditions • Screening having spillover effects • Stereotypes about disability • Stereotypes about who gets specific conditions

Non-human elements	Discursive constructions of non-human elements	Temporal elements	Spatial elements
• Amniocentesis • Antenatal screens • CVS • Family history • Fertility • Google/internet information • Heel prick test • Medical notes/histories • Medicines and management materials • Miscarriage • NHS • NIPT • (Non)visibility of condition • Nurseries • Private non-NHS services • Risk/chance statistics • Schools • Termination • The phone call • Written information	• Communicating (in)effectively • Dealing with loss • Holding on to hope • Negative screens as non-events • Positive screens inducing fear, anxiety, guilt • Purpose of scans • Risks and invasiveness of screens • Science behind genetics/screening as mystifying • Termination as (not) appropriate • Trust in NHS • Varying nature of condition(s)	• Cumulative effects of diagnosis • Feelings about condition over time • Future uncertainty • Historical eugenic practices • Pregnancy timing • Reproductive life course • Screening timing • Waiting periods • When to disclose diagnosis or condition	• Approaches in other countries • Local and regional variations in care availability • Neonatal and paediatric intensive care units • Room setting for scans/tests • Travel to and from healthcare settings

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TABLE 11 Situational analysis map of elements involved in antenatal and newborn screening (*continued*)

Individual human elements	Collective human elements	Implicated actors	Discursive constructions of human elements
Sociocultural elements	**Economic elements**	**Related discourses and debates**	
• Arranged marriages • Ethnicity contributing to chances of condition • Gendered caring practices • Parental sacrifice • Religious beliefs	• Charity organisation capacity • Individual financial resources • Medical and research funding allocation • NHS infrastructure and practices • Pharmaceutical companies • Private healthcare costs	• (Dis)ability in society • Expanding technology and the role of screening • Personal/bodily autonomy • Pronatalism • Quality of life • Termination	

Human elements involved in antenatal and newborn screening

The secondary analysis revealed that there are many varied human elements involved in antenatal and newborn screening. During antenatal screening, the mother's well-being is at the centre of these discussions. During newborn screening, the baby's well-being is at the centre of these discussions. Other family actors include the father, other children, and extended family members such as grandparents, aunts, or uncles. Friends can also be closely involved in screening conversations, as sources of information or support. In addition to the family members, our analysis shows the myriad types of HCPs involved in screening. This list includes, but is not limited to, general practitioners (GPs), specialist consultants, nurses, midwives, obstetricians, gynaecologists, genetic counsellors, physiotherapists, pharmacists and psychologists.

While HCPs provide tangible medical services to the mother, fetus/baby and other family members, our data also revealed the importance of other actors on the periphery. Data highlighted the importance of employers for understanding pregnancy and maternal health needs, particularly when things did not go as expected. Social workers were essential for connecting families with disparate services to manage living with conditions. Religious leaders, and church organisations, were named as sources of comfort and community, again especially important when screening resulted in the unexpected. Charity organisations and online communities that specialised in providing information about screening or screened-for conditions were named, repeatedly, as vital elements for (potential) parents on their screening journey. These organisations not only provide support and information, but also provide a collective sense of community for people at a time that may be emotionally challenging. Charities and online communities also link people going through screening to people who are living (or caring for someone) with a condition. People living with a condition, or those caring for someone with a condition, are a vital source of experiential knowledge that is valued as separate from what one may hear from other sources – such as the media or HCPs.

In addition to the named individual and collective human elements, our secondary analysis also implicated three important actors. The first is academic or scientific researchers – including ourselves. Researchers discuss what is (un)known about screening and screened-for conditions. Findings from research may be used by others to make political, healthcare or social care decisions. Researchers can develop treatment breakthroughs and give voice to those affected by screening. The second implicated actor is the UK NSC. The UK NSC advises the NHS and Members of Parliament (MPs) about screening programmes. An independent panel of experts, they weigh evidence to make recommendations on expanding screening programmes and support the implementation of existing programmes. While not always named in the data, the UK NSC makes decisions that shape the screening landscape. Similarly, MPs may go unnamed but are the decision-makers who determine screening and healthcare policies.

In addition to the individual and collective human elements, we noticed a number of recurring discourses constructed about humans and screening. Within the data, parents made assumptions made about their (partner's) pregnancy or newborn child. For those who had not previously had a screen-positive experience, participants generally assumed that nothing would come of the antenatal or newborn screening (i.e. 'everything will be fine'). Conversely, for those who had previously experienced unexpected news from antenatal or newborn screening, there were assumptions that perhaps their pregnancy or child would continue to have problems. For such people, this feeling of 'something could be wrong' continued through subsequent pregnancies.

Alongside the assumptions about one's pregnancy or newborn were regularly expressed points about what it was like to live with a condition or as a carrier. Constructions of what it was like to live with a condition varied based on perceived severity and nature of the condition as well as whether the participant had direct lived experience with the condition itself. Constructions of what it was like to be a carrier also varied based on whether the participant had direct experience with the condition but tended to centre on reproductive decision-making. These discourses intersected with (generally negative) stereotypes about what it was like to live with a disability, such as inability to join the workforce, having to attend specialist education, or leading a life that was somehow 'less than'. Similarly, there were stereotypes about who might be diagnosed with particular conditions which tended to focus on ethnicity (e.g. linking being of African or Caribbean background with sickle cell disease) or maternal age (e.g. linking 'older' motherhood with Down syndrome).

Within the data of people who had screen-positive experiences and/or lived experience of a condition, much was said about how little public awareness there is of screened-for conditions. This lack of awareness was perceived to make positive screening results more difficult to absorb, while also perpetuating stereotypes about life with the conditions. These same participants also talked regularly about what made HCPs (un)supportive. Supportive HCPs were constructed as listening to concerns, providing sufficient information, and being available to answer questions. Unsupportive HCPs, on the other hand, were those who tended to do the opposite. This included saying things that participants perceived as negative about a given condition, or focusing solely on clinical complications, rather than abilities and potential. Such unsupportive actions by HCPs ran counter to the recurring parental narratives that their child was special or a gift, and that their experiences had been far more positive than anticipated at the point of diagnosis. Finally, narratives tended to construct antenatal and newborn screening as having 'spillover effects'. There were regular references to how screening had significant personal, relational and resource implications on individuals above and beyond the medical purview of screening.

Non-human elements related to antenatal and newborn screening

The secondary analysis revealed a range of recurring non-human elements, such as technologies and materials, related to antenatal and newborn screening. These included the screening tools themselves [i.e. antenatal screens, non-invasive prenatal testing (NIPT), and the heel prick test] as well as diagnostic tests [i.e. amniocentesis and chorionic villus sampling (CVS)]. For antenatal screening, there were differing interpretations of the purpose of ultrasound scans. For those who had not had an unexpected screening result or pregnancy complications, scans were constructed as an opportunity to 'see' their unborn baby and viewed in a positive manner. For those who had pregnancy complications, scans were something that were medically necessary and worrying. If a diagnostic test was offered, pregnant women and their partners considered the invasiveness and potential risks in their decision-making. The policies and procedures around termination were of vital importance as were ideas about whether or not termination would be appropriate. The decision about whether or not to terminate was sometimes complicated by the wide spectrums of presentation associated with the conditions, such as Down syndrome. Similarly, concerns about, or experiences of, miscarriage were also central to testing decisions, particularly for conditions like Edwards syndrome or Patau syndrome where there were higher chances of not carrying to term. Women who terminated pregnancies for medical reasons or

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those who experienced a miscarriage (or stillbirth) described them as bereavements involving mourning and adjustment.

Individuals who received positive screening result frequently recalled the exact moment of 'getting the phone call' which first alerted them to the finding, and some held onto the hope that the screen was a false positive. 'Getting the phone call' was often followed up by considering one's family history and looking online or for other sources of information. Medical histories and notes might be accessed. Participants stressed how communication could drastically alter their experience of receiving this result, depending on what was said, how and by whom. Good communication was essential since the science behind screening, genetics and probability was constructed as mystifying. While people placed their trust in the NHS, this trust could be violated if communication was poor or if they felt misled. The NHS and private non-NHS services were sites of screening and follow-up, while nurseries and schools influenced how children living with screened-for conditions might learn and grow.

Temporal elements related to antenatal and newborn screening

Temporality was an important category related to antenatal and newborn screening. Within screening stories, the timing and journey to pregnancy were important factors. Some pregnancies were unintended; in these circumstances, antenatal screening was considered alongside decisions about proceeding with pregnancy overall. Other people spent months or years trying to conceive. These individuals had more time to think about pregnancy, screening and parenthood. Besides the timing of the pregnancy itself, it is important to consider overall the reproductive life course. Individuals bring their experiences with fertility, pregnancy, contraception, disability, health and relationships to their screening narratives. The moment of having blood drawn, or an ultrasound scan, and experiencing the results does not exist in a vacuum. Rather, the entirety of a person's history over time is implicated.

The timing of screening itself was also important. People discussed antenatal screening moments as pregnancy milestones for themselves and their unborn child. Newborn screening, on the other hand, was seen as a blurred moment in time where the tired parent is adjusting to caring for a baby, potentially for the first time. As a result, it became less of an event, particularly as it was often folded into a consultation with other well-baby checks (e.g. weight gain or feeding). For both antenatal and newborn screening, the period of time between receiving a positive screen result and getting additional (often diagnostic) information was a slowing down of time where hours felt like days and days like years.

For families who receive positive screening results, their feelings about the condition may vary over time. How people feel about the condition varies based on the condition, timing of diagnosis, and decision-making trajectory. For people living with a screened-for condition, or their carers, the cumulative effects of a diagnosis – the emotional, social, financial and physical toll – were important discussion points. These cumulative effects intersect with knowledge of historical eugenic practices in the past, which some contend continue into the present. People living with screened-for conditions, and their carers, also have to think about when it might be appropriate to disclose their diagnosis to others; a decision, which varies, again based on the condition and the nature of the relationship. This can be complicated by the future uncertainty over what an individual's future with the condition might look like.

Spatial elements related to antenatal and newborn screening

When it came to spatial elements, the data included many references to the sites of antenatal and newborn screening tests. People considered how rooms looked, noting that 'nicer' rooms were the ones where 'bad' news might be received. People also discussed how prior experiences in a particular room, unit or hospital, such as being told of a miscarriage, could haunt them in subsequent visits to the same place. These feelings held for sites of specialist intervention, such as neonatal intensive care units, the availability of which depended on location. Our data also touched on the need to travel to and from healthcare settings; the ease of travel depended on individual's geographic location, employment circumstances, financial resources, health (physical and mental), and caring responsibilities. The need to travel intersected with recognised local and regional variations in care. Differences in medical practices,

facilities and expertise were consistently referenced as important to the outcomes of antenatal and newborn screening. Further, international differences in approaches to screening and health care were referenced. The data mentioned the more liberal approaches to screening as performed in other countries, primarily other European nations or the USA, but also the benefits of free (at point of access) healthcare that is available in the UK but not in other countries.

Sociocultural elements related to antenatal and newborn screening

The secondary analysis revealed a range of recurring sociocultural elements related to antenatal and newborn screening. Much of the data reflected traditional gendered caring practices. Pregnant women and mothers of newborns were constructed as having heightened responsibility for reproduction – as needing to reduce working hours, manage the household and do the emotional work of being a (potential) parent. Male partners, on the other hand, were constructed as being less involved with pregnancy, including understanding the intricacies of screening, although they might provide 'strong but silent' emotional support. Regardless of gender, parents were constructed as accepting of making sacrifices for their pregnancy or child, wanting to provide the 'best'. However, there were varying interpretations of what the 'best' was; for some it was having all possible screening or diagnostic tests, for others it was declining what was offered.

In addition to gender and parenting, religious practices were also important to people on their screening journeys. While religious beliefs can affect how an individual approaches medical care, in the data it most often came up related to beliefs around termination or coping with loss. Similarly, the data indicated the importance of ethnicity as part of the antenatal or newborn screening experience. Ethnicity was implicated in discussions of an individual's chance of having a condition or being a carrier. The data held numerous references of people saying they were (not) likely to have a condition because they were (not) of a certain ethnic background. Ethnicity intersects with the practice of arranged marriages. While not common among those of white-European descent, arranged marriage continues to be practised among certain ethnic groups, including (but not limited to) people of Indian, Japanese and Pakistani descent. Arranged marriages take place in communities that have higher rates of carriers for certain conditions, such as sickle cell and thalassaemia. Participants discussed the importance of knowing one's carrier status prior to such arranged marriages in order to prevent passing conditions on to their unborn children.

Economic elements related to antenatal and newborn screening

Our situational mapping exercise revealed personal, organisational and structural economic elements related to antenatal and newborn screening. Personal financial and employment resources dictated whether or not individuals could afford or access private healthcare coverage to bypass or supplement what was available on the NHS. Additionally, greater financial resources could make travel, time off work, or caring for a child with a condition more feasible. From an organisational standpoint, much was made of the role of charities in providing essential information and support for people receiving unexpected screening news, yet the ability of charities to provide services is directly related to the financial and other resources they may have.

Our data regularly implicated the NHS infrastructure and practices, which are dependent on funding and other limited resources – including the number of HCPs. Related to screening, the structure of the NHS influences the amount of time people have with HCPs to ask questions, the availability of specialists to provide care and the types of treatments available. In some cases, people may consider private healthcare options. Typically, this meant paying for additional scans beyond the standard dating and anomaly scans, or paying for NIPT. While the NHS is dependent on government funding decisions, so too are medical and scientific researchers who often depend on grant dispensing organisations (e.g. NIHR) to drive forward screening and treatment innovations. Finally, while private pharmaceutical companies may not compete for government funding, they are also part of this landscape. These companies sell technologies and treatments related to screened-for conditions then reinvest the profits to continue development and production activities.

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Related discourses and debates surrounding antenatal and newborn screening

There were several larger discourses and debates related to screening. These include conversations about the rapidly expanding genetic and genomic technologies and the role of screening. The UK NSC currently has a more conservative set of criteria than other countries; they take into account the condition, the test, the intervention and available scientific evidence. As other countries expand their screening programmes, it is easy to imagine that pressure will correspondingly continue to mount to do so in the UK, especially as new treatments become available and methods of delivering screening (e.g. whole genome sequencing) expand. The debate about the role of screening intersects with conversations about what it means to live a 'quality life' and how people conceptualise (dis)ability. Within the data, these perceptions seem to be heavily based on individuals' (lack of) first-hand experiences with conditions. However, these conversations continue to be a source of debate within society.

Antenatal screening also comes with additional caveats that centre on termination. Currently, England, Scotland and Wales allow termination up to 24 weeks of pregnancy, although this limit does not apply if there is a risk to maternal life or if there is evidence of 'serious' fetal anomalies. Termination has long been a contested social arena. Debates position beliefs in women's rights to have bodily autonomy against beliefs about the rights of the (disabled) fetus/baby. These debates continue to shape the personal and social landscape of antenatal screening.

Strengths and limitations of the data set

Our analysis is strengthened by the large number of qualitative interview transcripts included, collected over an extended time frame. These transcripts covered a variety of (non)screened-for conditions and the views of people living with conditions and their family members. While the data set does not represent all conditions, those included are highly diverse, and the data therefore do provide rich insights into the practical and emotional experiences related to a range of screening outcomes from people of different genders, ethnicities and ages.

Discussion

The findings from the secondary analysis demonstrate that conversations about antenatal and newborn screening involve a complicated weaving of individuals, organisations, materials and discourses. By developing a situational map, we were able to identify elements that may (not) be involved in an individual's situation and consider implicated environments that shape the landscape of screening. This was an iterative, reflexive, subjective exercise. Its strength is that we could reduce a large, rich data set into a manageable representation that is not depleted by its simplicity. Instead, we have identified elements that may work in harmony or at cross-purposes, vary over time or space, and are subject to charged societal debates.

The primary output of the secondary analysis was to inform our primary data collection activities (see *Chapter 7*). By compiling the human elements, we generated a list of stakeholders that are central to screening conversations, such as various types of HCPs and charity organisations. Further, the data highlighted that the NSC is an important silent actor that we need to consider moving forward. These pieces of information were confirmed by our PPI and independent oversight committee members. Given the large number of temporal, spatial and discursive elements in our situational map, it also became apparent that our data collection activities with people who had gone through screening needed to solicit comprehensive reproductive histories, not just discuss screening itself. In this way, we could gain a broad understanding of how people consider the benefits and harms of antenatal screening within a larger framework of their lives.

Chapter 7 Work package 2: understanding stakeholders' experiences of screening: a thematic analysis using primary data collection

Introduction

Building on our meta-ethnography (see *Chapter 5*) and secondary analysis (see *Chapter 6*), we conducted a thematic analysis of primary data of stakeholders' screening experiences. We set out to speak with three prominent stakeholder groups that were informed by our analysis in the secondary analysis:

1. people who have made decisions about undertaking antenatal or newborn screening
2. charity and professional stakeholders involved in supporting those undergoing antenatal or newborn screening
3. HCPs involved in delivering antenatal or newborn screening.

We were mindful that this project would cover potentially contentious terrain with groups and individuals that hold strong and sometimes opposing views. We therefore used a variety of data collection methods to allow us to explore how views on screening are socially and culturally shaped without exposing participants to confrontation. We sampled purposively, to include a range of perspectives, both lay and expert, to give voice to these different views. Here we present the methods and findings for each of these subgroups in turn before summarising overarching themes from across the subgroups.

Methods

Ethical considerations

This study was approved by the University of Oxford's Central University Research Ethics Committee (approval R70422) on 22 July 2020 and was carried out in compliance with the research and information governance policies of the University of Oxford. Potential participants were directed to a study website that provided information about the research and AW's contact information. Interested people got in contact and AW sent a participant information sheet that detailed the aims and methods of the study (see *Appendix 8*). Participants had the opportunity to discuss participation with AW before agreeing to take part and gave consent to taking part in an interview or focus group. AW conducted the focus groups, with LH and AM also in attendance to support. AW collected all the interviews. We carefully planned the focus groups around shared experiences in order to minimise the risk of emotional harm, and participants were offered the option of a one-to-one interview if they preferred. All participants were informed that they were under no obligation to take part and could withdraw at any stage of the data collection process until the point of analysis, without questions asked. Each participant was offered a £20 voucher to thank them for their time. All research data have been treated in strict adherence to the General Data Protection Regulation. We have given participants pseudonyms and use those names here. While we have attempted to remove all personally identifiable information from the data, participants were made aware that in some cases – particularly if they are high-profile stakeholders or speaking about a rare condition – full anonymity could not be guaranteed.

Group 1: people who have made decisions about antenatal or newborn screening

This group was made up of people who had decided to use, or not use, antenatal or newborn screening within the past 4 years. Potential participants needed to be 18 years or older and live in the UK. We recruited participants through social media posts, our PPI network, professional contacts and

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paid Facebook advertising. We asked people who were interested in participating to complete a questionnaire to ascertain their experiences with screening and their demographic characteristics. We used this information to purposively sample a variety of people to participate in focus groups about screening experiences. We sought to recruit participants with a range of screening trajectories, including:

- people who declined (aspects of) screening
- people who received false-positive results from screening
- people who terminated a pregnancy for medical reasons following antenatal diagnosis
- people who continued a pregnancy following antenatal diagnosis
- people who experienced miscarriage or stillbirth
- people who received a positive newborn screening result.

We completed six focus groups from February to March 2021 (*n* = 30). We carefully planned the focus groups around shared experiences in order to minimise the risk of emotional harm. For example, we convened a focus group entirely of parents whose children are living with Down syndrome and another entirely with people who were pregnant for the first time. In addition, we reminded participants that they could decline to answer any question and that they were at liberty to leave the focus group at any point without giving a reason. Focus groups took place on a bespoke online platform over two, 1-hour-long sessions that took place several days apart. Each focus group had between three and six participants. For each chat, two or three researchers acted as moderators (AW, LH, AM) and drove the conversation. Our PPI partners helped shaped the focus group questions (see *Appendix 9*). The text from the chat functioned as the data from the focus groups.

After the first focus group session, we asked participants to respond to three fictional screening scenarios on a forum. Scenarios covered: (1) finding out about carrier status, (2) finding out about a positive newborn screening result and (3) finding out there is a high chance of a pregnancy resulting in a trisomy condition. We asked participants to read the scenarios and reflect on what they might be feeling or want to know if this happened to them. Participants could respond at any point between their first focus group chat session and the second chat session. The text from their responses was integrated into our analysis. Our PPI partners helped shaped the fictional scenarios.

We also offered participants who had sensitive or complex experiences the chance to take part in a telephone interview at a time of their choosing instead of participating in a focus group (*n* = 19). Our PPI partners helped shape the interview questions (see *Appendix 9*). AW reminded participants that they could decline to answer questions and end the interview at any point. AW attended to signs of emotional distress and offered to pause or halt interviews when participants became upset. Interviews lasted an average of 66 minutes (range 35–93 minutes). All interviews were audio-recorded and professionally transcribed verbatim.

Group 2: charity and professional stakeholders involved in antenatal or newborn screening

This group was made up of stakeholders involved in supporting those going through screening, or supporting families affected by conditions that can be identified through screening (*n* = 17). It also included people involved in shaping screening policy and practice within the UK. We purposively recruited stakeholder groups who were named in our situational mapping exercise or named by our PPI partners as important. We recruited some stakeholders through personal networking and others through cold e-mailing. AW e-mailed individuals or organisations, provided information about the study, and requested to conduct a 1-hour interview. Interviews took place between February and April 2021 over the telephone or using Microsoft Teams depending on participants' preferences. AW obtained consent to audio-record conversations (see *Appendix 9*). Interviews lasted an average of 60 minutes (range 42–76 minutes). All interviews were professionally transcribed verbatim.

Group 3: healthcare professionals involved in antenatal or newborn screening

We had intended to interview up to 20 HCPs involved in screening, such as midwives, sonographers, obstetricians and genetic counsellors. However, the ongoing pandemic during our recruitment period (spring 2021) meant that HCPs were overworked and had little time or energy to take part. We exhausted multiple recruitment avenues, including personal networks, multiple rounds of social media posts, and advertising with professional colleges and organisations. We managed to generate interest from a small number of midwives over several months but had no other leads as of June 2021.

After discussing within the research team and our independent oversight committee members, we decided that the best course was to conduct a focus group with the midwives who volunteered to take part at the end of June 2021 (n = 4). The purpose of the focus group was to sense-check the themes we had identified in the data collected from groups 1 and 2. AW and LH worked together to compile a discussion guide and met with the midwives for approximately 90 minutes using Microsoft Teams (see *Appendix 9*). Participants had the option of turning their cameras on or off; all opted to keep them on. With participants' permission, we recorded both the video and audio of the meeting. The audio was used to create a transcript. The video was used to confirm the identity of speakers during transcription before being deleted.

Analytical approach

All focus groups and interviews were recorded for transcription and analysis, and anonymised. We used thematic analysis to identify key themes in the data, including the benefits and harms of antenatal and newborn screening.[102,103] AW completed the initial data coding using NVivo12 software. The qualitative team (FB, LH, LL, AM, AW) met several times to discuss the coding progress and develop themes. While the codebook primarily focused on drawing out the benefits and harms of screening, it also captured other additional themes, such as emotional impacts, temporality, consent and information needs. These results are presented below (see *Methods*) but also informed WP3 (see *Chapter 8*).

Results

Group 1: results

We collected data from 49 individuals in total; 30 participated in focus groups and 19 participated in interviews (*Table 12*). Participants were between 24 and 48 years old, with a mean age of 35 years old. While most of our participants were women (reflecting trends observed in other research of screening), we also spoke with nine men about their experiences as current or expectant fathers. The majority of participants lived in England, were married, and had completed at least a bachelor's degree. We made concerted efforts to recruit people from ethnically diverse groups through multiple rounds of targeted recruitment; however, the majority of our participants identified as white. These participants represented a diversity of nationalities – including people who identified as American, English, Irish, Scottish, South African and Welsh – but the study may have been strengthened by those from additional ethnicities. We did our best to build a purposive sample that reflected a range of varying screening pathways from a variety of points of view (*Table 13*). Our data cover a variety of (non)screened-for conditions and the views of people living with conditions and their family members. While the data set does not represent all conditions, those included are highly diverse, and the data therefore do provide rich insights into the practical and emotional experiences related to a range of screening experiences and outcomes. See *Appendix 10* for additional demographic details.

Individuals discuss screening benefits

Participants named a number of screening benefits, namely (see *Report Supplementary Material 3* for supporting quote details):

- Screening may give people information so they can ask questions, consider termination, prepare, and adjust expectations.

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TABLE 12 Group 1: participants' characteristics (*n* = 49)

Pseudonym	Sex	Age	Country	Time since last birth	Household yearly income (£)	Relationship status	Ethnicity	Highest level of education	Data type
Ada	Woman	24	Wales	Between 13 and 18 months	30,000–39,999	Married	White	Sixth form/vocational	Interview
Alexander	Man	41	Wales	Between 2 and 4 years	70,000–79,999	Married	White	Advanced degree	Interview
Aria	Woman	29	England	< 3 months	50,000–59,999	Married	White	Advanced degree	Focus group
Beth	Woman	34	England	Currently pregnant	70,000–79,999	Married	White	Advanced degree	Interview
Daisy	Woman	31	England	Currently pregnant	40,000–49,999	Married	White	Bachelor's degree	Focus group
David	Man	41	Wales	Between 2 and 4 years	70,000–79,999	Married	White	Advanced degree	Focus group
Donna	Woman	36	England	< 3 months	60,000–69,999	Married	White	Bachelor's degree	Interview
Elizabeth	Woman	41	Scotland	Between 2 and 4 years	> 100,000	Married	White	Bachelor's degree	Focus group
Ella	Woman	38	England	Currently pregnant	70,000–79,999	Married	White	Bachelor's degree	Focus group
Elsie	Woman	32	England	Currently pregnant	Not reported	Married	White	Advanced degree	Focus group
Emily	Woman	31	England	Between 19 and 24 months	80,000–89,999	Married	White	Bachelor's degree	Interview
Erin	Woman	32	England	< 3 months	50,000–59,999	Partnered	White	Sixth form/vocational	Interview
Eva	Woman	38	England	Currently pregnant	70,000–79,999	Married	White	Advanced degree	Focus group
Evie	Woman	48	England	Between 2 and 4 years	30,000–39,999	Married	White	Bachelor's degree	Focus group
Florence	Woman	42	England	Between 2 and 4 years	Not reported	Married	White	Sixth form/vocational	Focus group
Hailey	Woman	39	Wales	< 3 months	30,000–39,999	Partnered	White	Bachelor's degree	Interview
Harper	Woman	32	England	Currently pregnant	80,000–89,999	Partnered	White	Advanced degree	Focus group
Heather	Woman	40	England	Between 13 and 18 months	> 100,000	Married	White	Advanced degree	Interview
Imogen	Woman	32	England	Between 4 and 6 months	30,000–39,999	Partnered	White	Advanced degree	Focus group
Isabella	Woman	34	England	< 3 months	70,000–79,999	Married	White	Advanced degree	Focus group
Isla	Woman	34	England	Between 7 and 12 months	> 100,000	Married	White	Advanced degree	Interview
Ivy	Woman	35	England	Between 19 and 24 months	80,000–89,999	Married	White	Bachelor's degree	Focus group
James	Man	32	England	Currently pregnant	70,000–79,999	Married	White	Advanced degree	Focus group
Jessica	Woman	27	England	Currently pregnant	30,000–39,999	Married	White	Bachelor's degree	Interview

Pseudonym	Sex	Age	Country	Time since last birth	Household yearly income (£)	Relationship status	Ethnicity	Highest level of education	Data type
Kelly	Woman	37	Scotland	Between 4 and 6 months	80,000–89,999	Partnered	White	Advanced degree	Interview
Layla	Woman	34	Wales	Between 4 and 6 months	30,000–39,999	Married	White	Advanced degree	Focus group
Lily	Woman	44	England	Between 7 and 12 months	20,000–29,999	Single	White	Sixth form/vocational	Focus group
Luna	Woman	32	Wales	< 3 months	70,000–79,999	Partnered	White	Advanced degree	Focus group
Maisie	Woman	31	England	< 3 months	80,000–89,999	Married	White	Advanced degree	Focus group
Matilda	Woman	31	England	Currently pregnant	90,000–99,999	Partnered	White	Bachelor's degree	Focus group
Maya	Woman	27	England	Currently pregnant	40,000–49,999	Married	White	Bachelor's degree	Focus group
Mia	Woman	42	England	Between 2 and 4 years	Not reported	Married	Asian	Bachelor's degree	Interview
Michael	Man	37	England	< 3 months	30,000–39,999	Married	White	Bachelor's degree	Focus group
Owen	Man	31	England	< 3 months	70,000–79,999	Married	White	Advanced degree	Interview
Phoebe	Woman	32	England	Currently pregnant	> 100,000	Married	White	Advanced degree	Focus group
Poppy	Woman	27	England	Between 7 and 12 months	60,000–69,999	Married	White	Bachelor's degree	Interview
Quinn	Woman	39	England	Between 19 and 24 months	40,000–49,999	Partnered	White	Advanced degree	Interview
Robert	Man	31	England	Currently pregnant	80,000–89,999	Partnered	White	Advanced degree	Focus group
Rosie	Woman	36	England	Between 4 and 6 months	< 20,000	Married	White	Bachelor's degree	Interview
Ruby	Woman	30	England	Currently pregnant	60,000–69,999	Married	White	Bachelor's degree	Focus group
Scarlett	Woman	37	England	Currently pregnant	70,000–79,999	Married	White	Advanced degree	Focus group
Sienna	Woman	27	England	Currently pregnant	30,000–39,999	Married	White	Sixth form/vocational	Focus group
Sophia	Woman	31	England	Between 13 and 18 months	60,000–69,999	Married	White	Bachelor's degree	Focus group
Sophie	Woman	43	England	Between 4 and 6 months	> 100,000	Married	Arab	Advanced degree	Focus group
Thomas	Man	29	England	Between 4 and 6 months	40,000–49,999	Married	White	Advanced degree	Interview
Tim	Man	34	England	Currently pregnant	40,000–49,999	Married	White	Sixth form/vocational	Interview
Vivian	Woman	34	Scotland	Between 19 and 24 months	50,000–59,999	Married	White	Bachelor's degree	Interview
William	Man	42	England	Between 2 and 4 years ago	50,000–59,999	Partnered	White	Bachelor's degree	Focus group
Willow	Woman	40	England	Between 19 and 24 months	30,000–39,999	Married	White	Sixth form/vocational	Focus group

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TABLE 13 Group 1: participants' experiences (*n* = 49)

Description	Number
Women who are currently pregnant	12
Women whose children do not have a known condition	13
Women whose children are living with a condition	11
Women who experienced perinatal loss	4
Men whose partners are currently pregnant	4
Men whose children do not have a known condition	4
Men whose children are living with a condition	1

- Screening may give reassurance.
- Screening allows people to connect with their pregnancy.
- Screening may prevent harm (includes treatment).
- Screening tests work and are done for a reason.
- Screening is free at point of service.
- Screening enables people to learn about conditions.

Across focus groups and interviews, the ability to get information was the most consistently referenced benefit of antenatal and newborn screening, reflecting a wide cultural belief that knowledge is power. Participants valued the information so that they could ask questions and consider pathway options. As Quinn (mother to child with rare genetic condition) said, 'What am I going to do from here? Am I going to seek support from somewhere, seek further information?' Participants could potentially use the information to consider if termination was the right choice for them. Elsie (currently pregnant) shared, 'I would have wanted more information and would have to consider termination if I was to have a child with potential health conditions'. Participants discussed using the information to prepare themselves and others to continue a pregnancy with the knowledge that it might (or will) result in the birth of a child with a condition. Florence (mother of child with Down syndrome) touched on this saying, 'I wanted the diagnosis to be able to prepare and learn as much as I could, and prepare my son's & also my children's grandparents'. Finally, the information from screening might also allow people to adjust their pregnancy and/or parenting expectations. Ella (mother, no positive screening results) discussed being 'glad that I had all the available scans and antenatal screenings offered' as it allowed her to 'manage my expectations and plan for the future'.

The second most referenced benefit of antenatal and newborn screening was the reassurance it gave participants. Participants like Elizabeth (mother, no positive screening results) mentioned that 'the screening journey helped me to feel that the pregnancy was more real'. Imogen (mother, no positive screening results) echoed this sentiment, calling screening tests 'milestones' that made her feel reassured that her 'babies were doing okay'. Some participants mentioned being worried through their pregnancies, but that the screens – especially the dating and anomaly scans – helped provide a sense of relief that things were going as expected. Thomas (father, no positive screening results) spoke about the security that screening brought him:

> *The various different checks you have it definitely makes you feel like there is a safety net there, that like a lot of the investigation, the, feeling constantly worried with newborns that there's something desperately wrong with them, and that they're poorly or something, and I think knowing that there are like this series of tests that have been taken that like basically guarantee like, whether that, I think both pre-birth and post-birth, that you know that there is this regular screening, that things that might go wrong have been screened for and picked up give you that additional sense of sort of security. And sort of calms a lot of worries, I think. At least that did for me.*

In addition to the sense of reassurance, another regularly mentioned benefit of antenatal scans was that they allowed participants to connect with their pregnancy. Participants mentioned being able to learn the sex of the fetus/baby as a 'nice little surprise' (Poppy, high chance antenatal screen, child born without condition). William (father, no positive screening results) was one of the few participants who acknowledged that the ultrasound scans may have resulted in unexpected news:

> *To be honest I think both of us actually looked forward to the scans. Even though they were times we could find out really serious news about the baby, we just saw them as an amazing chance to see an image of our child. Probably a bit naïve of us!*

While William called his perspective on scans 'naïve', most participants saw these scans as positive opportunities. Participants appreciated being able to 'connect' with their pregnancy even when they didn't 'feel the baby moving yet' (Harper, currently pregnant). And, seeing the baby and 'hearing his hear was everything' for Lily (mother of child with Down syndrome) when she was 'frightened' about her pregnancy.

In addition to giving information and letting participants connect with their pregnancies, participants also mentioned that screening could prevent harm and possibly save lives. Lily discussed how a prenatal diagnosis of Down syndrome meant 'when my baby was born the specialists were there ready if he needed immediate care'. Emily, whose children were diagnosed with PKU from the heel prick test, discussed how screening would 'maybe not have saved their lives but has you know dramatically enhanced their lives' by giving her early information about her children, paving the way to treatment. As Owen (father of child with unknown condition identified postnatally) said, you can't 'sort it out' if 'you don't look'.

The rhetoric that screening prevents harm aligns closely with another benefit mentioned, namely that screening tests work and are done for a reason. Several participants voiced their support for screening tests because 'you trust in the science and the doctors so they can give you and your child the best care' (Maisie, mother, no positive screening results). As Ada (high-chance pregnancy, termination for medical reasons) said, 'They're not just a tick box exercise'. The benefit is that the screening tests are effective. Moreover, another benefit is that, within the NHS, screening is free at point of service. This means that pregnant women don't need to say 'well I can't afford all these tests' (Kelly, mother, no positive screening results) as, on paper, they should be available for everyone.

The last benefit participants regularly mentioned was that screening allowed them to learn about conditions. As Aria (mother, no positive screening results) said, 'I had never heard of Edwards syndrome so without screening I would never have had to consider my baby could have it, but that is far outweighed by the positives – knowledge is power in my opinion!' The presence of screening programmes mean that people going through screening can learn about what might happen, giving them knowledge they otherwise might not get. Also, as Emily (mother to children with PKU) mentioned, 'learning about different conditions that you know that people have to sort of deal with I think gives you a bit more empathy', which was regarded as a good thing.

Individuals discuss screening harms

Participants named a number of screening harms (see *Report Supplementary Material 3* for supporting quote details):

- Standard screening practices do not suit everyone.
- Screening for conditions may imply that high-chance pregnancies should be terminated.
- People may be unprepared for unexpected results.
- Screening may cause emotional distress by introducing anxieties that were not there previously.
- False-positive results may cause residual emotional distress.
- It may be hard for people to understand what they are consenting to.

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- People may not understand that screening tests are not diagnostic tests.
- Communication about results may be unsatisfactory.
- Communication and support for high-chance results may not be appropriate.

Interestingly, participants felt that additional harm is that the harms of screening are not often acknowledged. Poppy (high-chance antenatal screen, child born without condition) said it was 'almost like there's nothing bad's gonna come out of' screening. While Owen (father of child with unknown condition identified postnatally) said, 'As with any screening, there is a potential harm of doing it. I'm not convinced it's acknowledged consistently at least'. Below we give voice to the various harms that participants described.

Participants discussed how standard screening pathways do not suit everyone. As Matilda (currently pregnant) put it, 'I suppose screening in the NHS has to be what is best for most women or most babies but it doesn't always mean that it is right for each of us'. Indeed, some participants pointed out that when they stepped outside of common pathways through screening, they felt that 'it has given people, or might potentially give people, reasons or excuses to find something wrong with my pregnancy or my conduct' (Daisy, currently pregnant). Similarly, there were some participants who felt that screening programme pathways implied that high-chance pregnancies should be terminated. Evie, a mother to a child with Down syndrome, shared:

> *I also agree that there should be openness about why screening happens. It is done with the language of choice but that immediately infers termination. There should be greater clarity about how it is all optional, which most people seem unaware of … To repeatedly offer termination as an option is not offering choice; it is putting pressure on parents who are already perhaps worried or upset about the diagnosis … by providing [this] literature when a diagnosis is given, it is presented as if that is the route it is assumed people are taking.*

Participants, particularly parents of children living with Down syndrome, called into question why antenatal screening programmes exist at all. For them, it seemed as if programmes were in place to discourage births of babies with specific conditions like theirs.

Participants also mentioned that it could be difficult to understand what they were consenting to. Maya (currently pregnant) explained that the 'language they use to label the tests is confusing' and 'there's so many tests you read about that you've never heard of before'. For people like Sienna (currently pregnant), this meant 'I never know what they're testing me for'. Difficulty comprehending the purpose of screening created another harm: people are unprepared for unexpected results. As Imogen (mother, no positive screening results) suggested, 'I would find myself just going along with everything and not prepared at all for bad news'.

Being unaware of tests, or being unprepared for what they might show, contributed to one of the most significant harms, that of emotional distress. Participants repeatedly described how screening caused anxiety and upset that can endure throughout the pregnancy and in subsequent pregnancies. Ella (mother, prior miscarriages) summarised this feeling:

> *Yes and I think once you have had bad news at a scan, or known someone have bad news, it is hard to ever see them in the same way. I cried my way through all scans until I saw a heartbeat, and then the reassurance they gave was only fleeting. I saw them very much as part of a journey, rather than an end point. I remember even when my babies were in my arms as newborns I was worrying about the cystic fibrosis screening on the heel prick for instance.*

The emotional toll of screening may be fleeting for some but linger for others. Residual emotional distress after experiencing a false-positive screening result is another harm. Poppy (high-chance

antenatal screen, child born without condition) explained that she always had the false-negative result 'at the back of (her) mind'. While she doesn't have these thoughts anymore, she worried through the first month 'could there actually still be something wrong with (baby) that they've just not discovered yet?' We discuss the emotional responses to screening further in *Group 1: results*.

Another harm of screening that some participants discussed was that people do not understand that screening tests are not definitive, diagnostic tests. Participants touched on how screening tests can give reassurance, but they are not always accurate. This meant that people could expect one outcome, but actually experience a different one. Or, perhaps, people may have made a decision on incorrect information. Sophie (mother of child with Down syndrome) discussed this:

> *Some of the harms – you could end up making a decision based on information that is constantly changing – e.g. our baby was not expected to live to term, and at any point I could have chosen to terminate based on this information, but in the end the baby was born with no health concerns whatsoever. So what was missing was for the medics to inform me that these scans/tests are not always 100% accurate and that babies are constantly growing and changing, so what they see 1 week might not be there at the next scan.*

The remaining harms centred on communication. Participants discussed how communication about screening results is often lacking. In many cases, we heard about the 'no news is good news' approach to screening where 'communication is lacking' and 'they seem to treat it on a need to know basis' (Scarlett, currently pregnant). As Harper (currently pregnant) said, 'It would be much better if they just let you know everything is okay'. While the lack of communication for negative screening results was deemed harmful, so too was the lack of communication and support for high-chance results. Ruby (currently pregnant, high-chance antenatal results) explained that she was 'blindsided by getting results I didn't even know I was tested for, for a problem I didn't know existed'. Further, there was a feeling that HCPs may not react as desired after receiving screening results. As Isla (mother, no positive screening results) shared, 'They wash their hands of it a little bit, that's it. You do the screening and then there's no follow-up or support'. While there are certainly HCPs who do provide support, the fact that some people receive results without expectation or pastoral care was deemed a significant harm of screening programmes.

Individuals questioning informed choice

With few exceptions, our participants opted to take up all offered screening tests. While accepting screening tests were right for some, our data suggest that women who declined, and therefore differed from the norm, met resistance from professionals. Isabella had declined blood tests for carrier screening and to check for anaemia during the third trimester. Drawing on her additional experience as a midwife, she felt that they were unnecessary for her. Isabella (mother) had also considered declining the newborn blood spot test but ended up accepting. She shared:

> *There is an expectation that you should have these things and I did not want to have to explain myself, so I just consented (to the heel prick) … I had declined other things and found it quite exhausting to keep explaining why I hadn't done the norm. Sometimes people were generally interested but other times just considered me a rebel.*

Isabella's experience helps us understand the subtle pressures and expectations that exist when women are asked to decide whether or not to accept screening tests. Since the tests are offered, people perceive them as important or necessary, and thus it becomes the norm to accept them. As more people accept, the tests become further normalised and more difficult for people, like Isabella, to decline, particularly as it might call into question how 'good' of a parent they are. Thus, some people may wish to decline but ultimately conform, which begs the question of whether screening itself is actually a choice.

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Similarly, our data suggest that participants faced difficulties when it came to receiving information about screening tests, diagnostic tests and screened-for conditions. For example, some participants felt that the information they were given was insufficient for their needs. Lily, whose combined test results indicated a higher chance of Down syndrome, shared: 'They talked about "making an informed decision" but actually you aren't really given helpful information'. Lily, and others whose pregnancies had higher chances of a condition, felt that information was overly medicalised and did not address what it might be like for a person to live with a condition. As a result, Lily sought out additional information from charities, support groups and the internet in order to feel that she was appropriately informed.

At the same time that some participants felt information was insufficient, others felt that there was almost too much information to understand and absorb. The participants reported receiving a cascade of new information, not just about the screening tests but about pregnancy and parenthood itself. It could be overwhelming to try to understand it all, let alone make an informed decision. As Isabella (mother) shared, 'I do not think it is fair to give some women so much info they are just lost and then step back and say "you now need to choose" '. In cases where participants felt overwhelmed by the sheer volume of information, they looked for simplified explanations from trusted sources – particularly peers who had recently been pregnant – before endeavouring to make decisions.

While the prior examples focus on antenatal screening, we also asked participants to reflect on what they knew about newborn screening. Below is an excerpt from a focus group discussion with women who gave birth within the last 6 months:

> *EVIE: I had no idea it was a choice. It's like antenatal blood tests. They are presented as something you do. I don't remember ever being told things were optional (apart from CVS of course).*
> *LILY: I said yes to all tests really as I always feel like it's a good thing they're available.*
>
> *IVY: It felt like something we had to get done. Same as Evie – I had no idea it was a choice.*
>
> *RESEARCHER: Do you all remember being asked for your consent for the heel prick?*
>
> *WILLOW: In a fairly casual way yes.*
>
> *FLORENCE: I'm sure we were, but I don't think it's made crystal clear that it's optional.*
>
> *IVY: No I don't remember giving consent, but it was all a bit of a blur to be honest.*
>
> *EVIE: I was asked for consent but we were in Special Care Baby Unit (SCBU) so there was a lot going on. I just agreed to everything!*
>
> *SOPHIE: I don't remember the heel prick being optional.*
>
> *LILY: It didn't concern me, so perhaps I didn't understand what it was. Maybe I still don't?*

Evie shared she did not know it was a choice, and that newborn screening is something you do. Ivy too said she had no idea it was a choice. We then asked if participants remembered giving consent for the heel prick. Willow said consent was a casual thing, while Florence agreed with earlier statements that it's not crystal clear that it was optional. Ivy did not remember giving consent, and Sophie again reiterated not knowing that it was option. Taken together, this excerpt highlights issues around consent around existing newborn screening programmes that must be considered moving forward.

These examples shed light on the complex informational needs of pregnant women and parents as they go through the screening process. It causes us to question how knowledge is conveyed and understood, and ultimately, how informed people are when presented with decision points. Increasingly, parents and

pregnant women are asked to absorb information about genetics, screening tests, diagnostic tests and then make decisions. This information comes from multiple sources and is presented with varying details and quality. Our data suggest that while women are at the centre of such screening decisions, their so-called 'individual informed choice' is instead one made within potentially partnered relationships, existing family structures, and broader communities. The implications of which may potentially affect the futures of the woman, her pregnancy, her partner, her other children, her extended family and others in her social network.

Individuals discussing the importance of time

While screening tests are presented as discrete events on the timeline, our data suggest that the tests actually have potentially long-reaching ramifications that spill out backwards and forwards in time. We interviewed a mother called Mia. Mia and her partner had tried to become pregnant for several years; she was concerned about the possibility of having a child with a genetic condition because of her age. Mia opted to have the combined test and her results indicated there was a low chance of a genetic condition. Mia had not thought about a diagnostic test because of her screening test results. Her daughter was diagnosed with Down syndrome postnatally. Mia shared,

> *Now, I also know that these tests aren't always accurate as (women) believe they are. They are just screening tests. Unless you have the amniocentesis nothing is accurate … it's so difficult isn't it to say what, say what the right thing is, but I, I do wish we'd had the (diagnostic) test but then I, maybe I would have made a difficult decision.*

While Mia spoke at length about how much she loved her daughter, she couldn't help but wonder what might have been different had she had a diagnostic test. This retrospective conflict continues to be a source of emotional distress that Mia carries with her, generated by and through the very existence of the screening process.

Participants who decided to have antenatal testing and received results that indicated everything was as expected often described their relief. And yet, there was an acknowledgement that the reassurance might be fleeting. Ella, who had no positive screening results, described this phenomenon as, 'I think with all the scans and prenatal testing now it almost gives false reassurance of a clean bill of health/development when of course there are so many issues and conditions that can't be screened for or only emerge later'. Even as antenatal and newborn screening tests seek to rule out possible conditions, they are not sureties. And, as Ella said, they do not guarantee a future without potential unexpected challenges. Indeed, while screening tests might minimise potential concerns in the present, they cannot fully predict how futures might unfold.

Questions still remain about the long-term futures of people living with conditions. Jessica's pre-teen daughter has a rare genetic condition which is not part of the newborn bloodspot test in the UK. She imagined what her daughter's life might be like in the years to come, saying,

> *We don't know how things like pregnancy will affect her. So, I guess it's little things like that where research isn't done. So that's a worry … It's sort of as you hit, as she gets older and starts to become an adult what will happen with the normal things?*

Jessica and other parents of people living with conditions often project forwards to imagine the long-term futures of their children. Among other things, this includes imaging the care their child will need, picturing how their child would perform so-called 'normal' activities, and even their own child's reproductive future imagining how the condition might be passed to future generations. Some conditions have the potential to have far-reaching implications that continue to exist long after they have been discovered, whether through screening or symptomatic diagnosis. One of the inherent difficulties of characterising the impact of screening programmes is that it can be difficult to separate

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concerns and anxieties related to the moment(s) of screening, the waiting periods, and possibly the condition(s) diagnosed.

Individuals facing complex emotional responses

In addition to the aforementioned themes, our data also touched on the complex emotional responses that people may have through their screening journey. For example, we asked participants who did not have lived experience with a condition to imagine their reactions to a positive newborn screening test for that condition. Many stated that, along with anxiety, they expected there would be a bit of relief to have the knowledge. Sienna, who was pregnant, shared, 'I think I would feel very worried, scared and out of my depth but also relieved to know early on'. While information from the newborn screening was valued, the information was connected to feelings of stress, frustration, and panic. This was exacerbated by the knowledge that 'the heel prick tests for some serious conditions' (Imogen, mother, no positive screening results). In order to combat these feelings, participants stated they would want to start learning what they could about a condition:

> *I feel like at the phone call I would be heartbroken and angry and worried and devastated and just in a spiral of worry and sadness … at the diagnosis, I'd feel quite overwhelmed with anxiety, protectiveness and a feeling that I need to rapidly get up to speed with how to look after it. (Elizabeth, mother, no positive screening results)*

While these participants had not gone through the experience of learning that their child tested positive, our data illustrate that there are potentially complex emotional needs that need to be recognised.

These findings of complex and sometimes contradictory emotional reactions were also observed amongst parents with children living with screened-for conditions. Elsie, who has two daughters with PKU, shared that while she had anxiety and fears about antenatal screening, she had never given much thought to the implications of newborn screening, knowing that it was for rare conditions. She went on to describe what it felt like to get the news that her first daughter tested positive, she said,

> *I think just that you have this, and I remember thinking at the time that you have this little tiny little miracle, you know an eight day old, nine day old little baby who you've waited nine months to see, and you've been through it, and I think obviously at the time as well, you're in sort of baby blues of no sleep and exhaustion, and then to be told that your little baby is not well, I mean she is still perfect, but you know at the time it felt like suddenly they had just taken that away. And I remember thinking that they'd taken the joy away of having this newborn. 'Cos we were in our own little dream and bubble of that newborn phase, and then yeah, I think it felt like I'd been hit by a bus a little bit.*

Our data reveal that parents are often unprepared to receive unexpected news about newborn screening results, particularly after not receiving any positive antenatal screening results, and there are very real emotional harms that need to be attended to that may be heightened by the physical and emotional aftermath of birth.

Group 2: results

We interviewed 17 stakeholders about the benefits and harms of antenatal and newborn screening (*Table 14*). We had conversations with people who represented single-condition charities and multiple-condition charities, both screened for and not screened for. We also spoke with people involved in charities with a wider focus around pregnancy or parenthood as well as a number of people involved in policy development (see *Table 14*). We cannot provide further details about our participants because they may become identifiable.

TABLE 14 Stakeholders' characteristics (*n* = 17)

Description	Number
Single-condition charity	6
Multiple-condition charity	3
Wider scope charity	3
Policy stakeholder	5

Charity and professional stakeholder views on the benefits of screening

Stakeholders named a variety of screening benefits (see *Report Supplementary Material 3* for supporting quote details):

- Screening may provide information for people to make informed choices.
- Screening may allow people to make informed decisions about their future reproductive intentions.
- Screening may prevent harm (includes treatment).
- Screening may provide reassurance.
- Screening is free at point of service.

As with the people we interviewed who had experiences with screening, the stakeholders suggested that the most important benefit of screening is the information it gives pregnant women or new parents about their pregnancy or baby. Participants mentioned that antenatal screening may allow people the opportunity to seek a diagnostic test, terminate a pregnancy, continue a pregnancy and prepare for a child with a condition. A stakeholder [9] said,

> *I think what is beneficial is that it allows people to make what's known as informed choice, right. Screening is not there to tell you don't have a baby with [condition]. It's there to give you all the information so that as parents-to-be you are able to make your own choices about whether if you're at risk of having a child with [condition], how you will deal with it, how you might need to care for it. So that's, to me, that's the benefit.*

While information from antenatal screening may lead someone down one of several trajectories, the information from newborn screening was viewed as more straightforward. Namely, newborn screening gives parents information about the health of their newborn. If the child has a condition, then treatment or management can begin. The ability to prevent harm through treatment was one of the other benefits stakeholders regularly mentioned. A stakeholder [4] summarised this point:

> *It is sensible to maintain health and wellbeing as long as possible and your best chance of doing that is by identifying the condition as early as possible and screening is the best way to do that by a long way.*

Stakeholders also mentioned how information from screening may allow people to make informed decisions about their future reproductive intentions. Participants shared that 'it's helpful for families to know that they have the genetic potential to have a child' with a condition because sometimes the 'decision to whether to have a second child' might be 'incredibly difficult' [4]. This information was considered 'a tremendous benefit' [10] for families as they considered what might be best for parents, living children, and potentially extended family members.

Stakeholders drew attention to the fact that, in the UK, screening is provided on the NHS as free at point of service. This means that people with 'rare or very serious health conditions' can be treated by 'one of the world's leading experts' free of charge [2]. Further, the NHS system was seen as one that can provide uniform care where the clinical community has produced 'consensus documents, guidelines, patient information leaflets' about screening and screened-for conditions [4].

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Finally, stakeholders also suggested that screening may provide a sense of reassurance or connect people to their pregnancy. Stakeholders, like the individuals interviewed, suggested that screening was beneficial because it let people know their pregnancy or newborn was as expected. One stakeholder [6] shared,

> *For some women it is you know they, they're utterly grateful and relieved to know that you know they can have screening and you know once they've got you know positive results then they can relax. Then they're going to be okay.*

Stakeholders expressed that finding out screening results were as expected could be a source of reassurance.

Charity and professional stakeholder views on the harms of screening

Interestingly, some stakeholders expressed the idea that a harm of screening can be its absence. These participants mentioned conditions that are currently screened for in other countries but not offered as part of the standardised NHS programmes in the UK. As one stakeholder said, these conditions 'could have, should have been prevented if only [children were] born in France or Germany or America or Singapore' [8]. Another stakeholder went on to say, 'I think the harm from our community's viewpoint is just where we're not screening' [10]. This subset of stakeholders suggested that by not screening for certain conditions, pregnant women or newborns might come to harm. Thus, this is a harm associated with how screening is implemented, and not screening itself.

Regarding screening programmes themselves, stakeholders named a variety of screening harms (see *Report Supplementary Material 3* for supporting quote details):

- Screening may provide unexpected news.
- Screening may lead to devastating emotional impacts.
- It is difficult to achieve fully informed consent.
- Screening may imply pressure to have a termination.
- Communication about screened-for conditions may not be handled well.
- Screening may identify carriers.
- It may be difficult for HCPs to retain specialist knowledge about conditions.

Stakeholders regularly mentioned the emotional toll that screening might have on individuals and families. They mentioned that it could be considered harmful to receive unexpected news from screening. Generally, stakeholders felt that people were 'nowhere near the position of being able to hear' unexpected news [1]. Another stakeholder shared that 'raising the possibility that that child is affected by a lifelong, you know, potentially a lethal condition through a screening test is potentially really, really difficult conversation to have' [4]. The unexpected news and fallout from screening may lead to devastating emotional impacts. Sometimes, 'women will blame themselves' and 'fall into a pit of guilt and shame' [6]. The effect, as one stakeholder [2] shared, can have long-term implications:

> *I think it's very difficult to explain, explain to people just how devastated parents are when they are faced with this sort of information and it leads to the loss of their baby, it completely destroys people's lives, not only in the short term but also in the very long term … it just devastates people and that requires, when you have to make a choice or when you are, you feel you're forced into making a choice about whether your baby lives or dies, that is a choice you have to live with for the rest of your life and all of the questions and things that surround that and that is, yeah, that is one of the hardest things people I think would ever be faced with.*

The emotional harms are exacerbated because of two other potential harms: (1) people may not understand what screening tests are for, and (2) it is difficult to achieve fully informed consent. Stakeholders routinely questioned what people knew about screening. As one participant said, 'I'm just a bit concerned that do people really know what they're screening for? Do they have an idea in

their heads of why this is a good thing and what they might do as a result?' [12]. Similarly, stakeholders discussed that it was difficult for HCPs to ensure informed consent because of the 'amount of information and tasks they have to perform in those initial [pregnancy] booking appointments' [5]. While HCPs might intend to 'have a proper discussion about screening', the fact is that 'various studies have shown that the average length of time that they spend talking about screening is a few minutes. And that probably isn't sufficient' [5]. We discuss the challenges with information provision further in *Charity and professional stakeholder views on the harms of screening*.

Another potential harm of screening stakeholders discussed was that offering screening may imply pressure to have a termination. While stakeholders generally affirmed the right to have a termination, some questioned whether people were making the decision to terminate 'without adequate information and support' [3]. They worried that screening inferred a judgement on 'which lives matter' [12] and suggested that in the future 'there'll be less and less people' with specific conditions [13]. This harm intersects with the harm that communication about screened-for conditions may not be well-handled. Stakeholders mentioned how HCPs might 'talk about anomalies, abnormality, disorder, problem, you know, and all of that has negative connotations and, you know, is prejudicial and it influences a person's perspective' [3]. Poor communication may be exacerbated by the fact that it can be difficult for HCPs to retain specialist knowledge about conditions. While this was considered a harm, it was understandable since HCPs would not be 'seeing cases on a sort of regular basis' [1].

Charity and professional stakeholder discussed information provision challenges

Stakeholders consistently brought up the challenges of providing information about screening programmes and associated conditions (see *Report Supplementary Material 3* for supporting quote details). This discussion was not necessity a benefit or a harm, but rather the articulation of a difficult reality. As one participant stated, the challenge is to 'make sure the information is absolutely correct and up to data, but you also want to make it accessible' [2]. Later in the interview, this participant also reflected on the fact that, while the NHS does provide information, it does not always do so in a way that is accessible. They conclude, the 'NHS tries to provide information on absolutely everything and it can't be good at absolutely everything'. Participants felt that charities played a large role in filling the information and support gap for people who received unexpected news from screening tests.

The difficulty though becomes how to pitch the information so it is accessible, accurate and appropriate. Stakeholders discussed that initial information probably 'has to be quite general and quite superficial' but the information provided when someone gets a higher chance result 'still needs quite a lot of work' [1]. This is complicated by the diversity of families' needs; some 'just wanting to know the very basics' while 'some families would want to know everything' [4]. Participants suggested that it is 'really helpful to be guided by the family's questions' and to 'follow up questions very quickly' [4]. Further, people 'will contact us at various stages' and their information needs may change over the course of their screening journey [5]. HCPs and support organisations recognised a need to be agile in responding to these needs but that 'we have to be pragmatic and realistic' [7]. Indeed, while stakeholders affirmed the right of people to make informed decisions, they drew attention to the point that 'if you wanted a women to be fully informed, you'd have to sit her down and go through a list of all the potential things' which would 'make it a white-knuckle ride for every single woman' [7]. It is a difficult line to walk, especially when 'it's a small percentage that will actually be confronted' with a positive screening result [7].

Group 3: results

We conducted an online focus group with four midwives to sense check the themes derived from people who have experienced screening and other stakeholders. The four women work in different regions in the UK: London, Birmingham, Yorkshire and Belfast. Each had experiences as a midwife involved in screening and two had additional training in sonography. Below we discuss how these participants considered the themes pulled from focus groups and interviews with the other two groups (see *Report Supplementary Material 3* for supporting quote details).

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Midwife focus group participants corroborated that antenatal and newborn screening can be emotionally challenging. Participants reflected that it was their job to sometimes tell 'devastating news'. In these cases, participants recognised it was good practice to ensure that patients 'know your contact details' so they could absorb information and get back in touch as needed. Participants also discussed how these emotionally laden moments with patients stick with them, sometimes for years. As one participant shared, 'that's probably the hardest part of the job'.

Participants also verified that people may feel pressured to accept screening because it was offered. One participant discussed having patients who have declined antenatal screening but have 'gone on to consultant appointments' where 'they are pressured quite a lot' to have had things done. Another participant countered that perhaps patients perceive pressure, but it is 'literally just trying to explain to them what could actually happen'. While participants were quick to affirm the right of anyone to make decisions about screening, they themselves wished that people would take it up, if only to catch any potential conditions or anomalies. In the event that someone does decline screening, one participant shared that it is her job to say 'you have the right to make this choice. And it is my responsibility to make sure that you understand the implications'. This way a patient's wishes are respected, but the midwife leaves feeling like 'I've done the best I can for them'.

Participants spent much of the conversation reflecting on the challenges of providing appropriate information while still maintaining informed choice. Participants mentioned the difficulty of providing comprehensive screening information when pregnant women and their partners are being 'bombarded' with 'the vast amount of information we're giving them at [the booking] appointment'. Participants realise they are 'up against Google' and wish that patients would ask HCPs to put information 'in context' rather than fixating on things that are statistically unlikely. Participants explained that it was difficult to know just how much information to give, saying, 'It's like where do you start and where do you stop?'. They did not want to scare patients but hold that 'a woman should know what she's consenting to'. Ultimately, participants questioned whether sharing all possible outcomes was 'necessary and does it add anything to it? I don't know'. There were no easy answers and participants acknowledged there was not one solution; much depended on how information was delivered and whom it was delivered to.

Summarised benefits and harms across all primary data groups

We have summarised the primary benefits and harms as discussed across our three primary data groups (*Table 15*). The 'X' marks indicate where one of the groups discussed a benefit or harm as primary theme in the data. The empty cells do not necessarily indicate that there was no evidence in our data of a topic, but rather that it was not a prominent theme within our data. While different stakeholders named different benefits and harms, there was a substantial amount of overlap between groups. Consistently named benefits included screening's ability to get information, prevent harm, and provide reassurance. Consistently named harms included possible pressure to have termination, lack of preparation for unexpected results, emotional distress and not understanding what screening tests are for.

Strengths and limitations

This primary qualitative study captured perspectives from a wide range of parents and stakeholders. For the parents we acknowledge that the sample was predominantly white, with two participants from an Asian and Arabic backgrounds. All participants spoke English as that was the only language that the two researchers undertaking data collection spoke and we were not able include funds for translation. However, our focus was on achieving diversity across a number of different domains, including socioeconomic status as well as education level and screening experience. In this, we have achieved a good range. We did not approach private companies/HCPs directly to support with recruitment due to

pandemic restrictions, although we did circulate recruitment notices through social and professional organisations, which could have included private practices. However, people in our sample had made some use of private companies, primarily for additional scans for reassurance or to find out the sex. Only a handful reported they had sought private NIPT. Private companies were not central to where our data led.

Reflexivity

We considered our reflexivity consistently throughout this highly sensitive project and discussed this regularly among the team of experienced post-doctoral qualitative researchers, all of whom are female (AW, LH, FB, AM). The researcher principally collecting the data, AW, is a US citizen and was well positioned as an outsider to the NHS to explore experiences of screening openly. She is a woman of reproductive age and therefore shared on the surface several characteristics with our participants, which could have aided building rapport. She is also experienced at interviewing men about their reproductive health and has found that they often find this topic easier to discuss with a woman. The experience of conducting focus groups and interviews on these sensitive topics was emotionally intense, particularly during COVID-19 lockdowns. The qualitative team undertook regular debriefs to both aid the

TABLE 15 Summary of benefits and harms across all primary data groups (*n* = 70)

Benefits	Individuals	Stakeholders	Midwives
Screening may provide information for people to make informed choices about their current pregnancy or newborn child	X	X	X
Screening may allow people to make informed decisions about their future reproductive intentions		X	
Screening may prevent harm	X	X	X
Screening may connect people to their pregnancy	X		X
Screening may provide reassurance	X	X	X
Screening is free at point of service	X	X	
Screening tests work and are done for a reason	X		X
Screening enables people to learn about conditions	X		
Harms			
Screening harms may not be acknowledged	X		
Normative screening practices do not suit everyone	X		X
Screening may imply pressure to have a termination	X	X	X
It is difficult to achieve fully informed consent	X	X	X
People may be unprepared for unexpected results	X	X	X
Screening may cause emotional distress	X	X	X
Communication and support may be unsatisfactory	X	X	
People may not understand what screening tests are for	X	X	X
Screening may not be implemented presently in the UK		X	
Screening may identify carriers		X	
It may be difficult for HCPs to retain specialist knowledge about conditions		X	

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analysis and provide mutual support to each other. During these debriefs we discussed our individual experiences, characteristics, decisions and attitudes. We were consistently attentive to what we brought into the research and strove to maintain an atmosphere where varying voices and views were respected and heard.

Qualitative study discussion

Every year the NHS offers over a million antenatal and newborn screening tests every year to assess their chances of having or developing a health condition. Pregnant women and parents of babies identified by an antenatal or newborn screening programme receive information and are potentially offered further tests and intervention. While the UK has traditionally adopted a more conservative approach to antenatal and newborn screening compared to other countries, the rapid development of genetic and genomic technologies, and their ability to detect large numbers of conditions simultaneously, has prompted new interest in screening policies. Debates around screening have tended to favour quantitative economic and clinical meta-analyses, with the potential of qualitative research to capture the complexity and nuance of personal experience largely overlooked.[99] Yet, such perspectives are vital in understanding how antenatal and newborn screening programmes are experienced and perceived by those offered such tests.

We conducted three different qualitative studies: a meta-ethnography, a secondary analysis and primary data collection with three different stakeholder groups. While we summarise the consistently named benefits and harms in *Results*, we also identified overarching themes. Each aspect of our qualitative work highlighted concerns over informed consent and the challenges of providing accurate, accessible information while still making clear that screening programmes are a choice for individuals to make. This is complicated by the fact that people come to screening with varying absorptive capacities and information needs.

Our data also highlight the importance of temporal considerations. Screening is not only a clinical moment in time but may also involve critical windows of waiting and receiving results, with backwards, and forwards implications. It is important to consider that people come to screening with a variety of life experiences and may return to screening multiple times throughout their life course. Individuals bring their experiences with fertility, pregnancy, contraception and relationships to their screening narratives. The moment of having blood drawn, or an ultrasound scan done, and experiencing the results does not exist in a vacuum. Rather, the entirety of a person's history over time is implicated.

The lure of expanding genomic technologies to potentially initiate early treatment and ultimately save lives is an appealing narrative of future medical success. However, our data highlight the already complex reality of participation by parents and parents-to-be which would likely be exacerbated by an expansion of screening programmes which may detect a far greater number of conditions, and therefore increase the number of people who receive positive or uncertain screening results. We find that the emotional fallout of receiving unexpected news is amplified when participants are not prepared for the possibility, particularly when they do not recall receiving an explanation about or consenting to the procedures. In the event of unexpected news, charities function as a vital source of information and support for individuals as they try to understand and move forward in the way that seems best for them.

Chapter 8 Work package 3: evidence synthesis

Introduction

We have conducted a systematic review of the benefits and harms considered by antenatal and newborn screening programmes (WP1) and a qualitative study to capture how stakeholders understand and experience screening programmes (WP2). This chapter brings together evidence from both WPs to understand how economic assessment methods and qualitative experiences of the public overlap and diverge in relation to identifying and characterising benefits and harms, ultimately highlighting areas of methodological strengths and limitations.

Methods

The thematically coded data from people who experienced screening (focus groups and interviews) and stakeholders (interviews) in WP2 were mapped onto the completed thematic framework (see *Appendix 6*, *Table 27*) derived in WP1. Our qualitative researcher (AW) reviewed the thematic framework in WP1 and, where possible, summarised the collected qualitative evidence providing illustrative quotes related to each subcategory from all the data available in WP2. LH and FB assisted in reviewing the evidence and refining the mapping exercise. In some cases, the qualitative data collected in WP2 did not cover theme subcategories, and we noted the absence. There were also themes from the qualitative data that could not be easily mapped onto the thematic framework. We have made a note of these and included them in the results below.

Results

The results of this mapping exercise presented as broad themes and first level of subthemes from WP1 and WP2 are summarised in *Table 16*. There were six themes related to antenatal and newborn screening programmes that were unique to WP2. Specific to antenatal screening, WP2 participants consistently discussed 'the importance of information for antenatal screening'. That is, people going through screening valued the information they received. The information allowed them to consider pathways, decisions and futures for themselves and their families. For both antenatal and newborn screening, WP2 participants consistently recognised the 'challenge of information provision to make sure choice is "informed" '. People come to screening with varying absorptive capacities – varying abilities to recognise, assimilate and apply new information – so it is difficult to determine how much information is needed to ensure choices are informed. Not being able to make an informed decision is potentially a harm of screening. The decision to accept or decline screening is further complicated by 'representations of conditions and disability'. Screening for conditions implies that they are concerning, and that a fetus/baby with a condition would potentially be problematic. Similarly, WP2 also found that 'having screening available indicates that it is endorsed/normative'. By offering screening tests, the NHS is endorsing that the tests are worth having. Thus, these tests become the normative standard and people may feel an implied pressure to accept, which is potentially harmful.

Across both antenatal and newborn screening, WP2 also identified broader factors that influence screening experiences, which are not accounted for in current economic assessment methods. It is vital to consider 'the importance of time' in relation to screening. People's experiences will vary based on when screening happens in a person's life (e.g. being 25 vs. being 40 years old), the duration between having a screening test and waiting for results (e.g. 24 hours or 1 week) and the duration between

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TABLE 16 Summarised themes and subtheme level 1 for WP1 and WP2 by screening type

Type	Theme	Subtheme level 1	WP1	WP2
Antenatal	Challenge of information provision to make sure choice is 'informed'		No	Yes
Antenatal	Diagnosis of screened for condition	Additional screening of partners	Yes	Yes
Antenatal	Diagnosis of screened for condition	Additional testing to reach diagnosis in the absence of screening (links to diagnostic odyssey)	Yes	No
Antenatal	Diagnosis of screened for condition	Born with condition	Yes	Yes
Antenatal	Diagnosis of screened for condition	Cases diagnosed at screening	Yes	Yes
Antenatal	Diagnosis of screened for condition	Cases diagnosed at screening rather than later symptomatically	Yes	Yes
Antenatal	Diagnosis of screened for condition	Cases missed at screening	Yes	Yes
Antenatal	Diagnosis of screened for condition	Confirmatory test and additional tests to reach diagnosis of screened for condition	Yes	Yes
Antenatal	Diagnosis of screened for condition	Confirmatory test and additional tests to reach diagnosis of screened for condition [invasive]	Yes	Yes
Antenatal	Having screening available indicates that it is endorsed/normative		No	Yes
Antenatal	Importance of information for antenatal screening		No	Yes
Antenatal	Importance of time		No	Yes
Antenatal	Life-years and health status adjustments	Infant life-years post birth	Yes	Yes
Antenatal	Life-years and health status adjustments	Maternal life-years	Yes	Yes
Antenatal	Life-years and health status adjustments	Psychological	Yes	Yes
Antenatal	Long-term cost associated with screened for condition	Cost savings from averted births of fetuses with anomalies	Yes	Yes
Antenatal	Long-term cost associated with screened for condition	Direct healthcare and non-healthcare cost	Yes	Yes
Antenatal	Long-term cost associated with screened for condition	Direct healthcare cost	Yes	Yes
Antenatal	Long-term cost associated with screened for condition	Direct non-healthcare cost	Yes	Yes
Antenatal	Long-term cost associated with screened for condition	Productivity gains	Yes	Yes
Antenatal	Long-term cost associated with screened for condition	Societal cost	Yes	Yes
Antenatal	Overdiagnosis	QALY decrement	Yes	No
Antenatal	Overdiagnosis	Unnecessary treatment	Yes	No
Antenatal	Pregnancy loss	Spontaneous	Yes	Yes
Antenatal	Pregnancy loss	Termination	Yes	Yes

TABLE 16 Summarised themes and subtheme level 1 for WP1 and WP2 by screening type (*continued*)

Type	Theme	Subtheme level 1	WP1	WP2
Antenatal	Pregnancy loss	Treatment/test related	Yes	Yes
Antenatal	Representations of conditions and disability		No	Yes
Antenatal	Taking a life course approach to screening journey		No	Yes
Antenatal	Treatment	Additional health care post diagnosis	Yes	Yes
Antenatal	Treatment	Comparison of earlier treatment after screen detection	Yes	Yes
Antenatal	Treatment	Comparison of earlier treatment after screen detection and later after symptomatic detection	Yes	Yes
Antenatal	Treatment	Hospital stay	Yes	Yes
Antenatal	Treatment	Missed due to false negative	Yes	Yes
Antenatal	Treatment	Prevention of screened for condition (infectious)	Yes	No
Antenatal	Treatment	Psychological	Yes	Yes
Antenatal	Treatment	Screened for condition-related treatment/management	Yes	Yes
Antenatal	Treatment	Treatment-related harm	Yes	No
Antenatal	Treatment	Unnecessary due to false positive	Yes	No
Newborn	Benefits to parents from child's diagnosis with genetic condition, through knowledge of their own genetic status		Yes	Yes
Newborn	Challenge of information provision to make sure choice is 'informed'		No	Yes
Newborn	Diagnosis of screened for condition	Additional testing to reach diagnosis in the absence of screening (links to diagnostic odyssey)	Yes	Yes
Newborn	Diagnosis of screened for condition	Born with condition	Yes	Yes
Newborn	Diagnosis of screened for condition	Cases diagnosed at screening	Yes	Yes
Newborn	Diagnosis of screened for condition	Cases diagnosed at screening rather than later symptomatically	Yes	Yes
Newborn	Diagnosis of screened for condition	Cases diagnosed at screening that would have become symptomatic	Yes	Yes
Newborn	Diagnosis of screened for condition	Cases missed at screening	Yes	Yes
Newborn	Diagnosis of screened for condition	Confirmatory test and additional tests to reach diagnosis of screened for condition	Yes	Yes
Newborn	Diagnosis of screened for condition	Screened for condition-related complications	Yes	Yes
Newborn	Having screening available indicates that it is endorsed/normative		No	Yes
Newborn	Importance of time		No	Yes

continued

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TABLE 16 Summarised themes and subtheme level 1 for WP1 and WP2 by screening type (*continued*)

Type	Theme	Subtheme level 1	WP1	WP2
Newborn	Life-years and health status adjustments	Infant life-years post birth	Yes	Yes
Newborn	Life-years and health status adjustments	Maternal life-years	Yes	Yes
Newborn	Life-years and health status adjustments	Parental QALYs	Yes	Yes
Newborn	Life-years and health status adjustments	Psychological	Yes	Yes
Newborn	Life-years and health status adjustments	Screened for condition associated mortality/treatment associated mortality/other causes mortality	Yes	Yes
Newborn	Long-term cost associated with screened for condition	Direct healthcare and non-healthcare cost	Yes	Yes
Newborn	Long-term cost associated with screened for condition	Direct healthcare cost	Yes	Yes
Newborn	Long-term cost associated with screened for condition	Direct non-healthcare cost	Yes	Yes
Newborn	Long-term cost associated with screened for condition	Productivity gains	Yes	No
Newborn	Long-term cost associated with screened for condition	Societal cost	Yes	Yes
Newborn	Overdiagnosis	QALY decrement	Yes	No
Newborn	Overdiagnosis	Unnecessary treatment	Yes	No
Newborn	Representations of conditions and disability		No	Yes
Newborn	Taking a life course approach to screening journey		No	Yes
Newborn	Treatment	Additional health care post diagnosis	Yes	Yes
Newborn	Treatment	Comparison of earlier treatment after screen detection	Yes	Yes
Newborn	Treatment	Comparison of earlier treatment after screen detection and later after symptomatic detection	Yes	Yes
Newborn	Treatment	Hospital stay	Yes	Yes
Newborn	Treatment	Screened for condition-related treatment/management	Yes	Yes
Newborn	Treatment	Treatment-related harm	Yes	Yes

unexpected results and follow-up options (e.g. same day, next day, a week). Other important temporal considerations may include the number of weeks gestation (antenatal) or the time child might have before a condition manifests (newborn). Similarly, WP2 highlighted the importance of 'taking a life course approach to the screening journey'. People bring an accumulation of experiences into screening and screening experiences (and potential outcomes) are carried forward.

Discussion

This chapter provides an evidence synthesis drawn from quantitative and qualitative evidence of benefits and harms associated with antenatal and newborn screening. We found a high degree of overlap between the quantitative and qualitative evidence. Notably, however, we identified specific subthemes that had been considered by previous economic assessments but not identified by the qualitative research. Similarly, we identified specific subthemes considered important to stakeholders in our primary data collection, but that had been excluded by previous economic assessments in this field. This overarching evidence synthesis provides a framework that can be used as a springboard for identifying the benefits and harms for inclusion within future economic assessments. The selection of benefits and harms for inclusion in future economic assessments should ultimately be informed by the condition being targeted by screening, and the methodological requirements for economic assessment set by the national screening agency. Where there is a requirement for cost–utility analysis or cost–benefit analysis to inform adoption decisions, the tractability of benefits and harms to valuation using preference-based techniques should additionally inform the selection process.

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Chapter 9 Work package 4: stakeholder workshops

A crucial final element of the VALENTIA research programme involved an assessment of whether and how economic valuation methods can be used to elicit preferences for scenarios of benefits and harms associated with antenatal and newborn screening. The intention here was to provide an early assessment of the feasibility of applying alternative economic valuation methods in future economic assessments of antenatal and newborn screening. This was achieved through two workshops held with patient and public members, which aimed to explore the use of alternative economic (preference-based) techniques to value plausible scenarios of benefits and harms. A separate workshop was held with a broad set of stakeholders to review the findings of the VALENTIA research programme and contribute to a set of recommendations about approaches for the measurement and valuation of outcomes that should be considered by future economic assessments of antenatal and newborn screening, and to highlight areas for future methodological enquiry.

Patient and public members' workshops

Invitations to participate in online workshops were sent to all 29 patient and public members that remained actively engaged with the VALENTIA research programme through to the final quarter of 2021. The invitations specified that the VALENTIA research team was seeking patient and public member perspectives on scenarios involving antenatal and newborn screening. The invitations specified that the workshops would each involve a maximum of six patient and public members and would be held on separate evenings. They were also informed that each online workshop would last for a maximum of 2 hours. A total of 10 out of the 29 patient and public members (34.5%) agreed to participate in the workshops with 6 attending the first workshop and 4 attending the second workshop. The patient and public members were reimbursed for their time following guidance from the NIHR Centre for Engagement and Dissemination. At each online workshop, members of the VALENTIA research team initially provided a brief overview of the VALENTIA study methods and the results of the systematic review, qualitative research and evidence synthesis. The patient and public members were then presented with alternative scenarios of antenatal and newborn screening that were delineated in terms of benefits and harms identified by the thematic framework outlined in *Chapter 8*. The views of the 29 patient and public members were then sought on the feasibility of applying alternative economic (preference-based) techniques to value those scenarios. Discussion at each online workshop was recorded and subsequently transcribed. Additionally, several patient and public members sent separate reflections to the VALENTIA research team via e-mail. The insights presented below are thus a combination of direct quotes from the online workshops and separate feedback from the patient and public members.

Developing scenarios for valuation

To assess the feasibility of applying alternative economic (preference-based) techniques to scenarios of antenatal and newborn screening, we developed two scenarios, one describing a scenario of antenatal screening and the other describing a scenario of newborn screening with each scenario reflecting benefits and harms identified by the thematic framework outlined in *Chapter 8*. It would clearly have been possible to have generated far more scenarios that reflect the permutations of benefits and harms described by the thematic framework. However, increasing the number of scenarios would have added significantly to participant burden. The final scenarios were presented as hypothetical, but nevertheless representative of the types of decisions people might have to make about antenatal or newborn screening.

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The preamble for the antenatal screening scenario asked participants to imagine a hypothetical women named Sophie and her partner Jamie who had been trying to have a baby for 3 years. The preamble for this antenatal screening scenario was presented as follows:

> *Sophie is currently pregnant after having two miscarriages. She had the combined test that showed there was a higher than average chance that Sophie's pregnancy would result in having a baby with an inherited genetic condition. Sophie had an amniocentesis test to see if the blood test was right. Results from the amniocentesis test confirmed that Sophie's pregnancy was affected by this condition. Sophie's doctor explained that pregnancies affected by this condition may end in miscarriage or still birth. The doctor also said that children born with the condition will require specialist care. The doctor says Sophie can work with a team to continue her pregnancy or she can terminate the pregnancy for medical reasons. The doctor tells Sophie about some support organisations and tells her to think about what she wants to do.*

The patient and public members were then presented with seven attributes that characterised this hypothetical antenatal screening scenario: history of prior miscarriages, accuracy of screening test, time to wait for screening test results, the risk of miscarriage associated with the diagnostic test, the psychological/emotional impact of a termination decision on the woman and her partner (Sophie and Jamie), the perceived severity of the diagnosed condition and the parents' ability to make a decision about screening. The potential attributes and levels of those attributes that might influence the antenatal screening decision are presented in *Table 17*.

The preamble for the newborn screening scenario asked participants to imagine a hypothetical newborn baby named Ella. The preamble for the newborn screening scenario framed around a parent's consent to the heel prick test for newborn Ella was presented as follows:

> *Thea has a newborn baby named Ella. Five days after Ella is born a midwife comes to the house. The midwife does a physical examination and asks Thea if she wants Ella to have newborn bloodspot*

TABLE 17 Attributes and levels of hypothetical antenatal screening scenario

Attributes	Levels
History of prior miscarriages	No prior miscarriages 1 prior miscarriage 2 or more prior miscarriages
Accuracy of screening test	90% accurate 95% accurate 99% accurate
Time to wait for screening test results	< 24 hours wait Between 1 and 3 days wait > 3 days wait
Diagnostic test risk of miscarriage	No risk of miscarriage < 1% risk of miscarriage > 1% risk of miscarriage
Psychological/emotional impact of termination decision on woman and her partner	No psychological impact Minor psychological impact Major psychological impact
Perceived severity of diagnosed condition	Condition considered minor Condition considered moderate Condition considered severe
Parents' ability to make a decision	It would be very easy to make a decision It would be easy to make a decision It would be hard to make a decision It would be very hard to make a decision

screening. Sometimes this is called the 'heel prick' test. The midwife explains that newborn blood spot screening involves taking a blood sample to find out if Ella might have one of a range of health conditions. Often, it is too early to tell if Ella might have a health condition any other way. The midwife explains that the blood spot screening is optional. Thea needs to decide what she wants to do.

The patient and public members were then presented with six attributes that characterised this hypothetical newborn screening scenario: age of child when symptoms manifest, timing of start of treatment, the likelihood of success of treatment, perceived severity of diagnosed condition, likelihood of a false-positive result, and likelihood of overdiagnosis. The potential attributes and levels of those attributes that might influence the newborn screening decision are presented in *Table 18*.

Selection of valuation methods

The VALENTIA research team reviewed alternative economic (preference-based) techniques that can be used to value the hypothetical antenatal and newborn screening scenarios described in *Developing scenarios for valuation*. A pool of 10 potential valuation techniques previously used by economists to value healthcare processes was initially identified: allocation of points, analytical hierarchical process, best–worst scaling, contingent valuation, discrete choice experiments, measure of value, person trade-off, rating scale, standard gamble and time trade-off.[104,105] The VALENTIA research team applied a number of criteria to prioritise the valuation techniques that could be applied in the patient and public member workshops. These included broader application of the valuation technique in health economics or healthcare decision-making contexts; foundation of the valuation technique in economic theory; applicability of the technique to the valuation of antenatal and newborn screening scenarios delineated in terms of benefits and harms described by our thematic framework; and practicality of application given the mode and time constraints of the online workshops. Allocation of points, analytical hierarchical process and measure of value were excluded on the basis of limited previous application in health economics or healthcare decision-making contexts. The rating scale approach and its variants were excluded because of disagreement among health economists of their theoretical basis as preference-based techniques.[106] The standard gamble and time trade-off approaches were excluded because of the challenges surrounding the labelling of upper and lower anchors in the context of the hypothetical antenatal and newborn screening scenarios where there is no meaningful risk of death or severe disability. Concerns around the practicality of the number of valuation techniques that could be

TABLE 18 Attributes and levels of hypothetical newborn screening scenario

Characteristic	Levels
Age of child when symptoms manifest	Symptoms develop in infancy Symptoms develop in childhood Symptoms develop in adulthood Symptoms do not manifest
Start of treatment	Treatment begins within a few weeks of birth Treatment begins within the first year of life Treatment begins during childhood
Success of treatment	Treatment will cure the condition Treatment will prevent the condition from getting worse Treatment will slow the worsening of the condition
Perceived severity of diagnosed condition	Condition considered minor Condition considered moderate Condition considered severe
False-positive result	There are many false-positive results There are few false-positive results
Overdiagnosis	There are many infants who are overdiagnosed There are few infants who are overdiagnosed

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applied within the online workshops then led to the selection of best–worst scaling and discrete choice experiments, which had previously been used to value scenarios of antenatal and newborn screening.[107] For both the hypothetical antenatal and newborn screening scenarios, the patient and public members were presented with a best–worst scaling task and a discrete choice experiment task. They were then asked to provide their insights on: (1) whether they were able to imagine the scenario that was being valued and what factors influenced their ability to imagine the scenario; (2) whether they understood each task; (3) their main considerations when attempting to complete the tasks; (4) whether they drew on personal experiences or experiences of their families/friends when completing the tasks; and (5) which valuation method they preferred and why. The best–worst scaling task that related to the hypothetical newborn screening scenario is presented in *Table 19*, while the discrete choice experiment task that related to the hypothetical antenatal screening scenario is presented in *Table 20*.

Insights from patient and public member workshops

When assessing the hypothetical antenatal and newborn screening scenarios that were being valued, participants could generally imagine the scenarios, although for some participants this highlighted the complexity of the screening decisions often made in the antenatal and newborn screening contexts:

> *Yeah. I think it was, in my opinion, easy to put yourself in either scenario and say, yes, that could apply with lots of, obviously, differing factors. But yes.*
>
> *Participant 5*

TABLE 19 Best–worst scaling task that related to the hypothetical newborn screening scenario

Which characteristic you consider best	Alternative	Which characteristic you consider worst
☐	Symptoms develop in infancy	☐
☐	Treatment begins within a few weeks of birth	☐
☐	Treatment will prevent the condition from getting worse	☐
☐	Condition considered minor	☐
☐	There are few false-positive results	☐
☐	There are many infants who are overdiagnosed	☐

TABLE 20 Discrete choice experiment task that related to the hypothetical antenatal screening scenario

Alternative 1	Alternative 2
Two or more prior miscarriages	No prior miscarriages
Screening test 90% accurate	Screening test 99% accurate
Waiting time for screening test results < 24 hours	Waiting time for screening test results > 3 days
No risk of miscarriage following diagnostic test	> 1% risk of miscarriage following diagnostic test
Major psychological impact if pregnancy terminated	Minor psychological impact if pregnancy terminated
Diagnosed condition considered moderate in severity	Diagnosed condition considered moderate in severity
Very easy for parents to make a decision about screening	Hard for parents to make a decision about screening
☐	☐

> *I find it easy enough to imagine myself in each of the scenarios, but I don't think … I don't know if this is what you're after, but for me, it wouldn't have been clear cut what the decision would've been for either [00:31:30] scenario. I don't think that was particularly easy to imagine the outcome, I guess, and how each would progress.*
>
> *Participant 2*

The level of understanding of each valuation task varied between patient and public members with some participants reporting that their level of understanding increased through the course of workshop and clarification provided by members of the VALENTIA research team and other patient and public members:

> *I think the more we've talked about it, the more I've understood it. I don't think I understood it to begin with, but with everybody having a discussion around the pair comparison I'm talking about, mostly. I have to say, I didn't understand it completely to begin with, but now I think I do.*
>
> *Participant 5*

Participants considered a number of factors when attempting to complete the valuation tasks or, at least, expressed a desire for more information on factors that would influence their preference structures. These factors included the background and reproductive history of the hypothetical parents described in the examples, the number of attributes reflected in the tasks, the labelling of adjectives such as 'minor' or 'major', which carried subjective connotations and timing at which a preference elicitation study would be conducted:

> *I think there's maybe additional information about the parents themselves that could be explored a little more, and their history, not just their history with pregnancy, but their history in a wider context.*
>
> *Participant 2*

> *I just was going to just agree with that point really. I found it a bit overwhelming some of the information in the two alternatives. And I agree, a lot of these things are quite hard. Well, take a lot of thought, and maybe just some of the variables, kind of reducing the difference in the number of variables would've been helpful.*
>
> *Participant 6*

> *And one of the things that is constantly asked is this idea of major or minor, and whether your participants understand what that means. Because a major psychological impact will mean something very, very different to different people. And they need to understand the context of what is meant by that and whether that's going to needs to be provided to them before they understand what does it mean? What does a major psychological impact mean?*
>
> *Participant 6*

> *Just quickly also, I guess one of the questions is you might be asking these, giving these surveys at a time that's quite a stress. And I don't know when you're going to give these to parents, for example, it might be quite a stressful time.*
>
> *Participant 6*

Several patient and public members revealed that they drew on their personal experiences or experiences of their families/friends when completing the tasks, perhaps reflecting the composition of the sample that was selected from:

> *But actually, I was pretty clueless in terms of how it did affect me. So this is where my personal experiences come in to definitely influence certain parts of my answer.*
>
> *Participant 4*

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> *I felt like my own experiences and priorities probably came into that quite a lot. But, in terms of kind of empathizing with the person in that situation, I could totally put myself in that context.*
>
> *Participant 9*

Finally, in terms of the two valuation methods that were assessed, there appeared to be a general preference for the best–worst scaling method with several participants describing it as easier to understand and process, although the one participant disputed the 'best' and 'worst' labels in the hypothetical scenarios provided:

> *The paired comparison, I felt, could be quite confusing. Because, the attributes that were there, some of them weren't really comparable. For me, it felt quite challenging to think 'I've got to choose between this one or this one.' Because, I think people value different things in different ways and what might be higher value to someone else is lower value to another.*
>
> *Participant 10*

> *And I really like the best-case, worst-case scenario. It's [inaudible] for me for just ease of understanding, and I could do it whilst sitting somewhere.*
>
> *Participant 6*

> *I have to say, I think the best worst scenarios are … I think the wording is potentially, I don't know, because there's no best scenario, I think, in some of them. So it may be the wording of how it's come across, but it's more easy to understand from my point of view. If that makes sense.*
>
> *Participant 5*

In summary, the patient and public participants in the online workshops highlighted a number of factors that influence their preferences for antenatal and newborn screening scenarios, but generally understood the two preference-based techniques presented. Notably, however, they were not presented with some methods developed by economists, such as contingent valuation, which could plausibly be applied to value scenarios delineated in terms of benefits and harms from our thematic framework (see *Chapter 4*).

Broader stakeholder workshop

A half-day online workshop with a broad set of stakeholders was held in January 2022 to disseminate the findings of the VALENTIA research programme, contribute to a set of recommendations about approaches for the measurement and valuation of outcomes that should be considered by future economic assessments of antenatal and newborn screening, and to highlight areas for future methodological enquiry. Discussion at the workshop was recorded and subsequently transcribed. Members of the VALENTIA research team and the VALENTIA Independent Oversight Committee nominated stakeholders from a breadth of backgrounds with a potential interest in the research and its methodological and policy implications. Snowballing techniques through academic and professional networks were used to widen the pool of individuals that were approached. The initial plan was to recruit a total of 30 individuals to participate in the workshop. A total of 31 stakeholders encompassing healthcare professionals, representatives from relevant academic disciplines, representatives from charities, outreach services and support groups, and representatives from policy-making bodies subsequently participated in the workshop. The workshop followed an overview of the methods and the results of the systematic review, qualitative research and evidence synthesis, and seeking feedback on the thematic framework of benefits and harms outlined in *Chapter 4*. The recommendations presented in the next chapter resulted from a combination of lessons drawn by the VALENTIA research team and feedback provided by the stakeholder group.

Chapter 10 Study recommendations and areas for future research

The VALENTIA research programme aimed to enhance knowledge about methods for valuing the benefits and harms of antenatal and newborn screening within economic assessments and make recommendations about health economic measurement tools that should be applied in this area in the future. The systematic review presented in *Chapter 3* identified health economic assessments that evaluated antenatal and newborn screening programmes in OECD countries over the past two decades. It described the benefits and harms adopted by those health economic assessments. *Chapter 4* presented a thematic framework of benefits and harms adopted by those studies and summarised the benefits and harms into seven core themes. *Chapter 5*–*7* summarise evidence from a body of qualitative research around attributes of relevance to stakeholders that should be considered for incorporation into future economic assessments of antenatal and newborn screening. Specifically, *Chapter 5* describes a systematic review of qualitative studies that focus on parents' experiences of newborn screening. *Chapter 6* reports a secondary analysis of existing qualitative interviews exploring experiences of, and attitudes towards, antenatal and newborn screening, as well as the experience of living with screened-for conditions. *Chapter 7* outlines a thematic analysis of primary data of stakeholders' screening experiences. *Chapter 8* synthesises the evidence extracted from the quantitative and qualitative WPs with the view to describing overlap and divergence between the two strands of evidence. Finally, *Chapter 9* provides an early assessment of the feasibility of applying alternative economic valuation methods in future economic assessments of antenatal and newborn screening. This feasibility work was conducted with patients and members of the public but was supplemented by input from a broad set of stakeholders. Each WP was informed by a PPI advisory group (see *Chapter 2*).

Each chapter of the report outlines the strengths and limitations of the methodological approaches applied, which require consideration when interpreting the results of each constituent element. Notably, we highlight the potential limitations arising from the composition of the PPI group (see *Chapter 2*); restriction of double data extraction to a 10% random sample of the articles and reports identified by the systematic review of economic assessments (see *Chapter 3*); lack of representation of all conditions in the secondary analysis of existing interviews exploring experiences of antenatal and newborn screening (see *Chapter 6*); restriction of primary data collection amongst healthcare professionals aimed at understanding stakeholders' experiences to midwives with the exclusion of input from sonographers, obstetricians and genetic counsellors (see *Chapter 7*); and restriction of valuation methods within the benefit valuation exercises to discrete choice experiments and best worst scaling (see *Chapter 9*).

This chapter presents recommendations for future research, drawing upon evidence from across the VALENTIA programme.

Overarching study recommendations

The VALENTIA study has identified a range of benefits and harms related to antenatal and newborn screening using mixed-methods research that triangulated evidence from a systematic review of economic assessments identified from the published and grey literature and a qualitative study that described the impacts of antenatal and newborn screening of importance to a range of stakeholders.

It is incumbent on researchers designing economic assessments of antenatal and newborn screening to consider the benefits and harms that we have identified that are likely to be of relevance to the research questions they are addressing. The thematic framework presented in *Chapter 4* and the synthesis of evidence presented in *Chapter 8*, and their accompanying appendices, provide a framework that can be used as a springboard for identifying the benefits and harms to consider within partial economic

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assessments, such as discrete choice experiments and best–worst scaling studies designed to elicit preferences for forms of antenatal and newborn screening. Notably, the evidence base we have generated can also be used to inform the benefits and harms that should be included within economic evaluations of antenatal and newborn screening targeted at specific conditions. This identification process should, in turn, inform the appropriate evaluative framework(s) that could be applied. There will be several circumstances where the breadth and nature of benefits and harms identified are likely to preclude the estimation of net health benefits within the QALY paradigm. For example, attributes of relevance to parents, such as the utility derived from information per se or reassurance following a screen-negative test result, and the disutility associated with a false-positive test result or overdiagnosis of disease, are likely to be missed, or at least inadequately covered, by standard approaches to health utility measurement, such as available multi-attribute utility measures (e.g. EQ-5D, SF-6D, HUI Mark 3).[25,26] In these circumstances, we recommend that alternative evaluative frameworks be considered, for example, cost–benefit analysis that provides a framework for valuing disparate benefits and harms in monetary terms, or cost–consequences analysis that provides a framework for disaggregating disparate consequences that might not necessarily be tractable to economic valuation. Methods guidance from screening organisations, such as the UK NSC, should specify the limitations of cost–utility analysis as an evaluative framework from antenatal newborn screening, at least using the approaches to health utility measurement that are currently available, and the circumstances in which alternative evaluate frameworks should be considered.

In the following sections, we outline areas of further research around identification, measurement and valuation of benefits of harms of antenatal and newborn screening that would enhance knowledge in this area.

Future research

Identification of benefits and harms

Our evidence synthesis around benefits and harms related to antenatal and newborn screening was informed by a systematic review of economic assessments identified from the published and grey literature and qualitative research that took the form of a meta-ethnography, a secondary analysis and primary data collection with three different stakeholder groups. As part of our primary data collection, we had intended to interview healthcare professionals from a breadth of healthcare backgrounds involved in antenatal and newborn screening, such as midwives, sonographers, obstetricians, neonatologists, neonatal nurses and genetic counsellors. However, despite multiple approaches through different routes, the ongoing pandemic during our recruitment period (Spring 2021) meant that healthcare professionals were overworked and had little time or energy to take part. This meant that our primary data collection from healthcare professionals was limited to a focus group conducted with four midwives. Clearly, this represents a limitation of our research and primary data collection from healthcare professionals operating at different stages of the screening pathways is likely to offer new perspectives and highlight potential gaps in our synthesis of benefits and harms. Their inclusion would most likely have offered further insight into our synthesis of relevant benefits and harms. Beyond the composition of the stakeholders from which we collected primary data, the topic guides for our focus groups and one-on-one interviews were necessarily constrained by the limited time available for each research contact. Further research around how people's feelings about positive screening results and/or diagnosis change over time after receiving results, and around how people's relationship to screening varies over the reproductive life course, may offer new perspectives on our study outputs.

Measurement of benefits and harms

Economic evaluations of antenatal and newborn screening are constrained by a number of methodological limitations that our research has highlighted. There is a particular need for further research, or methods guidance from screening organisations, in the following areas:

1. Where benefits and harms associated within antenatal screening are synthesised within composite outcome measures such as life-years or QALYs gained or DALYs averted, methods guidance is needed around approaches to aggregating consequences across the mother, fetus or unborn child and potentially other family members. This will clearly be influenced by moral perspectives on the status of the fetus or unborn child with different moral perspectives on when human life commences likely to have a significant impact upon cost effectiveness or cost–benefit estimates.[21,22] Beyond consideration of when to commence 'counting' the life of the fetus or unborn child in the calculus, this still leaves the issues of what weight to place on prenatal time lost or gained compared with postnatal time, and what weights to place on measures of consequence to the fetus or unborn child, the mother and potentially to other family members.
2. Where benefits and harms associated within newborn screening are synthesised within QALY metrics, there is a need for development of patient-reported outcome measures (PROMs) with preference-based value sets validated for use in infancy and across other stages of childhood. A recent system review[108] of generic multidimensional childhood PROMs revealed 17 measures (incorporating two versions each for the HUI2 and HUI3 and two variants of the EQ-5D-Y) designed to be accompanied by preference-based value sets. Notably, only 2 of the 17 measures, the Infant health-related Quality of Life Instrument (IQI)[109] and the Toddler and Infant health-related Quality of Life Instrument (TANDI),[110] have been validated for use during infancy and their preference-based value sets are still under development. No preference-based measure is validated for use across all developmental stages from infancy to adolescence, which constrains the potential for QALY estimation in economic evaluations that extrapolate cost effectiveness over a childhood time horizon or beyond.

Valuation of benefits and harms

Economists have developed several possible methods for valuing antenatal and newborn screening scenarios. Our feasibility work focused on testing the application of discrete choice experiments and best–worst scaling in these contexts. Other valuation methods, such as contingent valuation, could conceivably be applied in these contexts,[111,112] However, the application of such methods will need to be assessed drawing upon the broad sets of benefits and harms that our research has identified. Valuation techniques such as standard gamble and time trade-off approaches are widely used in other areas of health economics to value health states without consideration for non-health outcomes and process attributes. We identified methodological challenges surrounding the labelling of upper and lower anchors within standard gamble and time trade-off tasks aimed at valuing antenatal and newborn screening scenarios that do not contain a meaningful risk of death or severe disability. Research is required to test the application of these approaches in two-stage processes where the first stage is used to value scenarios of benefits and harms that our research has identified, and the second stage is used to score anchors on the full health-immediate death scale. Finally, consideration should be given to the development of methods for weighting disparate consequences of antenatal and newborn screening, drawn from our taxonomy and accompanying qualitative research, within a cost–consequences analysis framework.

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All authors contributed to the report and approved the final version.

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Inclusive language

We use the term 'women' throughout this publication to refer to those who are planning to become pregnant, are pregnant and give birth. We acknowledge that not all people who are pregnant and give birth identify as women, and it is important that evidence-based care for maternity, perinatal and postnatal health is inclusive. These should be taken to include people who do not identify as women but are pregnant or have given birth.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to data may be granted following review of data-sharing applications.

Ethics statement

Ethics approval was received for the studies included in the secondary analysis in *Chapter 6*:

Warwick University studies: Ethical Application Reference: BSREC 105/18-19. Biomedical and Scientific Research Ethics Committee, University of Warwick. 2019.

Oxford University studies: The studies were approved by the Berkshire Research Ethics Committee (12/SC/0495 12/09/2012).

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here [infocompliance@warwick.ac.uk]. Some data included in analysis were collected before the Data Protection Act (2018) and General Data Protection Regulation (EU GDPR) 2016/679 but complied with data protection rules, and ethics requirements, at the time of collection. Data were collected under the legal basis 9(2)j necessary for archiving purposes in public interest, scientific or historical research purposes.

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Appendix 1 List of websites searched

Type	Country	Organisation	Website link
Screening	Australia	Australian COAG Health Council Health Technology Reference Group	www.coaghealthcouncil.gov.au
Screening	Australia	Australian Government Department of Health, Medical Services Advisory Committee	www.msac.gov.au
Screening	Australia	Australian Government Department of Health, Standing Committee on Screening	www.health.gov.au
Screening	Belgium	Belgian Health Care KCE	https://kce.fgov.be/en
Screening	Belgium	Superior Health Council (Hoge Gezondheidsraad/Conseil Supérieur de la Santé)	www.health.belgium.be/en
Screening	Canada	Alberta Health Services	www.albertahealthservices.ca
Screening	Canada	Canadian Task Force on Preventive Health Care	https://canadiantaskforce.ca
Screening	Canada	HQCA	www.hqca.ca
Screening	Canada	Health Quality Ontario	www.hqontario.ca
Screening	Canada	INESSS (formerly AETMIS)	www.inesss.qc.ca/en/index.html
Screening	Canada	Public Health Agency of Canada	www.canada.ca/en.html
Screening	Canada	THETA Collaborative	https://theta.utoronto.ca
Screening	Denmark	National Board of Health (Sundhedsstyrelsen)	www.sst.dk/en/English/Corona-eng
Screening	Finland	NSC, Ministry of Health and Social Affairs (Social- och hälsovårdsministeriet)	http://stm.fi/en/frontpage
Screening	France	Haute Autorité de Santé	www.has-sante.fr/jcms/pprd_2986129/en/home
Screening	Germany	German Institute of Medical Documentation and Information (DIMDI)	www.dimdi.de/dynamic/en/homepage
Screening	Germany	The Federal Joint Committee (Gemeinsamer Bundesausschuss)	www.g-ba.de/english/
Screening	Ireland	HIQA	www.hiqa.ie
Screening	Italy	Osservatorio nazionale screening (National Centre for Screening Monitoring)	www.osservatorionazionalescreening.it
Screening	The Netherlands	The Health Council (Gezondheidsraad)	www.gezondheidsraad.nl
Screening	The Netherlands	Zorginstituut Nederland (National Health Care Institute Netherlands)	www.zorginstituutnederland.nl
Screening	New Zealand	National Screening Advisory Committee, National Screening Unit	www.nsu.govt.nz
Screening	Norway	NIPH	www.fhi.no/en

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Type	Country	Organisation	Website link
Screening	Spain	Instituto de Salud Carlos III (ISCIII)	https://eng.isciii.es/eng.isciii.es/Paginas/Inicio.html
Screening	Spain	Ministry of Health, Social Services and Equality (Ministerio de Sanidad, Servicios Sociales E Igualdad)	www.mscbs.gob.es/en/home.htm
Screening	Sweden	The National Board of Health and Welfare (Socialstyrelsen)	www.socialstyrelsen.se/en/
Screening	UK	Healthcare Improvement Scotland	www.healthcareimprovementscotland.org
Screening	UK	UK NSC	https://legacyscreening.phe.org.uk
Screening	USA	Advisory Committee on Heritable Disorders in Newborns and Children: Bloodspot	www.hrsa.gov/advisory-committees/heritable-disorders
Screening	USA	ACMG	www.acmg.net
Screening	USA	U.S. Preventive Services Task Force	www.uspreventiveservicestaskforce.org
Screening	USA	Washington State HCA	www.hca.wa.gov
Referred to/from initial organisation or experts	Australia	Australian Office of Population Health Genomics	https://ww2.health.wa.gov.au/Home
Referred to/from initial organisation or experts	Australia	Human Genetics Society of Australasia	www.hgsa.org.au/
Referred to/from initial organisation or experts	Canada	Canadian Organization for Rare Disorders	www.raredisorders.ca
Referred to/from initial organisation or experts	Denmark	Danish Statens Serum Institut	https://en.ssi.dk
Referred to/from initial organisation or experts	Finland	Finnish Office for HTA	www.inahta.org
Referred to/from initial organisation or experts	Italy	Società Italiana Studio Malattie Metaboliche Ereditarie (Italian Society for the Study of Hereditary Metabolic Diseases and Neonatal Screening)	www.simmesn.it
Referred to/from initial organisation or experts	Sweden	Karolinska Universitetssjukhuset (Karolinska University Hospital)	www.karolinska.se/en/karolinska-university-hospital
Public organisation	The Netherlands	Rijksinstituut voor Volksgezondheid en Milieu (Dutch National Institute of Public Health and the Environment)	www.rivm.nl/en
Public organisation	Spain	Gobierno de Canarias	www3.gobiernodecanarias.org/sanidad/scs/contenidoGenerico.jsp?idDocument=6e55e15a-02e0-11e5-9e16-d107cd1682ec&idCarpeta=993a9b1d-7aed-11e4-a62a-758e414b4260
Paediatrics organisation	Australia	Paediatrics and Child Health Division, The Royal Australasian College of Physicians (2016–8)	www.racp.edu.au/about/racps-structure/paediatrics-child-health-division
Paediatrics organisation	Austria	Austrian Society of Pediatrics and Adolescent Medicine	www.paediatrie.at/
Paediatrics organisation	Belgium	Belgian Society of Pediatrics	https://bvk-sbp.be
Paediatrics organisation	Canada	CPS	www.cps.ca

Type	Country	Organisation	Website link
Paediatrics organisation	Chile	Sociedad Chilena De Pediatria (Pediatric Society of Chile)	www.sochipe.cl/v3
Paediatrics organisation	Czech Republic	Czech National Pediatric Society	www.pediatrics.cz/en
Paediatrics organisation	Denmark	Dansk Paediatrisk Selskab (Danish Paediatric Society)	www.paediatri.dk
Paediatrics organisation	France	SFP	www.sfpediatrie.com
Paediatrics organisation	Germany	German Society of Pediatrics and Adolescent Medicine (DGKJ)	www.dgkj.de
Paediatrics organisation	Greece	Hellenic Pediatric Society (Greek Pediatric Society)	https://e-child.gr
Paediatrics organisation	Hungary	Hungarian Pediatric Association	www.gyermekorvostarsasag.hu
Paediatrics organisation	Ireland	IPA	www.irishpaediatricassociation.ie
Paediatrics organisation	Israel	Israel Paediatric Association	www.pediatrics.org.il/english
Paediatrics organisation	Italy	Societa Italiana di Pediatria (Italian Society of Pediatrics)	www.sip.it
Paediatrics organisation	Japan	The JPS	www.jpeds.or.jp/modules/en/index.php?content_id=1
Paediatrics organisation	Latvia	Latvian Pediatric Association	www.lpa.lv
Paediatrics organisation	Lithuania	Lithuanian Paediatric Association	www.pediatrija.org
Paediatrics organisation	Mexico	AMP A.C.	www.amp.org.mx
Paediatrics organisation	Mexico	CONAPEME	www.conapeme.org/v2
Paediatrics organisation	The Netherlands	NVK (Paediatric Association of the Netherlands)	www.nvk.nl
Paediatrics organisation	New Zealand	Paediatric Society of New Zealand	www.paediatrics.org.nz
Paediatrics organisation	Norway	Norwegian Pediatric Association	www.legeforeningen.no/foreningsledd/fagmed/norsk-barnelegeforening
Paediatrics organisation	Poland	Polish Pediatric Society	https://ptp.edu.pl
Paediatrics organisation	Portugal	Sociedade Portuguesa de Pediatria (Portuguese Society of Pediatrics)	www.spp.pt
Paediatrics organisation	Slovenia	Slovenian Paediatric Society	https://zzp.si
Paediatrics organisation	South Korea	The Korean Pediatric Society	www.pediatrics.or.kr/english/
Paediatrics organisation	Sweden	Swedish Pediatric Society	www.barnlakarforeningen.se
Paediatrics organisation	Turkey	Turk Pediatri Kurumu (Turkish Pediatric Association)	http://turkpediatri.org.tr
Paediatrics organisation	Turkey	Turkish National Pediatric Society	www.millipediatri.org.tr
Paediatrics organisation	UK	RCPCH	www.rcpch.ac.uk
Paediatrics organisation	USA	APA	www.academicpeds.org
Paediatrics organisation	USA	AAP	www.aap.org
Paediatrics organisation	USA	APS	www.aps1888.org

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Type	Country	Organisation	Website link
Obstetrics and gynaecology organisation	Australia	Royal Australian New Zealand College Obstetricians Gynaecologists	https://ranzcog.edu.au/
Obstetrics and gynaecology organisation	Austria	Oesterreichische Gesellschaft fur Gynakologie und Geburtshilfe Austrian Society Gynaecology Obstetrics	www.oeggg.at/
Obstetrics and gynaecology organisation	Belgium	GGOLFB	www.ggolfb.be
Obstetrics and gynaecology organisation	Belgium	Royal Belgian Society for Obstetrics and Gynaecology (VVOG)	www.vvog.be
Obstetrics and gynaecology organisation	Canada	Society Obstetricians Gynaecologists Canada/Societé des Obstétriciens et Gynécolgues du Canada	www.sogc.org
Obstetrics and gynaecology organisation	Chile	Sociedad Chilena de Obstetricia y Ginecología	https://sochog.cl
Obstetrics and gynaecology organisation	Czech Republic	Czech Gynecological Obstetrical Society	www.cgps.cz/en
Obstetrics and gynaecology organisation	Denmark	Dansk Selskab for Obstetric og Gynaekologi	www.dsog.dk
Obstetrics and gynaecology organisation	Estonia	Society Estonian Gynaecologists	www.ens.ee/en
Obstetrics and gynaecology organisation	Finland	Finnish Gynecological Association	https://gynekologiyhdistys.fi/in-english
Obstetrics and gynaecology organisation	France	Collège National des Gynécologues et Obstétriciens Français	www.cngof.fr
Obstetrics and gynaecology organisation	Germany	Deutsche Gesellschaft für Gynäkologie und Geburtshilfe	www.dggg.de
Obstetrics and gynaecology organisation	Greece	Hellenic Obstetrical Gynaecological Society	http://hsog.gr
Obstetrics and gynaecology organisation	Hungary	Hungarian Society Obstetrics Gynaecology	http://mnt.olo.hu
Obstetrics and gynaecology organisation	Iceland	Icelandic Society Obstetrics Gynecology	www.figo.org
Obstetrics and gynaecology organisation	Ireland	Institute Obstetricians Gynaecologists the Royal College Physicians Ireland	www.rcpi.ie
Obstetrics and gynaecology organisation	Israel	Israel Society Obstetrics Gynecology	https://gynecology.mednet.co.il
Obstetrics and gynaecology organisation	Italy	Società Italiana di Ginecologia e Ostetricia	www.sigo.it
Obstetrics and gynaecology organisation	Japan	Japan Society Obstetrics Gynecology	www.jsog.or.jp/modules/en/index.php?content_id=1
Obstetrics and gynaecology organisation	Lithuania	Lithuanian Association Obstetricians Gynecologists	www.lagd.lt
Obstetrics and gynaecology organisation	Luxembourg	Société Luxembourgeoise de Gynécologie et d'Obstétrique	www.slgo.lu

Type	Country	Organisation	Website link
Obstetrics and gynaecology organisation	Mexico	FEMECOG	https://femecog.org.mx
Obstetrics and gynaecology organisation	The Netherlands	Dutch Society Obstetrics Gynaecology	www.nvog.nl
Obstetrics and gynaecology organisation	Norway	Norsk gynekologisk Forening Norwegian Society for Gynecology Obstetrics	www.legeforeningen.no/foreningsledd/fagmed/norsk-gynekologisk-forening
Obstetrics and gynaecology organisation	Poland	Polish Society Gynecologists Obstetricians.	www.ptgin.pl
Obstetrics and gynaecology organisation	Portugal	FSPOG	www.fspog.com/en
Obstetrics and gynaecology organisation	South Korea	Korean Society Obstetrics Gynecology	www.ksog.org/eng
Obstetrics and gynaecology organisation	Spain	Sociedad Espanõla de Ginecología y Obstetricia	https://sego.es
Obstetrics and gynaecology organisation	Sweden	Svensk Förening För Obstetrik and Gynekologi (Swedish Society of Obstetrics and Gynecology)	www.sfog.se/start
Obstetrics and gynaecology organisation	Switzerland	Schweizerische Gesellschaft für Gynäkologie Geburtshilf/ Société Suisse de Gynécologie and Obstétrique	www.sggg.ch
Obstetrics and gynaecology organisation	Turkey	Turkish Society Obstetrics Gynecology	www.tjod.org
Obstetrics and gynaecology organisation	UK	Royal College Obstetricians Gynaecologists UK	www.rcog.org.uk
Obstetrics and gynaecology organisation	USA	American College Obstetricians Gynecologists	www.acog.org
Medical science organisation	Germany	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (German Association of the Scientific Medical Societies)	www.awmf.org
HTA organisation	Austria	ITA of the Austrian Academy of Sciences	www.oeaw.ac.at/en
HTA organisation	Canada	Alberta Health Evidence Reviews	www.alberta.ca/health-evidence-reviews.aspx
HTA organisation	Canada	CADTH	www.cadth.ca
HTA organisation	Canada	IHE	www.ihe.ca
HTA organisation	Finland	Finnish Office for HTA (Finohta), National Institute for Health and Welfare	https://thl.fi/en/web/thlfi-en
HTA organisation	France	CEDIT	http://cedit.aphp.fr
HTA organisation	Ireland	NCPE Ireland	www.ncpe.ie
HTA organisation	Spain	Galician Agency for HTA (Avalia-T)	http://avalia-t.sergas.es

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Type	Country	Organisation	Website link
HTA organisation	Spain	Health and Quality Assessment Agency of Catalonia (AQuAS)	https://aquas.gencat.cat/ca/sobre_aquas
HTA organisation	Sweden	Sahlgrenska Universitetssjukhuset – HTA-centrum	www.sahlgrenska.se/en
HTA organisation	Sweden	Swedish Agency for HTA and Assessment of Social Services (SBU)	www.sbu.se/en
HTA organisation	UK	NICE	www.nice.org.uk
HTA organisation	UK	NIHR Journals Library – HTA programme	www.journalslibrary.nihr.ac.uk

AAP, American Academy of Pediatrics; ACMG, American College of Medical Genetics and Genomics; AETMIS, Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé; AMP, Asociacion Mexicana de Pediatria; APA, Academic Pediatric Association; APS, American Pediatric Society; AQuAS (in Catalan), Health and Quality Assessment Agency of Catalonia (in English); CADTH, Canadian Agency for Drugs and Technologies in Health; CEDIT, Committee for Evaluation and Dissemination of Innovative Technologies; COAG, Council of Australian Governments; CONAPEME, Confederacin Nacional de Pediatra de Mexico; CPS, Canadian Paediatric Society; DIMDI (in German), German Institute of Medical Documentation and Information (in English),; DGKJ (in German), German Society of Pediatrics and Adolescent Medicine (in English); FEMECOG, Federación Mexicana de Colegios de Obstetricia y Ginecologia; FSPOG, Federação das Sociedades Portuguesas de Obstetricia e Ginecologia; GGOLFB, Groupement des Gynécologues Obstétriciens de Langue Française de Belgique; HCA, Health Care Authority; HIQA, Health Information and Quality Authority; HQCA, Health Quality Council of Alberta; IHE, Institute of Health Economics Alberta Canada; INESSS, Institut national d'excellence en santé et en services sociaux; IPA, Irish Paediatric Association; ISCIII, Institute of Health Carlos III; ITA, Institute of Technology Assessment; JPS, Japan Pediatric Society; KCE, Knowledge Centre; NCPE, National Centre for Pharmacoeconomics; NIPH, Norwegian Institute of Public health; NVK, Nederlandse Vereniging voor Kindergeneeskunde; RCPCH, Royal College of Paediatrics and Child Health; SBU (in Swedish), Swedish Agency for HTA and Assessment of Social Services (in English); SFP, Socit Franaise de Pdiatrie; THETA, Toronto Health Economics and Technology Assessment; VVOG (in Dutch), Royal Belgian Society for Obstetrics and Gynaecology (in English).

Appendix 2 Literature search strategy

TABLE 21 Database MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-process and Other Non-indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present. Search strategy: 22 January 2021

#	Query	Result
1	Ultrasonography, prenatal/	32,214
2	exp Prenatal diagnosis/	74,833
3	(ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echo-cardiogra* or nuchal translucen* or amniocentesis or chorionic villus sampl* or cvs or (((noninvasive prenatal or non-invasive prenatal) adj2 (test* or screen*)) or nipt)).ti,ab.	539,593
4	((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal or pregnant or pregnancy or trimester?) adj3 (screen* or test* or diagnos* or scan* or structural assessment* or structural survey*)).ti,ab.	74,649
5	screen*.ti.	183,100
6	exp Abortion, Induced/	40,453
7	((induced or therap*) adj3 abortion?).ab,kw. or abortion?.ti.	31,275
8	1 or 2 or 3 or 4 or 5 or 6 or 7	831,058
9	exp Congenital Abnormalities/	599,655
10	primary dysautonomias/ or dysautonomia, familial/ or Tay-Sachs Disease/	2826
11	Muscular Atrophy, Spinal/	3883
12	(dysautonomia? or tay sachs).ti,ab,kw.	3951
13	(congenital* adj2 (defect? or malformation? or abnormalit* or anomal* or aneuploid*)).ti,ab.	64,716
14	((fetal or foetal or fetus or foetus) adj2 (defect? or malformation? or abnormalit* or anomal* or aneuploid*)).ti,ab.	10,709
15	((structural or neural tube?) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.	25,396
16	((non-chromosom* or nonchromosom* or chromosom*) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.	24,057
17	(((down* or patau* or edward*) adj2 syndrome*) or trisomy 13 or trisomy 18 or trisomy 21).ti,ab.	28,599
18	spinal muscular atrophy.ti,ab,kw.	5274
19	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	678,982
20	8 and 19	74,766
21	exp Congenital Abnormalities/di, dg	169,523
22	Prenatal Care/ or Perinatal Care/	32,940
23	(fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal or pregnant or pregnancy or trimester?).ti,ab.	781,391
24	22 or 23	788,430
25	21 and 24	23,353

continued

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TABLE 21 Database MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-process and Other Non-indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present. Search strategy: 22 January 2021 (*continued*)

#	Query	Result
26	((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal) adj (screen* or test* or diagnos*)).ti.	16,689
27	20 or 25 or 26	86,726
28	Diabetes, Gestational/ or exp Hypertension, Pregnancy-Induced/	47,602
29	(eclampsia or preeclampsia or pregnancy induced hypertension).ti,ab,kw.	38,775
30	((gestational or pregnan* or maternal) adj2 diabet*).ti,ab,kw.	22,881
31	exp Obstetric Labor, Premature/ or Vasa Previa/ or Placenta Previa/ or Fetal Death/	53,095
32	((preterm or premature) adj2 labo?r).ti,ab,kw.	11,027
33	(f?etal death? or stillbirth? or still birth?).ti,ab,kw.	21,594
34	((placenta or vasa) adj pr?evia).ti,ab,kw.	3849
35	anemia, hemolytic, congenital/ or exp anemia, sickle cell/ or exp thalassemia/	45,108
36	(sickle cell or thalass?emia?).ti,ab,kw.	43,368
37	exp Syphilis/	27,968
38	syphilis.ti,ab,kw.	26,895
39	exp Hepatitis B/	59,076
40	Hepatitis B virus/	27,584
41	(hepatitis b or hbv).ti,ab,kw. or hepatitis.ti.	181,492
42	exp HIV/	100,335
43	exp HIV Infections/	287,519
44	(hiv or human immunodeficiency virus).ti,ab,kw.	339,214
45	exp Chlamydia Infections/ or exp Chlamydia/	25,264
46	chlamydia.ti,ab,kw.	25,588
47	exp Cytomegalovirus Infections/	26,032
48	cytomegalovirus.ti,ab,kw.	43,114
49	exp Streptococcal Infections/	79,648
50	(group b strep or strep b or (streptococc* adj infection?)).ti,ab,kw.	5123
51	exp Parvoviridae Infections/	6086
52	parovirus.ti,ab,kw.	21
53	Rubella/ or Rubella virus/ or Rubella Syndrome, Congenital/	9813
54	rubella.ti,ab,kw.	12,936
55	Toxoplasmosis/ or Toxoplasmosis, Congenital/	13,136
56	toxoplasmosis.ti,ab,kw.	15,606
57	exp Anemia/	162,962
58	exp Blood Group Antigens/	45,846
59	exp Thrombophilia/	25,631
60	thrombophilia?.ti,ab,kw.	6407

TABLE 21 Database MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-process and Other Non-indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present. Search strategy: 22 January 2021 (*continued*)

#	Query	Result
61	an?emia?.ti,ab,kw.	148,777
62	(blood group? or rhd status or rhesus positive or rhesus negative or rhesus status).ti,ab,kw.	23,199
63	exp Urinary Tract Infections/	47,147
64	('urinary tract infection*' or 'urine infection*' or uti or cystitis or bacteriuria).ti,ab,kw.	58,627
65	Vaginosis, Bacterial/	3115
66	vaginosis.ti,ab,kw.	4193
67	domestic violence/ or spouse abuse/	13,326
68	((spous* or intimate partner or domestic) adj2 (violence or abuse)).ti,ab,kw.	14,475
69	or/28-68	1,320,845
70	exp pregnancy/ or pregnant women/	907,431
71	exp fetus/	158,466
72	(pregnan$ or f?etal or f?etus or FVS).ti,ab.	707,872
73	preconception care/ or prenatal care/ or perinatal care/	34,729
74	(pregnan* or preconception* or pre-conception* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or perinatal or maternal or mother*).ti,ab.	875,611
75	70 or 71 or 72 or 73 or 74	1,403,268
76	Mass Screening/	105,761
77	screen*.ti,ab.	786,058
78	exp Population Surveillance/	70,787
79	Self Report/	34,734
80	(selfreport* or self-report* or ((oral or tak*) adj3 history)).ti,ab.	175,659
81	exp Hematologic Tests/ or Diagnostic Tests, Routine/ or Serologic Tests/	285,709
82	((h?ematolog* or blood or serum or serologic*) adj3 (test* or assay*)).ti,ab.	122,020
83	((sero* adj5 (test* or screen* or diagnos*)) or (serotest* or seroscreen* or serodiagnos*)).ti,ab.	54,196
84	exp immunoassays/	490,512
85	Polymerase Chain Reaction/	244,333
86	(immuno-assay* or immunoassay* or elisa or eia or Fluorescent antibody to membrane antibod* or fama or trfia).ti,ab.	239,119
87	(enzyme linked immunosorbent assay* or elisa or enzyme immunoassay* or eia or recombinant immunoblot assay* or riba).ti,ab.	246,491
88	(polymerase chain reaction or pcr).ti,ab.	658,262
89	(routine adj5 (test* or screen* or diagnos*)).ti,ab.	49,621
90	(test* or diagnos* or assay*).ti.	1,117,861
91	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90	3,540,051

continued

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TABLE 21 Database MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-process and Other Non-indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present. Search strategy: 22 January 2021 (*continued*)

#	Query	Result
92	69 and 75 and 91	53,922
93	Prenatal diagnosis/ or maternal serum screening tests/	37,872
94	((pregnan* or preconception* or pre-conception* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or perinatal or maternal or mother*) adj5 (screen* or diagnos* or test*)).ti,ab.	90,463
95	93 or 94	108,115
96	69 and 95	26,099
97	Diabetes, Gestational/di or exp Hypertension, Pregnancy-Induced/di or exp Obstetric Labor, Premature/di or Vasa Previa/di or Placenta Previa/di or Fetal Death/di or anemia, hemolytic, congenital/di or exp anemia, sickle cell/di or exp thalassemia/di	17,294
98	exp Syphilis/di or exp Hepatitis B/di or exp HIV Infections/di or exp Chlamydia Infections/di or exp Cytomegalovirus Infections/di or exp Streptococcal Infections/di or exp Parvoviridae Infections/di or Rubella/di or Rubella Syndrome, Congenital/di or Toxoplasmosis/di or Toxoplasmosis, Congenital/di	75,310
99	exp Anemia/di or exp Blood Group Antigens/di or exp Thrombophilia/di	25,632
100	exp Urinary Tract Infections/di or Vaginosis, Bacterial/di	9057
101	97 or 98 or 99 or 100	120,483
102	75 and 101	26,681
103	92 or 96 or 102	74,483
104	Neonatal Screening/	10,420
105	(heelprick* or heel prick*).ti,ab,kw.	373
106	((neonat* or newborn) adj2 screen*).ti,ab,kw.	11,756
107	exp Infant, Newborn/	616,683
108	(newborn? or neonat* or infant?).ti,ab,kw.	670,401
109	107 or 108	982,857
110	Physical Examination/	41,234
111	(physical adj3 exam*).ti,ab,kw.	74,051
112	Mass screening/	105,761
113	screen*.ti,ab,kw.	789,062
114	Genetic testing/	39,073
115	early diagnosis/	27,345
116	diagnostic tests, routine/	12,791
117	(routine adj5 (test* or diagnos*)).ti,ab,kw.	35,319
118	Serologic Tests/	20,745
119	serologic.ti,ab,kw.	27,433
120	((sero* adj5 diagnos*) or (serotest* or seroscreen* or serodiagnos*)).ti,ab,kw.	23,181
121	Dried Blood Spot Testing/	1569
122	(blood spot* or bloodspot*).ti,ab,kw.	6142
123	exp Hearing Tests/	46,951
124	((hearing or auditor* or acoustic* or otoacoustic*) adj3 (test* or diagnos*)).ti,ab,kw.	12,865

TABLE 21 Database MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-process and Other Non-indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present. Search strategy: 22 January 2021 (*continued*)

#	Query	Result
125	(automated auditory brainstem response? or aabr or otoacoustic emission? or aoae).ti,ab,kw.	5609
126	110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125	1,111,501
127	anemia, hemolytic, congenital/ or anemia, sickle cell/ or exp thalassemia/	43,774
128	(sickle cell or thalass?emia?).ti,ab,kw.	43,368
129	eye diseases/ or eye diseases, hereditary/ or cataract/ or vision disorders/ or exp blindness/	113,166
130	(cataract? or blind* or ((eye? or vision?) adj2 (disease? or disorder?))).ti,ab,kw.	375,117
131	exp Heart Defects, Congenital/	153,550
132	((heart or cardi* or septal or atrial or ventric*) adj2 (defect? or anomal* or malformation?)).ti,ab,kw.	49,837
133	((coarctat* adj2 aorta) or (valv* adj2 stenosis) or 'transdisposition of the great arter*' or patent ductus arteriosus or ebstein* anomal* or 'tetralogy of fallot' or hypoplastic left heart syndrome or tricuspid atresia or truncus arteriosus or anomalous pulmonary venous connection).ti,ab,kw.	34,089
134	Hip Dislocation/	6429
135	(hip? adj2 (dysplasia? or dislocat*)).ti,ab,kw.	7649
136	exp testicular diseases/	39,067
137	(((undescend* or retract*) adj2 testic*) or cryptorchid*).ti,ab,kw.	6394
138	exp Hearing Loss/	70,334
139	((hearing adj2 (loss or disorder?)) or deaf*).ti,ab,kw.	80,587
140	Cystic Fibrosis/	35,889
141	cystic fibrosis.ti,ab,kw.	45,649
142	Congenital Hypothyroidism/	4531
143	congenital hypothyroid*.ti,ab,kw.	3518
144	Biliary Atresia/	3167
145	biliary atresia.ti,ab,kw.	4585
146	exp Genetic Diseases, Inborn/ or exp 'Sex Chromosome Disorders of Sex Development'/	644,292
147	Muscular Dystrophy, Duchenne/ or exp Muscular Atrophy, Spinal/	10,773
148	(phenylketonuria? or medium chain acyl coa dehydrogenase deficien* or medium chain acylcoa dehydrogenase deficien* or mcadd or maple syrup urine disease? or msud or isovaleric acid?emia? or iso-valeric acid?emia? or glutaric aciduria? or homocystinuria? or amino acid metabolism disorder? or biotinidase deficiency or congenital adrenal hyperplasia or duchenne muscular dystrophy or oxidation disorder? or thrombocytop?enia? or galactos?emia? or kernicterus or dehydrogenase deficiency or lchadd or mucopolysaccharidosis or severe combined immunodeficienc* or spinal muscular atrophy or tyrosin?emia? or adrenoleukodystrophy or ccald or canavan or klinefelter syndrome or 22q11 deletion syndrome or digeorge syndrome).ti,ab.	102,379
149	127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148	1,466,960

continued

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#	Query	Result
150	109 and 126 and 149	21,205
151	104 or 105 or 106 or 150	27,708
152	27 or 103 or 151	178,276
153	Economics/	27,280
154	exp 'costs and cost analysis'/	241,793
155	Economics, Dental/	1915
156	exp economics, hospital/	24,905
157	Economics, Medical/	9116
158	Economics, Nursing/	4002
159	Economics, Pharmaceutical/	2969
160	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	840,136
161	(expenditure$ not energy).ti,ab.	31,192
162	value for money.ti,ab.	1799
163	budget$.ti,ab.	30,588
164	'Value of Life'/	5730
165	quality-adjusted life years/	12,795
166	Decision Theory/	943
167	(financ* or fiscal or funding or fee* or charge* or budget*).ti,ab.	1,023,207
168	(value adj2 (money or monetary)).ti,ab.	2520
169	('Value of life' or 'quality adjusted life year*' or qaly* or qald* or qale* or 'disability adjusted life year*' or daly).ti,ab.	19,592
170	(short form* or shortform*).ti,ab.	35,456
171	(sf6* or sf-6* or sf8 or sf-8 or sf10 or sf-10 or sf12 or sf-12 or sf16 or sf-16 or sf20 or sf-20 or sf36 or sf-36).ti,ab.	30,575
172	(euroqol or euro qol or 'euro quality of life' or euroqual or euro qual or eq5d or eq-5d).ti,ab.	12,134
173	(AQoL* or 'Assessment of Quality of Life').ti,ab.	1986
174	('16D Health Related Quality of Life' or 16D HRQoL or '17D Health Related Quality of Life' or 17D HRQoL).ti,ab.	4
175	('Child Health Utility 9 Dimension' or CHU9D or 'CHU-9D').ti,ab.	66
176	15 dimensional instrument.ti,ab.	7
177	('quality of wellbeing*' or 'quality of well being*' or qwb).ti,ab.	486
178	(hye or health* year equivalent*).ti,ab.	64
179	(health utilit* or disutilit*).ti,ab.	2675
180	(hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab.	1600
181	(health* adj2 priorities).ti,ab.	2924
182	(Adolescent Health Utility Measure or AHUM).ti,ab.	3

TABLE 21 Database MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-process and Other Non-indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present. Search strategy: 22 January 2021 (*continued*)

#	Query	Result
183	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab.	11,459
184	'preference based measure of HRQoL'.ti,ab.	2
185	(willingness adj2 pay).ti,ab.	6075
186	standard gamble.ti,ab.	856
187	(time trade off or time tradeoff or tto).ti,ab.	1929
188	(vas or visual analog*).ti,ab.	83,193
189	discrete choice*.ti,ab.	2241
190	(utility elicitation or direct elicitation).ti,ab.	102
191	scoring algorithm.ti,ab.	712
192	best worst scaling.ti,ab.	237
193	(multi attribute utility or multiattribute utility).ti,ab.	306
194	(markov or monte carlo method).ti,ab.	25,785
195	exp Resource Allocation/	17,956
196	Health Priorities/	10,971
197	((multicriteria or multi-criteria) adj2 (decision or analys* or decision aid* or decision making)).ti,ab.	1429
198	(benefit risk asessment or risk benefit assessment).ti,ab.	734
199	weighted product.ti,ab.	22
200	((analytic* hierarchy or analytic* network) adj process*).ti,ab.	1181
201	('measuring attractiveness by a categorical based evaluation technique' or 'goal programming' or 'elimination and choice expressing reality' or ELECTRE or 'preference ranking organization method of enrichment evaluation' or PROMETHEE or 'technique for order preference by similarity to ideal solution' or TOPSIS or 'measuring attractiveness by a categorical based evaluation technique' or MACBETH).ti,ab.	643
202	'Accountability for reasonableness'.ti,ab.	131
203	(decision* adj (tree* or model* or analysis)).ti,ab.	16,329
204	(resource* adj2 (use* or utilisation or allocat*)).ti,ab.	37,159
205	(ration or rationing).ti,ab.	11,346
206	exp Comparative Effectiveness Research/	3673
207	Comparative Effectiveness Research.ti,ab.	1790
208	or/153-207	2,099,102
209	152 and 208	12,338
210	((energy or oxygen) adj cost).ti,ab.	4210
211	(metabolic adj cost).ti,ab.	1476
212	((energy or oxygen) adj expenditure).ti,ab.	25,875
213	210 or 211 or 212	30,566

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#	Query	Result
214	209 not 213	12,335
215	(comment or letter or editorial or historical article).pt.	2,265,941
216	214 not 215	12,003
217	exp animals/ not humans/	4,779,072
218	216 not 217	11,821
219	limit 218 to yr='2000 -Current'	8933
220	(2020* or 2021*).ed,ez,yr.	2,333,538
221	219 and 220	1125

Database EMBASE (OvidSP) 1974 to present

#	Query	Result
1	exp fetus echography/	26,549
2	exp prenatal diagnosis/	110,715
3	(ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or nuchal translucen* or amniocentesis or chorionic villus sampl* or cvs or (((noninvasive prenatal or non-invasive prenatal) adj2 (test* or screen*)) or nipt)).ti,ab.	834,781
4	((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal or pregnant or pregnancy or trimester?) adj3 (screen* or test* or diagnos* or scan* or structural assessment* or structural survey*)).ti,ab.	99,268
5	screen*.ti.	239,563
6	exp induced abortion/	29,297
7	((induced or therap*) adj3 abortion?).ab,kw. or abortion?.ti.	29,267
8	1 or 2 or 3 or 4 or 5 or 6 or 7	1,206,080
9	exp *congenital malformation/ or *congenital disorder/	460,966
10	*dysautonomias/ or *Tay Sachs Disease/	989
11	*spinal muscular atrophy/	4401
12	(dysautonomia? or tay sachs).ti,ab,kw.	5531
13	(congenital* adj2 (defect? or malformation? or abnormalit* or anomal* or aneuploid*)).ti,ab.	83,139
14	((fetal or foetal or fetus or foetus) adj2 (defect? or malformation? or abnormalit* or anomal* or aneuploid*)).ti,ab.	15,887
15	((structural or neural tube?) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.	33,831
16	((non-chromosom* or nonchromosom* or chromosom*) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.	32,975
17	(((down* or patau* or edward*) adj2 syndrome*) or trisomy 13 or trisomy 18 or trisomy 21).ti,ab.	36,445
18	spinal muscular atrophy.ti,ab,kw.	7501

#	Query	Result
19	or/9-18	605,880
20	8 and 19	88,834
21	exp *congenital disorder/di	170,139
22	Prenatal Care/ or Perinatal Care/	54,527
23	(fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal or pregnant or pregnancy or trimester?).ti,ab.	964,183
24	22 or 23	974,555
25	21 and 24	21,664
26	((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal) adj (screen* or test* or diagnos*)).ti.	20,735
27	20 or 25 or 26	108,969
28	*maternal hypertension/ or exp *pregnancy diabetes mellitus/ or exp *'eclampsia and preeclampsia'/	54,333
29	(eclampsia or preeclampsia or pregnancy induced hypertension).ti,ab,kw.	57,146
30	((gestational or pregnan* or maternal) adj2 diabet*).ti,ab,kw.	34,209
31	*premature labor/ or *fetus death/ or *placenta previa/ or *vasa previa/	24,921
32	((preterm or premature) adj2 labo?r).ti,ab,kw.	15,776
33	(f?etal death? or stillbirth? or still birth?).ti,ab,kw.	27,946
34	((placenta or vasa) adj pr?evia).ti,ab,kw.	5095
35	*hereditary hemolytic anemia/ or exp *sickle cell anemia/ or exp *thalassemia/	46,844
36	(sickle cell or thalass?emia?).ti,ab,kw.	59,341
37	exp *Syphilis/	12,446
38	syphilis.ti,ab,kw.	24,347
39	exp *Hepatitis B/	59,048
40	*Hepatitis B virus/	24,060
41	(hepatitis b or hbv).ti,ab,kw. or hepatitis.ti.	242,504
42	exp *Human immunodeficiency virus/	99,310
43	exp *Human immunodeficiency virus infection/	261,668
44	(hiv or human immunodeficiency virus).ti,ab,kw.	434,224
45	*chlamydia trachomatis/ or *chlamydia/	10,817
46	chlamydia.ti,ab,kw.	32,612
47	*Cytomegalovirus Infection/	15,364
48	cytomegalovirus.ti,ab,kw.	53,800
49	*streptococcus infection/ or exp *group b streptococcal infection/	13,442
50	(group b strep or strep b or (streptococc* adj infection?)).ti,ab,kw.	5909
51	exp *Parvovirus Infection/	2617
52	parvovirus.ti,ab,kw.	10,983
53	*Rubella virus/ or *rubella/	6551
54	rubella.ti,ab,kw.	13,206

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#	Query	Result
55	exp *Toxoplasmosis/	13,980
56	toxoplasmosis.ti,ab,kw.	15,765
57	*Anemia/	35,165
58	exp *Blood Group Antigen/	6299
59	exp *Thrombophilia/	4525
60	thrombophilia?.ti,ab,kw.	12,487
61	an?emia?.ti,ab,kw.	212,496
62	(blood group? or rhd status or rhesus positive or rhesus negative or rhesus status).ti,ab,kw.	24,849
63	exp *Urinary Tract Infection/	40,185
64	('urinary tract infection*' or 'urine infection*' or uti or cystitis or bacteriuria).ti,ab,kw.	86,304
65	*Vaginosis/	5104
66	vaginosis.ti,ab,kw.	5890
67	*domestic violence/ or *battered woman/ or *exp partner violence/	6245
68	((spous* or intimate partner or domestic) adj2 (violence or abuse)).ti,ab,kw.	17,475
69	or/28-68	1,407,917
70	exp *pregnancy/ or pregnant woman/	248,097
71	exp *fetus/	22,840
72	(pregnan$ or f?etal or f?etus or FVS).ti,ab.	873,457
73	prepregnancy care/ or prenatal care/ or perinatal care/	56,204
74	(pregnan* or preconception* or pre-conception* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or perinatal or maternal or mother*).ti,ab.	1,082,572
75	70 or 71 or 72 or 73 or 74	1,273,058
76	Mass Screening/ or screening/ or screening test/	302,122
77	screen*.ti,ab.	1,099,879
78	Self Report/	126,013
79	(selfreport* or self-report* or ((oral or tak*) adj3 history)).ti,ab.	236,603
80	exp blood examination/ or diagnostic test/ or serology/	412,389
81	((h?ematolog* or blood or serum or serologic*) adj3 (test* or assay*)).ti,ab.	179,376
82	((sero* adj5 (test* or screen* or diagnos*)) or (serotest* or seroscreen* or serodiagnos*)).ti,ab.	69,144
83	exp *immunoassay/	62,192
84	exp *Polymerase Chain Reaction/	57,101
85	(immuno-assay* or immunoassay* or elisa or eia or Fluorescent antibody to membrane antibod* or fama or trfia).ti,ab.	364,591
86	(enzyme linked immunosorbent assay* or elisa or enzyme immunoassay* or eia or recombinant immunoblot assay* or riba).ti,ab.	362,170
87	(polymerase chain reaction or pcr).ti,ab.	897,453
88	(routine adj5 (test* or screen* or diagnos*)).ti,ab.	74,953
89	(test* or diagnos* or assay*).ti.	1,261,580
90	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89	4,029,117

#	Query	Result
91	69 and 75 and 90	59,357
92	Prenatal diagnosis/ or prenatal screening/	65,586
93	((pregnan* or preconception* or pre-conception* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or maternal or mother*) adj5 (screen* or diagnos* or test*)).ti,ab.	120,372
94	92 or 93	147,539
95	69 and 94	32,614
96	maternal hypertension/di or exp pregnancy diabetes mellitus/di or exp 'eclampsia and preeclampsia'/di or premature labor/di or fetus death/di or placenta previa/di or vasa previa/di	11,080
97	exp Syphilis/di or exp Hepatitis B/di or exp Human immunodeficiency virus infection/di or chlamydia trachomatis/di or chlamydia/di or Cytomegalovirus Infection/di or streptococcus infection/di or exp group b streptococcal infection/di or exp Parvovirus Infection/di or rubella/di or exp Toxoplasmosis/di	61,600
98	Anemia/di or exp Blood Group Antigen/di or exp Thrombophilia/di	8922
99	exp Urinary Tract Infection/di or Vaginosis/di	11,271
100	96 or 97 or 98 or 99	92,192
101	75 and 100	17,938
102	91 or 95 or 101	79,289
103	Newborn Screening/	19,656
104	(heelprick* or heel prick*).ti,ab,kw.	517
105	((neonat* or newborn) adj2 screen*).ti,ab,kw.	18,452
106	Newborn/	539,425
107	(newborn? or neonat* or infant?).ti,ab,kw.	791,794
108	106 or 107	1,009,940
109	exp Physical Examination/	256,612
110	(physical adj3 exam*).ti,ab,kw.	132,154
111	Mass Screening/ or screening/ or screening test/	302,122
112	screen*.ti,ab,kw.	1,114,541
113	Genetic screening/	90,457
114	early diagnosis/	110,269
115	diagnostic test/	79,976
116	(routine adj5 (test* or diagnos*)).ti,ab,kw.	53,921
117	Serology/	75,357
118	serologic.ti,ab,kw.	33,995
119	((sero* adj5 diagnos*) or (serotest* or seroscreen* or serodiagnos*)).ti,ab,kw.	26,940
120	Dried Blood Spot Testing/	4177
121	(blood spot* or bloodspot*).ti,ab,kw.	9565
122	exp Hearing Tests/	46,681
123	((hearing or auditor* or acoustic* or otoacoustic*) adj3 (test* or diagnos*)).ti,ab,kw.	16,131
124	(automated auditory brainstem response? or aabr or otoacoustic emission? or aoae).ti,ab,kw.	6533

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#	Query	Result
125	109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124	1,851,177
126	*hereditary hemolytic anemia/ or exp *sickle cell anemia/ or exp *thalassemia/	46,844
127	(sickle cell or thalass?emia?).ti,ab,kw.	59,341
128	*eye diseases/ or *eye diseases, hereditary/ or *cataract/ or *vision disorders/ or exp *blindness/	55,094
129	(cataract? or blind* or ((eye? or vision?) adj2 (disease? or disorder?))).ti,ab,kw.	518,908
130	*congenital heart disease/ or exp *congenital heart malformation/	93,263
131	((heart or cardi* or septal or atrial or ventric*) adj2 (defect? or anomal* or malformation?)).ti,ab,kw.	67,027
132	((coarctat* adj2 aorta) or (valv* adj2 stenosis) or 'transdisposition of the great arter*' or patent ductus arteriosus or ebstein* anomal* or 'tetralogy of fallot' or hypoplastic left heart syndrome or tricuspid atresia or truncus arteriosus or anomalous pulmonary venous connection).ti,ab,kw.	46,272
133	*hip dysplasia/	3762
134	(hip? adj2 (dysplasia? or dislocat*)).ti,ab,kw.	8501
135	*cryptorchism/	6210
136	(((undescend* or retract*) adj2 testic*) or cryptorchid*).ti,ab,kw.	8073
137	hearing impairment/ or exp congenital deafness/	62,953
138	((hearing adj2 (loss or disorder?)) or deaf*).ti,ab,kw.	94,074
139	*Cystic Fibrosis/	48,582
140	cystic fibrosis.ti,ab,kw.	69,317
141	*Congenital Hypothyroidism/	3789
142	congenital hypothyroid*.ti,ab,kw.	4927
143	*bile duct atresia/	3927
144	biliary atresia.ti,ab,kw.	6796
145	*congenital disorder/ or *DiGeorge syndrome/ or *canavan disease/ or *leukodystrophy/ or *'disorder of sex development'/ or *congenital adrenal hyperplasia/ or *klinefelter syndrome/ or *enzyme deficiency/ or *biotinidase deficiency/ or *medium chain acyl coenzyme a dehydrogenase deficiency/ or *multiple acyl coa dehydrogenase deficiency/ or exp *'inborn error of metabolism'/ or *congenital disorder/ or *maple syrup urine disease/ or *aminoaciduria/ or *phenylketonuria/	206,199
146	*duchenne muscular dystrophy/ or *muscular dystrophy/	19,137
147	(phenylketonuria? or medium chain acyl coa dehydrogenase deficien* or medium chain acylcoa dehydrogenase deficien* or mcadd or maple syrup urine disease? or msud or isovaleric acid?emia? or iso-valeric acid?emia? or glutaric aciduria? or homocystinuria? or amino acid metabolism disorder? or biotinidase deficiency or congenital adrenal hyperplasia or duchenne muscular dystrophy or oxidation disorder? or thrombocytop?enia? or galactos?emia? or kernicterus or dehydrogenase deficiency or lchadd or mucopolysaccharidosis or severe combined immunodeficienc* or spinal muscular atrophy or tyrosin?emia? or adrenoleukodystrophy or ccald or canavan or klinefelter syndrome or 22q11 deletion syndrome or digeorge syndrome).ti,ab.	152,173
148	or/126-147	1,249,017
149	108 and 125 and 148	27,457
150	103 or 104 or 105 or 149	38,434
151	27 or 102 or 150	214,131
152	Health Economics/	33,292
153	exp Economic Evaluation/	314,254

#	Query	Result
154	exp Health Care Cost/	298,571
155	pharmacoeconomics/	7480
156	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	1,098,743
157	(expenditure$ not energy).ti,ab.	42,295
158	value for money.ti,ab.	2489
159	budget$.ti,ab.	40,241
160	quality adjusted life year/	28,123
161	Decision Theory/	1753
162	(financ* or fiscal or funding or fee* or charge* or budget*).ti,ab.	1,235,512
163	(value adj2 (money or monetary)).ti,ab.	3409
164	('Value of life' or 'quality adjusted life year*' or qaly* or qald* or qale* or 'disability adjusted life year*' or daly).ti,ab.	31,384
165	(short form* or shortform*).ti,ab.	48,359
166	(sf6* or sf-6* or sf8 or sf-8 or sf10 or sf-10 or sf12 or sf-12 or sf16 or sf-16 or sf20 or sf-20 or sf36 or sf-36).ti,ab.	50,819
167	(euroqol or euro qol or 'euro quality of life' or euroqual or euro qual or eq5d or eq-5d).ti,ab.	22,332
168	(AQoL* or 'Assessment of Quality of Life').ti,ab.	3225
169	('16D Health Related Quality of Life' or 16D HRQoL or '17D Health Related Quality of Life' or 17D HRQoL).ti,ab.	4
170	('Child Health Utility 9 Dimension' or CHU9D or 'CHU-9D').ti,ab.	90
171	15 dimensional instrument.ti,ab.	7
172	('quality of wellbeing*' or 'quality of well being*' or qwb).ti,ab.	600
173	(hye or health* year equivalent*).ti,ab.	130
174	(health utilit* or disutilit*).ti,ab.	4541
175	(hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab.	2424
176	(health* adj2 priorities).ti,ab.	3389
177	(Adolescent Health Utility Measure or AHUM).ti,ab.	3
178	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab.	15,017
179	'preference based measure of HRQoL'.ti,ab.	3
180	(willingness adj2 pay).ti,ab.	9455
181	standard gamble.ti,ab.	1109
182	(time trade off or time tradeoff or tto).ti,ab.	2856
183	(vas or visual analog*).ti,ab.	126,460
184	discrete choice*.ti,ab.	3208
185	(utility elicitation or direct elicitation).ti,ab.	165
186	scoring algorithm.ti,ab.	1241
187	best worst scaling.ti,ab.	348
188	(multi attribute utility or multiattribute utility).ti,ab.	401

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#	Query	Result
189	(markov or monte carlo method).ti,ab.	32,415
190	Resource Allocation/	21,579
191	Health Priorities/	92,152
192	((multicriteria or multi-criteria) adj2 (decision or analys* or decision aid* or decision making)).ti,ab.	1881
193	(benefit risk asessment or risk benefit assessment).ti,ab.	1009
194	weighted product.ti,ab.	21
195	((analytic* hierarchy or analytic* network) adj process*).ti,ab.	1628
196	('measuring attractiveness by a categorical based evaluation technique' or 'goal programming' or 'elimination and choice expressing reality' or ELECTRE or 'preference ranking organisation method of enrichment evaluation' or PROMETHEE or 'technique for order preference by similarity to ideal solution' or TOPSIS or 'measuring attractiveness by a categorical based evaluation technique' or MACBETH).ti,ab.	808
197	'Accountability for reasonableness'.ti,ab.	146
198	(decision* adj (tree* or model* or analysis)).ti,ab.	23,197
199	(resource* adj2 (use* or utilisation or allocat*)).ti,ab.	50,101
200	(ration or rationing).ti,ab.	13,511
201	Comparative Effectiveness/	96,471
202	Comparative Effectiveness Research.ti,ab.	2494
203	or/152-202	2,846,296
204	151 and 203	18,388
205	((energy or oxygen) adj cost).ti,ab.	4479
206	(metabolic adj cost).ti,ab.	1583
207	((energy or oxygen) adj expenditure).ti,ab.	32,825
208	205 or 206 or 207	37,761
209	204 not 208	18,383
210	(editorial or letter or note).pt.	2,677,181
211	209 not 210	17,760
212	(exp animals/ or nonhuman/) not human/	6,670,870
213	211 not 212	17,491
214	limit 213 to yr='2000 -Current'	15,132
215	(2020* or 2021*).dc,dd,yr.	2,435,504
216	214 and 215	1572

TABLE 22 Database NHS Economic Evaluation Database (via CRDWeb)

Query	Result
(preconcept* or pre-concept* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal or maternal or pregnant or pregnancy or prepregnancy or trimester* or neonat* or newborn*) AND ((screen* or test* or diagnos* or scan* or structural assessment* or structural survey*) OR (Heelprick or heel prick or dried blood spot test* or dried blood spot diagnos*)) – limited to 2000–21	777

TABLE 23 EconLit (Proquest)

#	Query	Result
S1	((preconcept* or pre-concept* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or pregnant or pregnancy or prepregnancy or trimester* or neonat* or newborn*) NEAR/5 (screen* or test* or diagnos* or scan* or 'structural assessment*' or 'structural survey*'))	106
S2	Heelprick OR 'heel prick' OR 'dried blood spot test*' OR 'dried blood spot diagnos*'	0
S3	S1 AND S2	106
S4	S1 and S2 – limited to 2000 onwards	94

TABLE 24 Science Citation Index, Social Science Citation Index and Conference Proceedings Citation Index – Science (Web of Science Core Collection) 1945 to present

#	Query	Result
1	TS=(((preconcept* or pre-concept* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal or pregnant or pregnancy or prepregnancy or trimester* or neonat* or newborn*) NEAR/5 (screen* or test* or diagnos* or scan* or 'structural assessment*' or 'structural survey*'))) OR TS=(Heelprick OR 'heel prick' OR 'dried blood spot test*' OR 'dried blood spot diagnos*')	118,575
2	TS=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*) OR TS=(financ* or fiscal or funding or fee* or charge* or budget*) OR TS=('Value of life' or 'quality adjusted life year*' or qaly* or qald* or qale* or 'disability adjusted life year*' or daly) OR TS=('health utilit*' or disutilit*)	5,191,685
3	#2 AND #1	8016
4	(#2 AND #1) *AND* LANGUAGE: (English)	6999
5	(#2 AND #1) *AND* LANGUAGE: (English) Refined by: [excluding] DOCUMENT TYPES: (EDITORIAL MATERIAL OR REVIEW OR LETTER OR NEWS ITEM OR BOOK CHAPTER) AND PUBLICATION YEARS: (2021 OR 2009 OR 2020 OR 2008 OR 2019 OR 2007 OR 2018 OR 2006 OR 2017 OR 2005 OR 2016 OR 2004 OR 2015 OR 2003 OR 2014 OR 2002 OR 2013 OR 2001 OR 2012 OR 2000 OR 2011 OR 2010)	6019

TABLE 25 CINAHL (EBSCO*host*) 1982 to present (*n* = 3602)

#	Query
S1	(MH 'Prenatal Diagnosis+')
S2	TI ((ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or nuchal translucen* or amniocentesis or chorionic villus sampl* or cvs or (((noninvasive prenatal or non-invasive prenatal) N2 (test* or screen*)) or nipt))) OR AB ((ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or nuchal translucen* or amniocentesis or chorionic villus sampl* or cvs or (((noninvasive prenatal or non-invasive prenatal) N2 (test* or screen*)) or nipt)))
S3	TI (((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal or pregnant or pregnancy or trimester?) N3 (screen* or test* or diagnos* or scan* or structural assessment* or structural survey*))) OR AB (((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal or pregnant or pregnancy or trimester?) N3 (screen* or test* or diagnos* or scan* or structural assessment* or structural survey*)))
S4	TI screen*
S5	(MH 'Abortion, Induced')
S6	AB (((induced or therap*) N3 abortion?)) OR TI abortion*
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6

continued

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TABLE 25 CINAHL (EBSCOhost) 1982 to present (n = 3602) (*continued*)

#	Query
S8	(MH 'Congenital, Hereditary, and Neonatal Diseases and Abnormalities+')
S9	TI ((dysautonomia? or tay sachs)) OR AB ((dysautonomia? or tay sachs))
S10	TI ((congenital* N2 (defect? or malformation? or abnormalit* or anomal* or aneuploid*)).ti,ab.) OR AB ((congenital* N2 (defect? or malformation? or abnormalit* or anomal* or aneuploid*)).ti,ab.) OR TI (((fetal or foetal or fetus or foetus) N2 (defect? or malformation? or abnormalit* or anomal* or aneuploid*))) OR AB (((fetal or foetal or fetus or foetus) N2 (defect? or malformation? or abnormalit* or anomal* or aneuploid*))) OR TI (((structural or neural tube?) N2 (defect? or malformation? or abnormalit* or anomal*))) OR AB (((structural or neural tube?) N2 (defect? or malformation? or abnormalit* or anomal*))) OR TI (((non-chromosom* or nonchromosom* or chromosom*) N2 (defect? or malformation? or abnormalit* or anomal*))) OR AB (((non-chromosom* or nonchromosom* or chromosom*) N2 (defect? or malformation? or abnormalit* or anomal*))) OR TI ((((down* or patau* or edward*) N2 syndrome*) or trisomy 13 or trisomy 18 or trisomy 21)) OR AB ((((down* or patau* or edward*) N2 syndrome*) or trisomy 13 or trisomy 18 or trisomy 21)) OR TI spinal muscular atrophy OR AB spinal muscular atrophy
S11	S8 OR S9 OR S10
S12	S7 AND S11
S13	(MH 'Congenital, Hereditary, and Neonatal Diseases and Abnormalities+/DI/US')
S14	(MH 'Prenatal Care') or (MH 'Perinatal Care')
S15	TI ((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal or pregnant or pregnancy or trimester?)) OR AB ((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal or pregnant or pregnancy or trimester?))
S16	S14 OR S15
S17	S13 AND S16
S18	TI ((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal) N1(screen* or test* or diagnos*))
S19	S12 OR S17 OR S18
S20	(MH 'Diabetes Mellitus, Gestational') OR (MH 'Pregnancy-Induced Hypertension+')
S21	TI ((eclampsia or preeclampsia or pregnancy induced hypertension)) OR AB ((eclampsia or preeclampsia or pregnancy induced hypertension)) OR TI (((gestational or pregnan* or maternal) N2 diabet*)) OR AB (((gestational or pregnan* or maternal) N2 diabet*))
S22	(MH 'Labor, Premature') OR (MH 'Placenta Praevia') OR (MH 'Childbirth, Premature') OR (MH 'Perinatal Death')
S23	TI (((preterm or premature) N2 labo?r)) OR AB (((preterm or premature) N2 labo?r)) OR TI ((f?etal death? or stillbirth? or still birth?)) OR AB ((f?etal death? or stillbirth? or still birth?)) OR TI (((placenta or vasa) adj pr?evia)) OR AB (((placenta or vasa) adj pr?evia))
S24	(MH 'Hemoglobinopathies+')
S25	TI ((sickle cell or thalass?emia?)) OR AB ((sickle cell or thalass?emia?))
S26	(MH 'Syphilis+') OR (MH 'Chlamydia Infections+') OR (MH 'Human Immunodeficiency Virus+') OR (MH 'HIV Infections+') OR (MH 'Cytomegalovirus Infections+') OR (MH 'Hepatitis B+')
S27	TI syphilis OR AB syphilis OR AB ('hepatitis b' or hbv) OR TI hepatitis OR TI (hiv OR 'human immunodeficiency virus') OR AB (hiv OR 'human immunodeficiency virus') OR TI chlamydia OR AB chlamydia OR TI cytomegalovirus OR AB cytomegalovirus
S28	(MH 'Streptococcal Infections+') OR (MH 'Rubella') OR (MH 'Toxoplasmosis+')
S29	TI ((group b strep or strep b or (streptococc* N1 infection?))) OR AB ((group b strep or strep b or (streptococc* N1 infection?))) OR TI parovirus OR AB parovirus OR TI rubella OR AB rubella OR TI toxoplasmosis OR AB toxoplasmosis
S30	(MH 'Anemia')
S31	TI thrombophilia? OR AB thrombophilia? OR TI an?emia? OR AB an?emia? OR TI ((blood group? or rhd status or rhesus positive or rhesus negative or rhesus status)) OR AB ((blood group? or rhd status or rhesus positive or rhesus negative or rhesus status))

TABLE 25 CINAHL (EBSCOhost) 1982 to present (n = 3602) (*continued*)

#	Query
S32	(MH 'Urinary Tract Infections+') OR (MH 'Vaginosis, Bacterial')
S33	TI (('urinary tract infection*' or 'urine infection*' or uti or cystitis or bacteriuria)) OR AB (('urinary tract infection*' or 'urine infection*' or uti or cystitis or bacteriuria)) OR TI vaginosis OR AB vaginosis
S34	(MH 'Domestic Violence')
S35	TI (((spous* or intimate partner or domestic) N2 (violence or abuse))) OR AB (((spous* or intimate partner or domestic) N2 (violence or abuse)))
S36	S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35
S37	(MH 'Pregnancy+') OR (MH 'Expectant Mothers') OR (MH 'Fetus+') OR (MH 'Prepregnancy Care') OR (MH 'Prenatal Care') or (MH 'Perinatal Care')
S38	TI ((pregnan$ or f?etal or f?etus or FVS)) OR AB ((pregnan$ or f?etal or f?etus or FVS)) OR TI ((pregnan* or preconception* or pre-conception* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or perinatal or maternal or mother*)) OR AB ((pregnan* or preconception* or pre-conception* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or perinatal or maternal or mother*))
S39	S37 OR S38
S40	(MH 'Health Screening') OR (MH 'Population Surveillance')
S41	TI screen* OR AB screen* OR TI ((selfreport* or self-report* or ((oral or tak*) N3 history))) OR AB ((selfreport* or self-report* or ((oral or tak*) N3 history)))
S42	(MH 'Hematologic Tests+') OR (MH 'Diagnostic Tests, Routine') OR (MH 'Serologic Tests+') OR (MH 'Polymerase Chain Reaction+')
S43	TI (((h?ematolog* or blood or serum or serologic*) 3 (test* or assay*))) OR AB (((h?ematolog* or blood or serum or serologic*) 3 (test* or assay*))) OR TI (((sero* N5 (test* or screen* or diagnos*)) or (serotest* or seroscreen* or serodiagnos*))) OR AB (((sero* N5 (test* or screen* or diagnos*)) or (serotest* or seroscreen* or serodiagnos*))) OR TI ((immuno-assay* or immunoassay* or elisa or eia or Fluorescent antibody to membrane antibod* or fama or trfia)) OR AB ((immuno-assay* or immunoassay* or elisa or eia or Fluorescent antibody to membrane antibod* or fama or trfia)) OR TI ((enzyme linked immunosorbent assay* or elisa or enzyme immunoassay* or eia or recombinant immunoblot assay* or riba)) OR AB ((enzyme linked immunosorbent assay* or elisa or enzyme immunoassay* or eia or recombinant immunoblot assay* or riba)) OR TI ((polymerase chain reaction or pcr)) OR AB ((polymerase chain reaction or pcr)) OR AB ((routine N5 (test* or screen* or diagnos*))) OR TI ((test* or diagnos* or assay*))
S44	S40 OR S41 OR S42 OR S43
S45	S36 AND S39 AND S44
S46	(MH 'Prenatal Diagnosis')
S47	TI (((pregnan* or preconception* or pre-conception* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or perinatal or maternal or mother*) N5 (screen* or diagnos* or test*))) OR AB (((pregnan* or preconception* or pre-conception* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or perinatal or maternal or mother*) N5 (screen* or diagnos* or test*)))
S48	S46 OR S47
S49	S36 AND S48
S50	S45 OR S49
S51	(MH 'Neonatal Assessment+')
S52	TI ((heelprick* or heel prick*)) OR AB ((heelprick* or heel prick*)) OR TI (((neonat* or newborn) N2 screen*)) OR AB (((neonat* or newborn) N2 screen*))
S53	(MH 'Infant, Newborn+')
S54	TI ((newborn? or neonat* or infant?)) OR AB ((newborn? or neonat* or infant?))

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TABLE 25 CINAHL (EBSCOhost) 1982 to present (n = 3602) (*continued*)

#	Query
S55	S53 OR S54
S56	(MH 'Physical Examination') OR (MH 'Health Screening') OR (MH 'Serologic Tests') OR (MH 'Diagnostic Tests, Routine') OR (MH 'Genetic Screening')
S57	TI (physical N3 exam*) OR AB (physical N3 exam*) OR TI screen* OR AB screen* OR TI ((routine N5 (test* or diagnos*))) OR AB ((routine N5 (test* or diagnos*))) OR TI (((sero* N5 diagnos*) or (serotest* or seroscreen* or serodiagnos*))) OR AB (((sero* N5 diagnos*) or (serotest* or seroscreen* or serodiagnos*))) OR TI ((blood spot* or bloodspot*)) OR AB ((blood spot* or bloodspot*))
S58	(MH 'Hearing Tests+')
S59	TI (((hearing or auditor* or acoustic* or otoacoustic*) N3 (test* or diagnos*))) OR AB (((hearing or auditor* or acoustic* or otoacoustic*) N3 (test* or diagnos*))) OR TI ((automated auditory brainstem response? or aabr or otoacoustic emission? or aoae)) OR AB ((automated auditory brainstem response? or aabr or otoacoustic emission? or aoae))
S60	S56 OR S57 OR S58 OR S59
S61	(MH 'Hemoglobinopathies+')
S62	TI ((sickle cell or thalass?emia?)) OR AB ((sickle cell or thalass?emia?))
S63	(MH 'Eye Diseases, Hereditary') OR (MH 'Cataract')
S64	TI ((cataract? or blind* or ((eye? or vision?) N2 (disease? or disorder?)))) OR AB ((cataract? or blind* or ((eye? or vision?) N2 (disease? or disorder?))))
S65	(MH 'Heart Defects, Congenital+')
S66	TI (((heart or cardi* or septal or atrial or ventric*) N2 (defect? or anomal* or malformation?))) OR AB (((heart or cardi* or septal or atrial or ventric*) N2 (defect? or anomal* or malformation?))) OR TI (((coarctat* N2 aorta) or (valv* N2 stenosis) or 'transdisposition of the great arter*' or patent ductus arteriosus or ebstein* anomal* or 'tetralogy of fallot' or hypoplastic left heart syndrome or tricuspid atresia or truncus arteriosus or anomalous pulmonary venous connection)) OR AB (((coarctat* N2 aorta) or (valv* N2 stenosis) or 'transdisposition of the great arter*' or patent ductus arteriosus or ebstein* anomal* or 'tetralogy of fallot' or hypoplastic left heart syndrome or tricuspid atresia or truncus arteriosus or anomalous pulmonary venous connection))
S67	(MH 'Hip Dislocation, Congenital')
S68	TI ((hip? N2 (dysplasia? or dislocat*))) OR AB ((hip? N2 (dysplasia? or dislocat*)))
S69	(MH 'Cryptorchidism')
S70	TI ((((undescend* or retract*) N2 testic*) or cryptorchid*)) OR AB ((((undescend* or retract*) N2 testic*) or cryptorchid*))
S71	(MH 'Hearing Disorders+')
S72	TI (((hearing N2 (loss or disorder?)) or deaf*)) OR AB (((hearing N2 (loss or disorder?)) or deaf*))
S73	(MH 'Cystic Fibrosis') OR (MH 'Congenital Hypothyroidism') OR (MH 'Metabolism, Inborn Errors+') OR (MH 'Biliary Atresia') OR (MH 'Muscular Dystrophy, Duchenne+') OR (MH 'Sex Chromosome Disorders of Sex Development+')
S74	TI cystic fibrosis OR AB cystic fibrosis OR TI congenital hypothyroid* OR AB congenital hypothyroid* OR TI biliary atresia OR AB biliary atresia OR TI ((phenylketonuria? or medium chain acyl coa dehydrogenase deficien* or medium chain acylcoa dehydrogenase deficien* or mcadd or maple syrup urine disease? or msud or isovaleric acid?emia? or iso-valeric acid?emia? or glutaric aciduria? or homocystinuria? or amino acid metabolism disorder? or biotinidase deficiency or congenital adrenal hyperplasia or duchenne muscular dystrophy or oxidation disorder? or thrombocytop?enia? or galactos?emia? or kernicterus or dehydrogenase deficiency or lchadd or mucopolysaccharidosis or severe combined immunodeficienc* or spinal muscular atrophy or tyrosin?emia? or adrenoleukodystrophy or ccald or canavan or klinefelter syndrome or 22q11 deletion syndrome or digeorge syndrome)) OR AB ((phenylketonuria? or medium chain acyl coa dehydrogenase deficien* or medium chain acylcoa dehydrogenase deficien* or mcadd or maple syrup urine disease? or msud or isovaleric acid?emia? or iso-valeric acid?emia? or glutaric aciduria? or homocystinuria? or amino acid metabolism disorder? or biotinidase deficiency or congenital adrenal hyperplasia or duchenne muscular dystrophy or oxidation disorder? or thrombocytop?enia? or galactos?emia? or kernicterus or dehydrogenase deficiency or lchadd or mucopolysaccharidosis or severe combined immunodeficienc* or spinal muscular atrophy or tyrosin?emia? or adrenoleukodystrophy or ccald or canavan or klinefelter syndrome or 22q11 deletion syndrome or digeorge syndrome))

TABLE 25 CINAHL (EBSCOhost) 1982 to present (n = 3602) (*continued*)

#	Query
S75	S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74
S76	S55 AND S60 AND S75
S77	S51 OR S52 OR S76
S78	S19 OR S50 OR S77
S79	(MH 'Economic Value of Life') OR (MH 'Resource Allocation+')
S80	(MH 'Quality-Adjusted Life Years')
S81	TI ((economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$)) OR AB ((economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$)) OR TI ((expenditure$ not energy)) OR AB ((expenditure$ not energy)) OR TI 'value for money' OR AB 'value for money' OR TI ((financ* or fiscal or funding or fee* or charge* or budget*)) OR AB ((financ* or fiscal or funding or fee* or charge* or budget*)) OR TI ((value N2 (money or monetary))) OR AB ((value N2 (money or monetary))) OR TI (('Value of life' or 'quality adjusted life year*' or qaly* or qald* or qale* or 'disability adjusted life year*' or daly)) OR AB (('Value of life' or 'quality adjusted life year*' or qaly* or qald* or qale* or 'disability adjusted life year*' or daly))
S82	TI ((short form* or shortform*)) OR AB ((short form* or shortform*)) OR TI ((sf6* or sf-6* or sf8 or sf-8 or sf10 or sf-10 or sf12 or sf-12 or sf16 or sf-16 or sf20 or sf-20 or sf36 or sf-36)) OR AB ((sf6* or sf-6* or sf8 or sf-8 or sf10 or sf-10 or sf12 or sf-12 or sf16 or sf-16 or sf20 or sf-20 or sf36 or sf-36)) OR TI ((euroqol or euro qol or 'euro quality of life' or euroqual or euro qual or eq5d or eq-5d)) OR AB ((euroqol or euro qol or 'euro quality of life' or euroqual or euro qual or eq5d or eq-5d)) OR TI ((AQoL* or 'Assessment of Quality of Life')) OR AB ((AQoL* or 'Assessment of Quality of Life')) OR TI (('16D Health Related Quality of Life' or 16D HRQoL or '17D Health Related Quality of Life' or 17D HRQoL)) OR AB (('16D Health Related Quality of Life' or 16D HRQoL or '17D Health Related Quality of Life' or 17D HRQoL)) OR TI (('Child Health Utility 9 Dimension' or CHU9D or 'CHU-9D' or '15 dimensional instrument')) OR AB w,(('Child Health Utility 9 Dimension' or CHU9D or 'CHU-9D' or '15 dimensional instrument'))
S83	(('quality of wellbeing*' or 'quality of well being*' or qwb)) OR (('quality of wellbeing*' or 'quality of well being*' or qwb)) OR ((hye or health* year equivalent*)) OR ((hye or health* year equivalent*)) OR ((health utilit* or disutilit*)) OR VI ((health utilit* or disutilit*)) OR ((hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3)) OR ((hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3)) OR (health* N2 priorities).ti,ab. OR (health* N2 priorities).ti,ab. OR ((Adolescent Health Utility Measure or AHUM)) OR VI ((Adolescent Health Utility Measure or AHUM))
S84	TI ((preference* N3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments))) OR AB ((preference* N3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments))) OR TI ('preference based measure of HRQoL' or (willingness N2 pay) or standard gamble or 'time trade off' or 'time tradeoff' or tto or vas ir visual analog or discrete choice or utility elicitation or direct elicitation or scoring algorithm or best worst scaling or 'multi attribute utility' or 'multiattribute utility' or markov or monte carlo) OR AB ('preference based measure of HRQoL' or (willingness N2 pay) or standard gamble or 'time trade off' or 'time tradeoff' or tto or vas ir visual analog or discrete choice or utility elicitation or direct elicitation or scoring algorithm or best worst scaling or 'multi attribute utility' or 'multiattribute utility' or markov or monte carlo) OR TI (((multicriteria or multi-criteria) N2 (decision or analys* or decision aid* or decision making))) OR AB (((multicriteria or multi-criteria) N2 (decision or analys* or decision aid* or decision making))) OR TI ((benefit risk asessment or risk benefit assessment or weighted product)) OR AB ((benefit risk asessment or risk benefit assessment or weighted product)) OR TI (((analytic* hierarchy or analytic* network) N1 process*)) OR AB (((analytic* hierarchy or analytic* network) N1 process*)) OR TI (('measuring attractiveness by a categorical based evaluation technique' or 'goal programming' or 'elimination and choice expressing reality' or ELECTRE or 'preference ranking organisation method of enrichment evaluation' or PROMETHEE or 'technique for order preference by similarity to ideal solution' or TOPSIS or 'measuring attractiveness by a categorical based evaluation technique' or MACBETH)) OR AB (('measuring attractiveness by a categorical based evaluation technique' or 'goal programming' or 'elimination and choice expressing reality' or ELECTRE or 'preference ranking organization method of enrichment evaluation' or PROMETHEE or 'technique for order preference by similarity to ideal solution' or TOPSIS or 'measuring attractiveness by a categorical based evaluation technique' or MACBETH))
S85	TI 'Accountability for reasonableness' OR AB 'Accountability for reasonableness' OR TI ((decision* N1 (tree* or model* or analysis))) OR AB ((decision* N1 (tree* or model* or analysis))) OR TI ((resource* N2 (use* or utilisation or allocat*))) OR AB ((resource* N2 (use* or utilisation or allocat*))) OR TI ((ration or rationing)) OR AB ((ration or rationing)) OR TI Comparative Effectiveness Research OR AB Comparative Effectiveness Research

continued

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TABLE 25 CINAHL (EBSCOhost) 1982 to present (n = 3602) (*continued*)

#	Query
S86	S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85
S87	S78 AND S86
S88	TI (((energy or oxygen) N1 cost)) OR AB (((energy or oxygen) N1 cost)) OR TI (metabolic N1 cost) OR AB (metabolic N1 cost) OR TI (((energy or oxygen) N1 expenditure)) OR AB (((energy or oxygen) N1 expenditure))
S89	S87 NOT S88
S90	S87 NOT S88 Limiters – Publication Type: Anecdote, Book Review, Commentary, Editorial, Historical Material, Interview, Letter, Response, Teaching Materials
S91	S89 NOT S90 Limiters – Published Date: 20000101–20211231

TABLE 26 PsycINFO (OvidSP) 1806 to present

#	Query	Result
1	exp Prenatal diagnosis/	710
2	(ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or nuchal translucen* or amniocentesis or chorionic villus sampl* or cvs or (((noninvasive prenatal or non-invasive prenatal) adj2 (test* or screen*)) or nipt)).ti,ab.	6786
3	((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part* or antenatal or ante-natal or perinatal or pregnant or pregnancy or trimester?) adj3 (screen* or test* or diagnos* or scan* or structural assessment* or structural survey*)).ti,ab.	4089
4	screen*.ti.	20,929
5	Induced Abortion/	2692
6	((induced or therap*) adj3 abortion?).ab. or abortion?.ti.	2551
7	1 or 2 or 3 or 4 or 5 or 6	34,112
8	exp Neonatal Disorders/ or exp Congenital Disorders/	15,798
9	[(dysautonomia? or tay sachs).ti,ab,kw.]	0
10	(congenital* adj2 (defect? or malformation? or abnormalit* or anomal* or aneuploid*)).ti,ab.	1728
11	((fetal or foetal or fetus or foetus) adj2 (defect? or malformation? or abnormalit* or anomal* or aneu-ploid*)).ti,ab.	409
12	((structural or neural tube?) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.	2597
13	((non-chromosom* or nonchromosom* or chromosom*) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.	698
14	(((down* or patau* or edward*) adj2 syndrome*) or trisomy 13 or trisomy 18 or trisomy 21).ti,ab.	7671
15	spinal muscular atrophy.ti,ab.	522
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	22,001
17	7 and 16	1195
18	exp obstetrical complications/	1587
19	(eclampsia or preeclampsia or pregnancy induced hypertension).ti,ab.	641
20	((gestational or pregnan* or maternal) adj2 diabet*).ti,ab.	765
21	Premature Birth/	5735
22	((preterm or premature) adj2 labo?r).ti,ab.	271

TABLE 26 PsycINFO (OvidSP) 1806 to present (*continued*)

#	Query	Result
23	(f?etal death? or stillbirth? or still birth?).ti,ab.	905
24	((placenta or vasa) adj pr?evia).ti,ab.	26
25	exp obstetrical complications/	1587
26	(sickle cell or thalass?emia?).ti,ab.	1666
27	exp Sexually Transmitted Diseases/	46,974
28	syphilis.ti,ab.	1674
29	(hepatitis b or hbv).ti,ab. or hepatitis.ti.	2795
30	(hiv or human immunodeficiency virus).ti,ab.	53,140
31	chlamydia.ti,ab.	922
32	cytomegalovirus.ti,ab.	515
33	(group b strep or strep b or (streptococc* adj infection?)).ti,ab.	254
34	parovirus.ti,ab.	1
35	viral disorders/ or rubella/	2700
36	rubella.ti,ab.	424
37	toxoplasmosis.ti,ab.	244
38	thrombophilia?.ti,ab.	72
39	an?emia?.ti,ab.	2033
40	(blood group? or rhd status or rhesus positive or rhesus negative or rhesus status).ti,ab.	209
41	('urinary tract infection*' or 'urine infection*' or uti or cystitis or bacteriuria).ti,ab.	869
42	vaginosis.ti,ab.	80
43	domestic violence/ or intimate partner violence/	21,067
44	((spous* or intimate partner or domestic) adj2 (violence or abuse)).ti,ab.	18,740
45	or/18-44	103,937
46	exp pregnancy/	43,025
47	exp fetus/	2134
48	(pregnan$ or f?etal or f?etus or FVS).ti,ab.	55,568
49	prenatal care/	1914
50	(pregnan* or preconception* or pre-conception* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or perinatal or maternal or mother*).ti,ab.	192,754
51	46 or 47 or 48 or 49 or 50	207,329
52	screening/ or exp health screening/ or exp screening tests/	29,936
53	screen*.ti,ab.	100,420
54	Self Report/	18,358
55	(selfreport* or self-report* or ((oral or tak*) adj3 history)).ti,ab.	130,100
56	((h?ematolog* or blood or serum or serologic*) adj3 (test* or assay*)).ti,ab.	4809
57	((sero* adj5 (test* or screen* or diagnos*)) or (serotest* or seroscreen* or serodiagnos*)).ti,ab.	1493

continued

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TABLE 26 PsycINFO (OvidSP) 1806 to present (*continued*)

#	Query	Result
58	(immuno-assay* or immunoassay* or elisa or eia or Fluorescent antibody to membrane antibod* or fama or trfia).ti,ab.	4582
59	(enzyme linked immunosorbent assay* or elisa or enzyme immunoassay* or eia or recombinant immunoblot assay* or riba).ti,ab.	4746
60	(polymerase chain reaction or pcr).ti,ab.	10,291
61	(routine adj5 (test* or screen* or diagnos*)).ti,ab.	3748
62	(test* or diagnos* or assay*).ti.	148,890
63	or/52-62	385,529
64	45 and 51 and 63	2487
65	Prenatal diagnosis/	710
66	((pregnan* or preconception* or pre-conception* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or perinatal or maternal or mother*) adj5 (screen* or diagnos* or test*)).ti,ab.	9424
67	65 or 66	9593
68	45 and 67	1259
69	64 or 68	2966
70	(heelprick* or heel prick*).ti,ab.	33
71	((neonat* or newborn) adj2 screen*).ti,ab.	781
72	newborn/	0
73	(newborn? or neonat* or infant?).ti,ab.	90,167
74	72 or 73	90,167
75	(physical adj3 exam*).ti,ab.	7333
76	screening/ or exp health screening/ or exp screening tests/	29,936
77	screen*.ti,ab.	100,420
78	Genetic testing/	1820
79	(routine adj5 (test* or diagnos*)).ti,ab.	1888
80	serologic.ti,ab.	340
81	((sero* adj5 diagnos*) or (serotest* or seroscreen* or serodiagnos*)).ti,ab.	330
82	(blood spot* or bloodspot*).ti,ab.	279
83	((hearing or auditor* or acoustic* or otoacoustic*) adj3 (test* or diagnos*)).ti,ab.	5708
84	(automated auditory brainstem response? or aabr or otoacoustic emission? or aoae).ti,ab.	785
85	or/75-84	122,164
86	sickle cell disease/	1097
87	(sickle cell or thalass?emia?).ti,ab.	1666
88	(cataract? or blind* or ((eye? or vision?) adj2 (disease? or disorder?))).ti,ab.	56,607
89	((heart or cardi* or septal or atrial or ventric*) adj2 (defect? or anomal* or malformation?)).ti,ab.	665
90	((coarctat* adj2 aorta) or (valv* adj2 stenosis) or 'transdisposition of the great arter*' or patent ductus arteriosus or ebstein* anomal* or 'tetralogy of fallot' or hypoplastic left heart syndrome or tricuspid atresia or truncus arteriosus or anomalous pulmonary venous connection).ti,ab.	172

TABLE 26 PsycINFO (OvidSP) 1806 to present (*continued*)

#	Query	Result
91	(hip? adj2 (dysplasia? or dislocat*)).ti,ab.	57
92	(((undescend* or retract*) adj2 testic*) or cryptorchid*).ti,ab.	75
93	((hearing adj2 (loss or disorder?)) or deaf*).ti,ab.	23,914
94	cystic fibrosis.ti,ab.	1216
95	congenital hypothyroid*.ti,ab.	138
96	biliary atresia.ti,ab.	19
97	(phenylketonuria? or medium chain acyl coa dehydrogenase deficien* or medium chain acylcoa dehydrogenase deficien* or mcadd or maple syrup urine disease? or msud or isovaleric acid?emia? or iso-valeric acid?emia? or glutaric aciduria? or homocystinuria? or amino acid metabolism disorder? or biotinidase deficiency or congenital adrenal hyperplasia or duchenne muscular dystrophy or oxidation disorder? or thrombocytop?enia? or galactos?emia? or kernicterus or dehydrogenase deficiency or lchadd or mucopolysaccharidosis or severe combined immunodeficienc* or spinal muscular atrophy or tyrosin?emia? or adrenoleukodystrophy or ccald or canavan or klinefelter syndrome or 22q11 deletion syndrome or digeorge syndrome).ti,ab.	3299
98	or/86-97	86,003
99	74 and 85 and 98	663
100	70 or 71 or 99	1061
101	17 or 69 or 100	5071
102	economics/ or health care economics/ or pharmacoeconomics/	24,376
103	exp 'costs and cost analysis'/	43,479
104	resource allocation/	3391
105	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	220,424
106	(expenditure$ not energy).ti,ab.	8321
107	value for money.ti,ab.	526
108	budget$.ti,ab.	8938
109	(financ* or fiscal or funding or fee* or charge* or budget*).ti,ab.	346,980
110	(value adj2 (money or monetary)).ti,ab.	986
111	('Value of life' or 'quality adjusted life year*' or qaly* or qald* or qale* or 'disability adjusted life year*' or daly).ti,ab.	2617
112	(short form* or shortform*).ti,ab.	14,029
113	(sf6* or sf-6* or sf8 or sf-8 or sf10 or sf-10 or sf12 or sf-12 or sf16 or sf-16 or sf20 or sf-20 or sf36 or sf-36).ti,ab.	6173
114	(euroqol or euro qol or 'euro quality of life' or euroqual or euro qual or eq5d or eq-5d).ti,ab.	2355
115	(AQoL* or 'Assessment of Quality of Life').ti,ab.	586
116	('16D Health Related Quality of Life' or 16D HRQoL or '17D Health Related Quality of Life' or 17D HRQoL).ti,ab.	1
117	('Child Health Utility 9 Dimension' or CHU9D or 'CHU-9D').ti,ab.	31
118	15 dimensional instrument.ti,ab.	1
119	('quality of wellbeing*' or 'quality of well being*' or qwb).ti,ab.	296
120	(hye or health* year equivalent*).ti,ab.	30

continued

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TABLE 26 PsycINFO (OvidSP) 1806 to present (*continued*)

#	Query	Result
121	(health utilit* or disutilit*).ti,ab.	765
122	(hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab.	598
123	(health* adj2 priorities).ti,ab.	644
124	(Adolescent Health Utility Measure or AHUM).ti,ab.	1
125	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab.	7890
126	'preference based measure of HRQoL'.ti,ab.	0
127	(willingness adj2 pay).ti,ab.	2028
128	standard gamble.ti,ab.	219
129	(time trade off or time tradeoff or tto).ti,ab.	409
130	(vas or visual analog*).ti,ab.	8086
131	discrete choice*.ti,ab.	1079
132	(utility elicitation or direct elicitation).ti,ab.	45
133	scoring algorithm.ti,ab.	228
134	best worst scaling.ti,ab.	125
135	(multi attribute utility or multiattribute utility).ti,ab.	262
136	(markov or monte carlo method).ti,ab.	3931
137	((multicriteria or multi-criteria) adj2 (decision or analys* or decision aid* or decision making)).ti,ab.	466
138	(benefit risk asessment or risk benefit assessment).ti,ab.	105
139	weighted product.ti,ab.	8
140	((analytic* hierarchy or analytic* network) adj process*).ti,ab.	514
141	('measuring attractiveness by a categorical based evaluation technique' or 'goal programming' or 'elimination and choice expressing reality' or ELECTRE or 'preference ranking organization method of enrichment evaluation' or PROMETHEE or 'technique for order preference by similarity to ideal solution' or TOPSIS or 'measuring attractiveness by a categorical based evaluation technique' or MACBETH).ti,ab.	369
142	'Accountability for reasonableness'.ti,ab.	29
143	(decision* adj (tree* or model* or analysis)).ti,ab.	3717
144	(resource* adj2 (use* or utilisation or allocat*)).ti,ab.	12,294
145	(ration or rationing).ti,ab.	1031
146	Comparative Effectiveness Research.ti,ab.	248
147	or/102-104	67,563
148	101 and 147	82
149	((energy or oxygen) adj cost).ti,ab.	278
150	(metabolic adj cost).ti,ab.	99
151	((energy or oxygen) adj expenditure).ti,ab.	2628
152	149 or 150 or 151	2925
153	148 not 152	82
154	(comment reply or editorial or letter or 'review book' or 'review media' or 'review software other').dt.	317,639
155	153 not 154	78
156	limit 155 to yr='2000-Current'	70

Appendix 3 Fields in the data extraction form – Consolidated Health EconomicEvaluation Reporting Standards checklist

Item no.	Section	Data field	Data field description
1	General	Completed by	State the name initials of person who has filled out the data extraction sheet.
2	General	Literature type	Published or grey literature.
3	General	First author	State first author's last name.
4	General	Year	State year of publication.
5	General	Publication type	Describe type of publication (e.g. journal article, HTA report, conference abstract, book chapters, thesis).
6	Title	Title	Identify the study as an economic evaluation or use more specific terms such as 'cost-effectiveness analysis', and describe the interventions compared.
7	Abstract	Abstract	Indicate if article provided a structured summary of objectives, perspective, setting (geographical or organisational), methods (including study design and inputs), results (including base-case and uncertainty analyses) and conclusions.
8	Introduction	Research question/ objective	Specify the main research question(s) or objective(s).
9	Methods	Country/jurisdiction	State country/jurisdiction (or region if available) that the study was conducted in.
10	Methods	Setting of screening	Describe setting of screening (e.g. inpatient, outpatient, home, community).
11	Methods	Population	Indicate if population is *healthy pregnancy*, *pregnancy at risk*, *pregnant women and their partner/relative*, *healthy infant and/or infant at risk* (state gestational week if available).
12	Methods	Condition(s) screened	Specify condition(s) screened using specified test(s).
13	Methods	Study type	State if study is a type A, B, or C evaluation: • Type A evaluation is a *single study-based* evaluation that relies on clinical, epidemiological and resource use evidence from a single study (e.g. within-trial economic evaluation). • Type B evaluation is based on data from multiple data sources and *using decision-analytical model* (e.g. decision tree, Markov, DES), such as published studies, unpublished reports, hospital records and expert opinion. • Type C evaluation is based on data from multiple data sources and *using other model types* (other mathematical models), such as published studies, unpublished reports, hospital records and expert opinion.
14	Methods	Size of study population	If type A evaluation, specify the sample size. If type B or C evaluation, specify the number of people in the starting cohort.
15	Methods	Design	If type A evaluation, state design of underpinning study (e.g. randomised controlled trial, retrospective cohort, and prospective cohort). If type C evaluation, state design of underpinning model. If type B evaluation, (1) state the type of underpinning model (e.g. decision-analytic model, transition state probability model, time-dependent multistage transition probability model, Markov model); and (2) indicate whether they have stated the reasons.

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Item no.	Section	Data field	Data field description
16	Methods	Type of economic evaluation	State type of economic evaluation (e.g. cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost-minimisation analysis, cost-consequences analysis).
17	Methods	Perspective	State perspective of study (e.g. health care, payer, societal) in base-case analysis.
18	Methods	Comparators	1. Describe the interventions or strategies being compared. 2. Indicate whether they state why they were chosen.
19	Methods	Time horizon	1. State time horizon of study (if cost and outcome time horizon are different, report both). 2. Indicate whether they state why it is appropriate.
20	Methods	Discount rate for costs	1. Specify discount rate (in %) made to cost if applicable. 2. If applicable, indicate whether they state why it is appropriate.
21	Methods	Discount rate for outcome	1. Specify discount rate (in %) made to outcome if applicable. 2. If applicable, indicate whether they state why it is appropriate.
22	Methods	Choice of outcomes	Indicate whether the article expressed outcomes in natural units and/or adjusted in utility weights.
23	Methods	Measurement: Approaches for measuring outcomes (benefits and harms)	Describe approaches for measuring outcomes (benefits and harms).
24	Methods	Measurement and valuation of preference-based outcomes	If applicable, describe the population and methods used to elicit preferences for outcomes. If applicable, describe the preference-based technique used to value benefits and harms.
25	Methods	Reporting of preference-based outcomes in cost-utility analysis	If applicable, state if preference-based outcome was reported for mother (maternal) and/or infant.
26	Methods	Estimating resources and costs	If type A/C evaluation, indicate whether the article described sources and approaches used to estimate resource use and valuing each resource item in terms of its unit cost for all interventions. If type B evaluation, indicate whether the article described sources and approaches used to estimate resource use and valuing each resource item in terms of its unit cost for model health states.
27	Methods	Currency, reference year	State currency and reference year of currency.
28	Methods	Conversion	Describe methods for converting costs into a common currency base and the exchange rate or purchasing power parity if applicable.
29	Methods	Model assumptions	Describe all structural or other assumptions underpinning the decision-analytical model.
30	Methods	Analytical methods	Describe all analytical methods supporting the evaluation. If type A/C evaluation, indicate whether the article reported the methods and results of regression models that disentangle differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients. If type B evaluation, indicate whether the article described and reported how they estimated parameters (e.g. how they transformed transition probabilities between events or health states into functions of age or disease severity); the handling of uncertainty and separation of hetero-geneity from uncertainty; and time-dependent input parameters (e.g. in relation to uptake of prenatal diagnosis and termination of pregnancy) where applicable.

Item no.	Section	Data field	Data field description
31	Results	Study parameters	Indicate if article reported the (1) values, ranges, references and, if used, probability distributions for all parameters; (2) reasons or sources for distributions used to represent uncertainty where appropriate; and (3) a table to show the input values (strongly recommended).
32	Results	Incremental costs and outcomes	1. For each intervention, indicate if article reported the mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. 2. Indicate if article reported the base-case economic evaluation results (e.g. incremental cost-effectiveness ratio, net monetary benefit).
33	Results	Characterising uncertainty	If type A/C evaluation, indicate whether the article described the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective). If type B evaluation, indicate whether the article described the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.
34	Results	Characterising heterogeneity	If applicable, indicate whether the article reported differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.
35	Discussion	Study findings, limitations, general-isability and current knowledge	Indicate whether the article summarised key study findings and describe how they support the conclusions reached; as well as discussed limitations and the generalisability of the findings and how the findings fit with current knowledge.
36	Discussion	Recommendation	Indicate if the authors made any policy recommendation based on their cost-effective evidence.
37	General	Source of funding	Describe how the study was funded and the role of the funder in the identification, design, conduct and reporting of the analysis. Describe other non-monetary sources of support.
38	General	Affiliations	Indicate if affiliation is industry, non-industry, or both.
39	General	Conflicts of interest	Indicate any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.
40	General	Potential conflicts of interest	Based on 'Source of funding', 'Conflicts of interest' and 'Affiliations', is there potential vested interest in promoting screening/particular screening mechanism? For a 'yes', two conditions need to be met: Condition 1: a study is funded by an industry sponsor unless it is an unrestricted grant AND Condition 2: at least one of the authors is clearly employed by the industry sponsor.
41	General	Industry-sponsored	Based on 'Source of funding', is the study sponsored by industry?
42	Methods/ Results	PPI in economic evaluation	Was there any PPI? If yes, describe the role of PPI in the study.
43	General	JIF quartile	JIF quartile during year that the article was published (sources: Clarivate and SCImago)

DES, discrete-event simulation; JIF, Journal Impact Factor.

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Appendix 4 Fields in the data extraction form – bespoke form

Item no.	Section	Data field	Data field description
0	–	Completed by	Completed by
0.1	–	First author	First author
0.2	–	Year	Year
0.3	–	Publication type	Publication type
1	–	Screening population	What was the eligible screening population?
2	–	Stage of disease pathway	What stage of the disease pathway, as defined by Raffle and Gray,[1] was the screening test administered? 1. Person at risk but no pathological changes present; 2. Symptomless stage with pathologically definable change present; 3. Signs and/or symptoms exist but condition undiagnosed; 4. Clinical phase
3	–	Phase(s) of screening programme	What phases of a screening programme were included in the health economic assessment/model? 1. Screening; 2. Diagnostic; 3. Intervention
4	–	Structure of model reported	Was the structure of the model/decision tree reported?
5	–	True positive	Did the authors include consequences for **true positives** in the screening/diagnostic phase? *If yes, answer 5.1, 5.2 and 5.3.*
5.1	–	True positive – benefit	Were benefits included in the assessment? *If yes, answer 5.1.1.*
5.1.1	–	True positive – benefit, specify	What was/were the benefit(s) and how was it included?
5.2	–	True positive – harm	Were harms evaluated in the assessment (e.g. adverse events of the test)? *If yes, answer 5.2.1.*
5.2.1	–	True positive – harm, specify	What was/were the harm(s) and how was it included?
5.3	–	True positive – inconsequential disease	Were outcomes for true positives in the case of inconsequential disease included? Inconsequential disease refers to those who 'feel exactly the same as the true positives, are managed in the same way, and are indistinguishable from them because all have to be offered treatment. It is not possible to distinguish those with inconsequential conditions from those whose condition would progress', as defined by Raffle and Gray.[1] *If yes, answer 5.3.1.*
5.3.1	–	True positive – inconsequential disease, specify	What were the benefits and/or harms and how were they included?

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Item no.	Section	Data field	Data field description
6	–	True negative	Did the authors include consequences for **true negatives** in the screening/diagnostic phase that did not mirror the benefits/harms for the true positives? *If yes, answer 6.1 and 6.2.*
6.1	–	True negative – benefit	Were benefits included in the assessment? *If yes, answer 6.1.1.*
6.1.1	–	True negative – benefit, specify	What was/were the benefit(s) and how was it included?
6.2	–	True negative – harm	Were harms evaluated in the assessment (e.g. adverse events of the test)? *If yes, answer 6.2.1.*
6.2.1	–	True negative – harm, specify	What was/were the harm(s) and how was it included?
7	–	False positive	Did the authors include consequences for **false positives** in the screening/diagnostic phase that did not mirror the benefits/harms for the true positives? *If yes, answer 7.1.*
7.1	–	False positive – harm, specify	What harms were included (e.g. additional tests, increase anxiety) and how was it included?
8	–	False negative	Did the authors include consequences for **false negatives** in the screening/diagnostic phase that did not mirror the benefits/harms for the true positives? *If yes, answer 8.1 and 8.2.*
8.1	–	False negative – harm, specify	What harms were included and how was it included?
8.2	–	False negative – inconsequential disease	Were outcomes for false negative in the case of inconsequential disease included? Inconsequential disease refers to those who 'are better off not being picked up on screening because they avoid the psychological and physical consequences from being part of the overdiagnosis problem, involving pointless investigation and treatment for a condition that never would have caused any illness' as defined by Raffle and Gray.[1] *If yes, answer 8.2.1.*
8.2.1	–	False negative – inconsequential disease, specify	What were the benefits and/or harms and how were they included?
9	–	Treatment	Did the authors include consequences associated with the **treatment**? *If yes, answer 9.1.*
9.1	–	Treatment – specify	What benefits/harms were included and how was it included?
10	–	Notes of interest	Notes mentioned by the authors that might be of interest but not covered by the questions in the ancillary form.

Appendix 5 Summary of reporting quality of articles and reports (excluding conference abstracts) assessed using Consolidated Health EconomicEvaluation Reporting Standards checklist

CHEERS item no.	CHEERS item	Articles and reports assessing antenatal screening (%)			Articles and reports assessing newborn screening (%)		
		Satisfied	Not satisfied	Not applicable	Satisfied	Not satisfied	Not applicable
Title and abstract							
1	Title	155 (85.6)	26 (14.4)	0 (0)	70 (86.4)	11 (13.6)	0 (0)
2	Abstract	21 (11.6)	160 (88.4)	0 (0)	13 (15.7)	69 (83.1)	1 (1.2)
Introduction							
3	Background and objectives	181 (100)	0 (0)	0 (0)	83 (100)	0 (0)	0 (0)
Methods							
4	Target population and subgroups	181 (100)	0 (0)	0 (0)	83 (100)	0 (0)	0 (0)
5	Setting and location	65 (35.9)	116 (64.1)	0 (0)	30 (36.1)	53 (63.9)	0 (0)
6	Study perspective	134 (74)	47 (26)	0 (0)	67 (80.7)	15 (18.1)	1 (1.2)
7	Comparators	159 (87.8)	22 (12.2)	0 (0)	75 (90.4)	8 (9.6)	0 (0)
8	Time horizon	28 (15.5)	153 (84.5)	0 (0)	15 (18.1)	67 (80.7)	1 (1.2)
9	Discount rate	51 (28.2)	130 (71.8)	0 (0)	29 (34.9)	53 (63.9)	1 (1.2)
10	Choice of health outcomes	181 (100)	0 (0)	0 (0)	82 (98.8)	0 (0)	1 (1.2)
11	Measurement of effectiveness	178 (98.3)	3 (1.7)	0 (0)	82 (98.8)	1 (1.2)	0 (0)
12	Measurement and valuation of preference-based outcomes	48 (26.5)	34 (18.8)	99 (54.7)	19 (22.9)	13 (15.7)	51 (61.4)
13	Estimate resources and cost	168 (92.8)	13 (7.2)	0 (0)	79 (95.2)	3 (3.6)	1 (1.2)
14	Currency, price date, and conversion	139 (76.8)	42 (23.2)	0 (0)	64 (77.1)	18 (21.7)	1 (1.2)
15	Choice of model	28 (15.5)	153 (84.5)	0 (0)	28 (33.7)	55 (66.3)	0 (0)
16	Assumptions	131 (72.4)	20 (11)	30 (16.6)	60 (72.3)	6 (7.2)	17 (20.5)
17	Analytic method	116 (64.1)	65 (35.9)	0 (0)	63 (75.9)	20 (24.1)	0 (0)
Results							
18	Study parameters	155 (85.6)	26 (14.4)	0 (0)	73 (88)	9 (10.8)	1 (1.2)
19	Incremental costs and outcomes	168 (92.8)	13 (7.2)	0 (0)	75 (90.4)	7 (8.4)	1 (1.2)
20	Characterising uncertainty	161 (89)	20 (11)	0 (0)	69 (83.1)	13 (15.7)	1 (1.2)
21	Characterising heterogeneity	24 (13.3)	3 (1.7)	154 (85.1)	4 (4.8)	0 (0)	79 (95.2)

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CHEERS item no.	CHEERS item	Articles and reports assessing antenatal screening (%)			Articles and reports assessing newborn screening (%)		
		Satisfied	Not satisfied	Not applicable	Satisfied	Not satisfied	Not applicable
Discussion							
22	Study funding, limitation, general-isability and current knowledge	58 (32.0)	123 (68.0)	0 (0)	23 (27.7)	59 (71.1)	1 (1.2)
Other							
23	Source of funding	100 (55.2)	81 (44.8)	0 (0)	55 (66.3)	28 (33.7)	0 (0)
24	Conflict of interest	107 (59.1)	74 (40.9)	0 (0)	51 (61.4)	32 (38.6)	0 (0)

Appendix 6 Results of thematic framework analysis

TABLE 27 Thematic framework of benefits and harms adopted by health economic assessments evaluating antenatal and newborn screening programmes

Theme no.	Theme	Subtheme level 1	Subtheme level 2	Subtheme level 3	Subtheme level 4	Antenatal screening	Newborn screening
1	Diagnosis of screened for condition	Additional screening of partners				113	–
1	Diagnosis of screened for condition	Additional testing to reach diagnosis in the absence of screening (links to diagnostic odyssey)				114–116	117
1	Diagnosis of screened for condition	Born with condition	Reduction in children born with condition through effective treatment of the screened for condition			118–139	140,141
1	Diagnosis of screened for condition	Born with condition	Reduction in children born with condition through termination of pregnancy			142–168	–
1	Diagnosis of screened for condition	Cases diagnosed at screening				5,116,142–144,146,151,157, 158,168–189	117,190–204
1	Diagnosis of screened for condition	Cases diagnosed at screening rather than later symptomatically				150,164,166,205–207	208–215
1	Diagnosis of screened for condition	Cases diagnosed at screening that would have become symptomatic				–	216
1	Diagnosis of screened for condition	Cases diagnosed at screening	Maternal			145	–
1	Diagnosis of screened for condition	Cases missed at screening				126,162,171,176,177,187,188, 217,218	219,220
1	Diagnosis of screened for condition	Cases missed at screening	Legal cost of reimbursing false negatives			–	221
1	Diagnosis of screened for condition	Confirmatory test and additional tests to reach diagnosis of screened for condition				142–144,164,169,222–226	117,192,194,227–229

continued

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TABLE 27 Thematic framework of benefits and harms adopted by health economic assessments evaluating antenatal and newborn screening programmes (*continued*)

Theme no.	Theme	Subtheme level 1	Subtheme level 2	Subtheme level 3	Subtheme level 4	Antenatal screening	Newborn screening
1	Diagnosis of screened for condition	Confirmatory test and additional tests to reach diagnosis of screened for condition (invasive)				115,162	–
1	Diagnosis of screened for condition	Confirmatory test and additional tests to reach diagnosis of screened for condition	Early vs. late			–	194
1	Diagnosis of screened for condition	Confirmatory test and additional tests to reach diagnosis of screened for condition	Unnecessary due to false positive			5,113,116,118,120–124,128–130, 133–135,137–139,145,148,150, 151,153,158,162,163,166, 170,171,174,176,181,182,184, 205–207,230–254	141,190,191,193, 195–204,208,210–214, 216,219,221,229,255–284
1	Diagnosis of screened for condition	Confirmatory test and additional tests to reach diagnosis of screened for condition	Unnecessary due to false positive (invasive)			115,152,157,159,160,165,172,173, 175,177,178,180,183,185,187,188, 217,285–289	–
1	Diagnosis of screened for condition	Confirmatory test and additional tests to reach diagnosis of screened for condition	Unnecessary due to false positive	Time spent attending		–	190
1	Diagnosis of screened for condition	Screened for condition-related complications	Morbidity			–	197
2	Life-years and health status adjustments	Infant life-years post birth	DALYs			137,242	229,290
2	Life-years and health status adjustments	Infant life-years post birth	Morbidity			133,233,291,292	203
2	Life-years and health status adjustments	Infant life-years post birth	Mortality			121,132,133,139,147,189, 238,254,291,293,294	196,203,280
2	Life-years and health status adjustments	Infant life-years post birth	QALYs			121,133,135,139,147,225, 230–232,239,243,248,295–309	140,202,203,219,229, 256,257,260–262,264, 267,271,272,276,282, 310–313
2	Life-years and health status adjustments	Infant life-years post birth	Replacement of affected aborted fetus with subsequent unaffected pregnancy and life			167	–
2	Life-years and health status adjustments	Infant life-years post birth	Years			120,123,125,134,145,163, 233,246,247,249,293,296, 314,315	117,140,141,194,203,208, 221,228,257,258,260,263, 265,266,270,273–278, 281,283,284,313,316,317
2	Life-years and health status adjustments	Infant life-years post birth	Years	Monetary value		–	318

TABLE 27 Thematic framework of benefits and harms adopted by health economic assessments evaluating antenatal and newborn screening programmes (*continued*)

Theme no.	Theme	Subtheme level 1	Subtheme level 2	Subtheme level 3	Subtheme level 4	Antenatal screening	Newborn screening
2	Life-years and health status adjustments	Maternal life-years	Mortality			128,133	319
2	Life-years and health status adjustments	Maternal life-years	QALYs			5,135,147,154–156,172,179, 181,189,218,223–226,230, 233,235,239–241,244, 245,247,250,252–254,285,286, 288,292,294,295, 300,302,306,320–332	227,229,269,276,279,280,318
2	Life-years and health status adjustments	Maternal life-years	QALYs	Decrement due to caring for child with screened for condition		333	–
2	Life-years and health status adjustments	Maternal life-years	Years			120,145,163,233,246, 247,249,314,315	140,141,203,228,258, 260,263,265,270, 273–276,281,283,284,313
2	Life-years and health status adjustments	Parental QALYs				–	208,221,255,268
2	Life-years and health status adjustments	Psychological	Anxiety from genetic variants of unclear penetrance			–	227
2	Life-years and health status adjustments	Psychological	Disutility due to knowledge of disease			244	–
2	Life-years and health status adjustments	Psychological	Disutility due to knowledge of disease in those with positive screening results (stress and anxiety)			181	–
2	Life-years and health status adjustments	Psychological	Early diagnosis-induced anxiety			–	227
2	Life-years and health status adjustments	Psychological	False-positive anxiety			183	198,257
2	Life-years and health status adjustments	Psychological	False-positive anxiety	Parental QALYs		–	221
2	Life-years and health status adjustments	Psychological	Genetic variants of unclear penetrance	Unclear harms including behavioural changes	QALYs	–	227

continued

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TABLE 27 Thematic framework of benefits and harms adopted by health economic assessments evaluating antenatal and newborn screening programmes (*continued*)

Theme no.	Theme	Subtheme level 1	Subtheme level 2	Subtheme level 3	Subtheme level 4	Antenatal screening	Newborn screening
2	Life-years and health status adjustments	Screened for condition associated mortality/treatment associated mortality/other causes mortality				–	317
3	Treatment	Additional health care post diagnosis				119,291	215,227,256
3	Treatment	Comparison of earlier treatment after screen detection and later after symptomatic detection	Increase in treatment required for false negative			320,333	199,228
3	Treatment	Comparison of earlier treatment after screen detection and later after symptomatic detection	Increase in treatment required for false negative	Prior to diagnosis		–	271
3	Treatment	Comparison of earlier treatment after screen detection and later after symptomatic detection	Reduction in treatment required			114,334	–
3	Treatment	Comparison of earlier treatment after screen detection and later after symptomatic detection	Reduction in treatment required	Costs		128,129,181,235,248, 296,308,322,325,335–337	194,203,221,228, 258,259,265,269, 276,277,281,283
3	Treatment	Comparison of earlier treatment after screen detection	Adverse complications of screened for condition averted			113,127–129,170,174,226,236, 238,242,247,251,306,307,315, 320,322,327,329,331,337–339	140,212,216,274,280,340
3	Treatment	Hospital stay				237,301,341	264,278
3	Treatment	Missed due to false negative				130	–
3	Treatment	Prevention of screened for condition (infectious)	Increase in future earning potential			341	–
3	Treatment	Prevention of screened for condition (infectious)	Unnecessary prophylaxis in false positives			127,130,131,133,135, 138,232,248,304,309, 320,334,337,341	–
3	Treatment	Prevention of screened for condition (infectious)	Unnecessary prophylaxis in false positives	Allergic reaction		330	–
3	Treatment	Psychological	Counselling about genetic diagnosis			142,157	–
3	Treatment	Psychological	Counselling about screening or confirmatory test	False positive		135,165,166,183,304	–

TABLE 27 Thematic framework of benefits and harms adopted by health economic assessments evaluating antenatal and newborn screening programmes (*continued*)

Theme no.	Theme	Subtheme level 1	Subtheme level 2	Subtheme level 3	Subtheme level 4	Antenatal screening	Newborn screening
3	Treatment	Psychological	Counselling about screening or confirmatory test			113,157	–
3	Treatment	Screened for condition-related treatment/ management				113,137,142,169,181,218, 224–226,234,306,342	194,228,229,284,317
3	Treatment	Screened for condition-related treatment/ management	Unnecessary in false positives with no confirm-atory test			119–123,126,130,136, 139,145,163,181,230, 235,238–240,244,247, 250,291,292,296, 299–301,303,307,308, 314,315,323–325,328, 331,333,339	210,215,221,258,261,274,278, 282,311,312,318,343
3	Treatment	Treatment-related harm	Adverse reaction to treatment			131,133,239,245,249,251,309, 322,330,333	263,266,270,274,278,281,344
3	Treatment	Treatment-related harm	Antibiotic resistance			119	–
3	Treatment	Treatment-related harm	Disutility of treatment			247	–
3	Treatment	Treatment-related harm	Treatment-related anxiety			–	276
3	Treatment	Unnecessary due to false positive				134,233,305,306	–
4	Long-term cost associated with screened for condition	Cost savings from averted births of fetuses with anomalies				114	–
4	Long-term cost associated with screened for condition	Direct healthcare and non-healthcare cost	Health care and productivity gains			167	–
4	Long-term cost associated with screened for condition	Direct healthcare and non-healthcare cost	Health care and social services			–	279
4	Long-term cost associated with screened for condition	Direct healthcare and non-healthcare cost	Health care, education and social services			–	227,262
4	Long-term cost associated with screened for condition	Direct healthcare and non-healthcare cost	Social services			139	–
4	Long-term cost associated with screened for condition	Direct healthcare and non-healthcare cost	Treatment and caregiving			163	–

continued

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TABLE 27 Thematic framework of benefits and harms adopted by health economic assessments evaluating antenatal and newborn screening programmes (*continued*)

Theme no.	Theme	Subtheme level 1	Subtheme level 2	Subtheme level 3	Subtheme level 4	Antenatal screening	Newborn screening
4	Long-term cost associated with screened for condition	Direct healthcare cost				120,122,123,125,135,153,159,161, 167,217,222,233,238,243,246,253, 293,294,296,305,308,309,314,324, 328,337,341,342	141,208,209,212,221,256, 260,261,264,265,274,275, 345,346
4	Long-term cost associated with screened for condition	Direct non-healthcare cost				145	–
4	Long-term cost associated with screened for condition	Direct non-healthcare cost	Caregiving			144,232,287,347	343
4	Long-term cost associated with screened for condition	Direct non-healthcare cost	Child protective services investigation and foster care placements if mothers successfully completed substance abuse treatment			293	–
4	Long-term cost associated with screened for condition	Direct non-healthcare cost	Education and social services			–	194
4	Long-term cost associated with screened for condition	Direct non-healthcare cost	Social care			–	265
4	Long-term cost associated with screened for condition	Productivity gains				129,324	311
4	Long-term cost associated with screened for condition	Societal cost				116,172,184,241,285,288	210,255,311
5	Overdiagnosis	QALY decrement				239	276
5	Overdiagnosis	Unnecessary test/treatment				236,239	221,262,276
6	Pregnancy loss	Spontaneous				116,119,143,144,147,162,166, 186,237,252,333	–
6	Pregnancy loss	Termination				115,147,178,189,332	–
6	Pregnancy loss	Termination	Date/trimester			157,172,285	–
6	Pregnancy loss	Termination	Of unaffected fetus due to false-positive test result			5,146–148,150,151,160, 165,175,176,179,183,186	141,340
6	Pregnancy loss	Termination	Of unaffected fetus due to false-positive test result	Psychological consequences		178	–

TABLE 27 Thematic framework of benefits and harms adopted by health economic assessments evaluating antenatal and newborn screening programmes (*continued*)

Theme no.	Theme	Subtheme level 1	Subtheme level 2	Subtheme level 3	Subtheme level 4	Antenatal screening	Newborn screening
6	Pregnancy loss	Termination	Prevent downstream adverse maternal outcomes			289	–
6	Pregnancy loss	Termination	Prevent later miscarriage			119,157	–
6	Pregnancy loss	Termination	Psychological consequences			178,289,333	–
6	Pregnancy loss	Treatment/ test-related				5,115,116,143,144,148–152, 154,155,157,158,160,162, 164–166,168,169,171–173, 175,176,178–180,183–188,206, 207,217,231,241,252,288,289, 308,332,333	–
6	Pregnancy loss	Treatment/test related	Unaffected			115,142	–
7	Spillover effects	Benefits to parents from child's diagnosis with genetic condition, through knowledge of their own genetic status				–	318

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Appendix 7 Characteristics of studies included in meta-ethnography (*n* = 36)

#	Author (date)	Date	Country	Condition(s) addressed	Research aim	Participants	Data
1	Boyse *et al.*	2014	USA	CAH	To characterise the experiences and expressed needs of parents following diagnosis of their newborn with CAH	Parents of children diagnosed with CAH (*n* = 6)	Individual interviews
2	Buchbinder and Timmermans	2011	USA	MCADD	To examine how parents and clinical staff work out the social significance of uncertain newborn screening results	Representative case study of one family with positive newborn screen for MCADD	Ethnographic observation, individual interviews
3	Buchbinder and Timmermans	2011	USA	Metabolic conditions	To explore the potential for newborn screening to diagnose mothers with genetic disorders, requiring a reconceptualisation of traditional views of family 'benefit'	Parents of newborn screening patients (*n* = 7 families)	Ethnographic observation, individual interviews
4	Buchbinder and Timmermans	2012	USA	Metabolic conditions	To explore parents' perceptions of the initial communication of newborn screening results	Parents of newborn screening patients (*n* = 75 families)	Ethnographic observation, individual interviews
5	Carpenter *et al.*	2018	UK	PKU	To explore the experiences of parents of children with PKU under the age of 2	Parents of children with PKU under the age of 2 (*n* = 7)	Individual interviews
6	Chudleigh *et al.*	2016	UK	Cystic fibrosis or sickle cell disease	To explore parents' experiences of receiving the initial positive newborn screening result for their child with cystic fibrosis or sickle cell disease	Parents whose children had been diagnosed with cystic fibrosis or sickle cell disease and were < 1 year old at time of interview (*n* = 22)	Individual interviews
7	DeLuca *et al.*	2011	USA	Metabolic conditions	To describe parents' experiences with testing for rare metabolic conditions	Parents of children undergoing testing for metabolic conditions (*n* = 44); 9 children with positive diagnoses, 8 negative, 13 equivocal confirmatory results	Longitudinal interviews during and after metabolic testing process
8	Dillard and Carson[348]	2005	USA	Cystic fibrosis	To identify how family members communicatively manage the uncertainty created by a positive newborn screening result	Families of children who had a positive newborn screening test result for cystic fibrosis (*n* = 17)	Video recordings of medical interactions with families

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#	Author (date)	Date	Country	Condition(s) addressed	Research aim	Participants	Data
9	Grob	2006	USA	Cystic fibrosis	To examine parents' experiences of newborn screening	Parents of children who received genetic diagnoses via newborn screening for cystic fibrosis (*n* = 25)	Individual interviews
10	Grob	2008	USA	Cystic fibrosis	To examine parents' experiences of newborn screening	Parents of children who were diagnosed with cystic fibrosis via newborn screen (*n* = 16); prenatally (*n* = 4); or after the development of symptoms (*n* = 15)	Individual interviews
11	Johnson *et al.*	2019	UK	Cystic fibrosis	To explore the psychological impact of receiving a 'CFSPID' result on parents	Parents of children who received CFSPID (*n* = 8)	Individual interviews
12	Kerruish[349]	2011	New Zealand	Type 1 diabetes	To explore the psychosocial impact of screening newborns for genetic susceptibilities using type 1 diabetes as an example of a common disorder with multiple significant genetic contributors to its aetiology	Parents of children who had received increased risk results in a study that involved newborn screening for genetic susceptibility to type 1 diabetes (*n* = 11)	Individual interviews
13	Kerruish[350]	2016	New Zealand	Type 1 diabetes	To explore the later effects of screening for genetic susceptibility to a single, complex disorder: type 1 diabetes	Parents of children who had been tested for genetic susceptibility to type 1 diabetes 12 years previously (*n* = 15)	Individual interviews
14	Locock and Kai	2008	UK	Sickle cell, thalassaemia, other haemoglobin variants	To explore parents' experiences and attitudes towards antenatal and newborn screening for haemoglobin disorders	Parents who had experienced gene-carrier identification through antenatal and newborn screening for sickle cell, thalassaemia, and other haemoglobin variants within the previous 2 years (*n* = 39)	Individual interviews
15	Moran *et al.*	2007	UK	Cystic fibrosis	To investigate the emotional impact of false-positive diagnoses	Parents who received false-positive IRT cystic fibrosis test result (*n* = 21)	Individual interviews
16	Nicholls	2010	UK	None	To highlight differences between parental knowledge of newborn screening and their understanding of what actually took place	Parents whose children had newborn screening tests (*n* = 18)	Individual interviews

#	Author (date)	Date	Country	Condition(s) addressed	Research aim	Participants	Data
17	Nicholls	2012	UK	None	To explore parents' experiences with the newborn screening consent process	Parents who had children born in the prior 2 years (*n* = 18)	Individual interviews
18	Nicholls and Southern	2013	UK	None	To understand the factors that influence parental decisions in accepting newborn screening and roles they play in the process	Parents who had children born in the prior 2 years (*n* = 18)	Individual interviews
19	Parsons *et al.*	2007	UK	None	To explore mothers' experiences with newborn screening	Mothers who were offered newborn screening and had negative results (*n* = 18)	Individual interviews
20	Patterson *et al.*	2015	USA	Cystic fibrosis or sickle cell disease	To explore the role of the internet after parents receive abnormal newborn screening results	Parents who received abnormal newborn screening results and mentioned the internet in their interview (*n* = 146)	Secondary analysis of existing individual interviews
21	Priddis *et al.*[351]	2009	Australia	Cystic fibrosis	To explore the experiences of mother's whose children were diagnosed with cystic fibrosis through newborn screening	Mothers whose children were diagnosed with cystic fibrosis (*n* = 19)	Individual interviews
22	Priddis *et al.*[352]	2010	Australia	Cystic fibrosis	To explore the impact of cystic fibrosis diagnosis on fathers	Fathers whose children were diagnosed with cystic fibrosis (*n* = 15)	Individual interviews
23	Pruniski *et al.*	2018	USA	PD	To examine the effects of receiving a positive newborn screening result for PD on families	Mothers of children who were diagnosed with PD through newborn screening (*n* = 9)	Individual interviews
24	Raz *et al.*	2019	Israel	PKU, CAH, hypothyroidism, MSUD, homocystinuria, or G6PD	To examine the interface between newborn screening and prenatal diagnosis from the point of view of parents of screen-positive children	Parents whose child was screen positive (*n* = 34)	Individual interviews
25	Raz *et al.*	2018	Israel	PKU, CAH, hypothyroidism, MSUD, homocystinuria, or G6PD	To examine the patterns of communication and interaction for peer support among parents of screen-positive children	Parents whose child was screen positive (*n* = 34)	Individual interviews
26	Salm *et al.*	2012	USA	Cystic fibrosis or hypothyroidism	To examine parents' reactions to newborn screening results and their recommendations for improving communication	Parents of screen-positive children (*n* = 106 interviews, 203 parents)	Individual or couple interviews

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#	Author (date)	Date	Country	Condition(s) addressed	Research aim	Participants	Data
27	Schmidt *et al.*[353]	2012	USA	None	To describe the experiences of families who receive a false-positive newborn screening result in an attempt to discover ways to help improve the newborn screening communication process for families	Parents whose children (ages 6–16 months) underwent follow-up testing after newborn screening and whose follow-up test results indicated that the newborn screening result was a false positive (*n* = 27)	Individual interviews and focus groups
28	Schwan *et al.*	2019	USA	X-linked ALD	To examine the impact of a positive newborn screening result for ALD on families	Mothers of children who were identified via newborn screening for ALD (*n* = 10)	Individual interviews
29	Timmermans and Buchbinder	2010	USA	Metabolic conditions	To examine how parents and clinical staff work out the social significance of uncertain newborn screening results	Families of children who visited metabolic genetic disorder clinic, 24 families had 'deeply ambiguous' diagnosis (*n* = 55)	Ethnographic observation, individual interviews
30	Tluczek *et al.*	2006	USA	Cystic fibrosis	To understand parents' perceptions of genetic counselling while awaiting their child's sweat test results	Parents of children who had at least one CFTR mutation at time of sweat test (*n* = 31 couples and 2 single mothers); 25 false positives, 8 true positives	Individual or couple interviews
31	Tluczek *et al.*	2009	USA	Cystic fibrosis or hypothyroidism	To understand how parents learnt about newborn screening and their suggestions for improving the process	Parents of 100 newborns recruited from four groups: cystic fibrosis diagnosis, cystic fibrosis carriers, hypothyroidism diagnosis or normal screens (*n* = 194)	Content analysis of prior individual interviews
32	Tluczek *et al.*	2010	USA	Cystic fibrosis	To examine the psychosocial consequences of newborn screening when cases are clinically ambiguous	Parents of five infants who received abnormal newborn screening results with gene mutations (*n* = 10)	Individual interviews
33	Tluczek *et al.*	2011	USA	Cystic fibrosis	To understand parents' perspectives about the psychosocial consequences of false-positive newborn screening results for cystic fibrosis	Parents of children who had false-positive screening results for cystic fibrosis (*n* = 87)	Individual or couple interviews

#	Author (date)	Date	Country	Condition(s) addressed	Research aim	Participants	Data
34	Ulph *et al.*	2011	UK	Haemoglobin disorders	To explore the origins and content of service users' prior knowledge of universal antenatal and newborn screening for haemoglobin disorders	People who used antenatal and newborn screening for haemoglobin disorders (*n* = 37)	Individual interviews
35	Ulph *et al.*	2014	UK	Cystic fibrosis or sickle cell disease	To examine parents' intentions to inform their child of newborn screening carrier results	Family members of children who received a carrier result following newborn screening (*n* = 67)	Individual interviews
36	Ulph *et al.*	2015	UK	Cystic fibrosis or sickle cell disease	To explore parents' responses to receiving sickle cell or cystic fibrosis carrier results for their child following newborn screening	Family members of children who received a carrier result following newborn screening (*n* = 67)	Individual interviews

CAH, congenital adrenal hyperplasia; CFSPID, cystic fibrosis screen positive, inconclusive diagnosis; CFTR, cystic fibrosis transmembrane conductance regulator; G6PD, glucose-6-phosphate dehydrogenase; IRT, immunoreactive trypsinogen; MCADD, Medium-chain acyl-CoA dehydrogenase deficiency; MSUD, Maple syrup urine disease; PD, Pompe disease.

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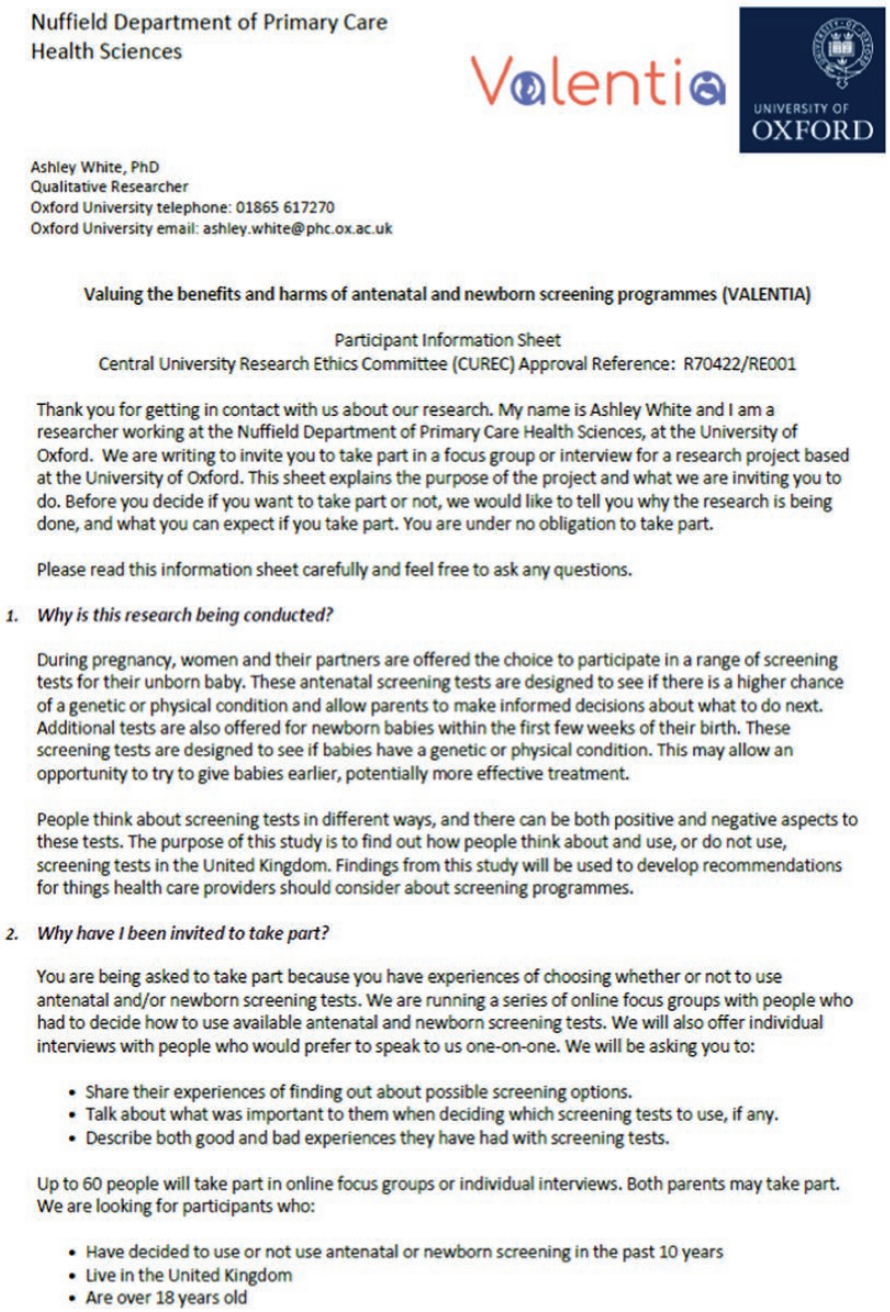
Appendix 8 Participant recruitment materials



Nuffield Department of Primary Care
Health Sciences

Valentia

UNIVERSITY OF OXFORD

Ashley White, PhD
Qualitative Researcher
Oxford University telephone: 01865 617270
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Valuing the benefits and harms of antenatal and newborn screening programmes (VALENTIA)

Participant Information Sheet
Central University Research Ethics Committee (CUREC) Approval Reference: R70422/RE001

Thank you for getting in contact with us about our research. My name is Ashley White and I am a researcher working at the Nuffield Department of Primary Care Health Sciences, at the University of Oxford. We are writing to invite you to take part in a focus group or interview for a research project based at the University of Oxford. This sheet explains the purpose of the project and what we are inviting you to do. Before you decide if you want to take part or not, we would like to tell you why the research is being done, and what you can expect if you take part. You are under no obligation to take part.

Please read this information sheet carefully and feel free to ask any questions.

1. ***Why is this research being conducted?***

During pregnancy, women and their partners are offered the choice to participate in a range of screening tests for their unborn baby. These antenatal screening tests are designed to see if there is a higher chance of a genetic or physical condition and allow parents to make informed decisions about what to do next. Additional tests are also offered for newborn babies within the first few weeks of their birth. These screening tests are designed to see if babies have a genetic or physical condition. This may allow an opportunity to try to give babies earlier, potentially more effective treatment.

People think about screening tests in different ways, and there can be both positive and negative aspects to these tests. The purpose of this study is to find out how people think about and use, or do not use, screening tests in the United Kingdom. Findings from this study will be used to develop recommendations for things health care providers should consider about screening programmes.

2. ***Why have I been invited to take part?***

You are being asked to take part because you have experiences of choosing whether or not to use antenatal and/or newborn screening tests. We are running a series of online focus groups with people who had to decide how to use available antenatal and newborn screening tests. We will also offer individual interviews with people who would prefer to speak to us one-on-one. We will be asking you to:

- Share their experiences of finding out about possible screening options.
- Talk about what was important to them when deciding which screening tests to use, if any.
- Describe both good and bad experiences they have had with screening tests.

Up to 60 people will take part in online focus groups or individual interviews. Both parents may take part. We are looking for participants who:

- Have decided to use or not use antenatal or newborn screening in the past 10 years
- Live in the United Kingdom
- Are over 18 years old

FIGURE 9 Participant information sheet. (*continued*)

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We are interested in hearing about why you decided to have or not have screening tests. We are also interested in hearing about what happened after you made those decisions. We seek to hear a broad range of experiences. If you are willing to share your thoughts and experiences with us, then we would like to hear from you.

3. ***Do I have to take part?***

No. You can ask questions about the research before deciding whether or not to take part. If you do agree to take part, you may withdraw yourself from the study, without giving a reason, by advising us of this decision. If you wish to leave during the study, you are free to do so. If you want us to, we can make every effort to remove your comments from the focus group record or delete your interview transcript for up to six months after the end of the study.

4. ***What will happen to me if I take part in the research?***

If you would like to take part, you will be asked to complete and send back the attached screening questionnaire by email or pre-paid envelope in the post. We will contact you to let you know when and where the focus group or interview will be held. You can ask us any questions you may have at this stage. If you do decide to take part, we will give you a consent form to sign before the focus group or interview takes place.

You will be asked to:

- Share your experiences of finding out about possible screening options.
- Talk about what was important when deciding which screening tests to use, if any.
- Describe both good and bad experiences you have had with screening tests.

Online focus groups will include up to 10 people and two researchers who will facilitate the discussion. You will have been given a fake name to use during the focus group so only the researcher will know who you are. We will do our best to ensure that each focus group will include people who made similar decisions and had similar outcomes with screening tests. The focus groups will start with a one-hour live chat where the researchers will ask everyone questions about antenatal and newborn screening in real time. Over the following week, you will be asked to respond to questions posted on the chat. You can respond whenever you have time and share as much or as little as you want. You will be alerted when new questions are posted. At the end of the week, there will be another one-hour live chat session in real-time to wrap up and finish the focus group. Because the focus groups are online, we will have a written record of everyone's responses. After the focus groups, researchers will analyse what was said to find out what the important issues are for people who might use, or refuse, screening tests during pregnancy or after birth.

If you want to participate, but do not feel comfortable talking about your experiences in a group, you can let us know. We can arrange to do an individual interview with over the phone or over a web conference. People who choose an interview will be asked the same type of questions as people who choose to join a focus group. Interviews will be one-on-one and last about an hour. Because we want to pick up everything that people say in the interview, we will ask to record the conversations. However, if you do not wish to have the interview recorded you may still take part. Just like with the focus groups, researchers will analyse what was said to find out what the important issues are for people who might use screening tests during pregnancy or after birth. Interview participants will be given a fake name to be used for all study-related activity; no one but the research team will know their identity.

5. ***Are there any potential risks in taking part?***

There is a risk that you may become emotionally distressed talking about these experiences. We will do our best to make sure that focus groups only have people who had similar experiences so that everyone feels safe. You can take breaks during focus groups or interviews, or completely stop participating altogether. You can also change to a one-to-one interview if a focus group setting does not feel right. We will also

FIGURE 9 Participant information sheet. (*continued*)

provide a list of support resources for you to access. If you decide to take part in the project, you can withdraw at any point before, during, or after the focus group or interview.

There is also a risk of breach of confidentiality, however, we will do our best to ensure that your confidentiality is maintained. You will be identified only by a pseudonym on all documents and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be de-identified as soon as it is practical to do so. Whilst confidentiality will be given the utmost priority within this research project, there will be limits to how far this confidentiality can be guaranteed. If disclosures are made within the interviews, which suggest that you are at substantial risk of harm (whether from yourself or someone else), then action will be taken. This action may include contacting relevant health care professionals or agencies (e.g., social care services) as appropriate.

6. ***Are there any benefits in taking part?***

The benefits of taking part are that people often say they have found the experience rewarding. You may be motivated to take part because you want a chance to influence the way screening tests are implemented and offered in the United Kingdom.

7. ***Expenses and payments***

Participants will receive a £20 voucher to say thank you for their time, even if they withdraw during the study.

8. ***What happens to the data provided?***

The information you provide during the study is the **research data**. Any research data from which you can be identified (such as your name, contact details, audio recording) is known as **personal data**. This includes more sensitive categories of personal data such as your racial or ethnic origin, sexual orientation, or data concerning your health.

Personal / sensitive data will be stored on a secure computer server or locked cabinets at the Nuffield Department of Primary Care Health Sciences, University of Oxford. Electronic data will be password protected. Only the research team will have access to the data. We will keep screening questionnaires and audio files from individual interviews until the end of the study in June 2021. We may keep contact details for up to 6 months after the study has finished in case we need to get in touch with participants.

Other research data (including consent forms) will be securely at the University of Oxford for 10 years for future analysis if further research questions arise.

The research team will have access to the research data. Audio recordings of interviews will be given to a typist who will type out everything as it was said the interview. The typist signs an agreement to keep everything they have typed confidential. Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the research.

9. ***Will the research be published?***

The research may be published in a peer review journal. The researchers will also write a report for the National Institute of Health Research. The researchers may use quotes from the focus groups and interviews in their reports but will only use the fake names of participants.

10. ***Who is funding the research?***

The research is funded by the National Institute of Health Research. It is part of a larger study about the potential benefits and harms of antenatal and newborn screening.

FIGURE 9 Participant information sheet. (*continued*)

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11. ***Who has reviewed this study?***

This study has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee (Reference number: R70422/RE001).

12. ***Who do I contact if I have a concern about the study or I wish to complain?***

If you have a concern about any aspect of this study, please contact Dr. Ashley White at ashley.white@phc.ox.ac.uk / 01865 617270 or Dr. Lisa Hinton at lisa.hinton@thisinstitute.cam.ac.uk / 01223 731573, and we will do our best to answer your query. We will acknowledge your concern within 10 working days and give you an indication of how it will be dealt with. If you remain unhappy or wish to make a formal complaint, please contact the Chair of the Research Ethics Committee at the University of Oxford who will seek to resolve the matter as soon as possible:

Chair, **Medical Sciences Inter-Divisional Research Ethics Committee**;
Email: ethics@medsci.ox.ac.uk;
Address: Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD

13. ***Data Protection***

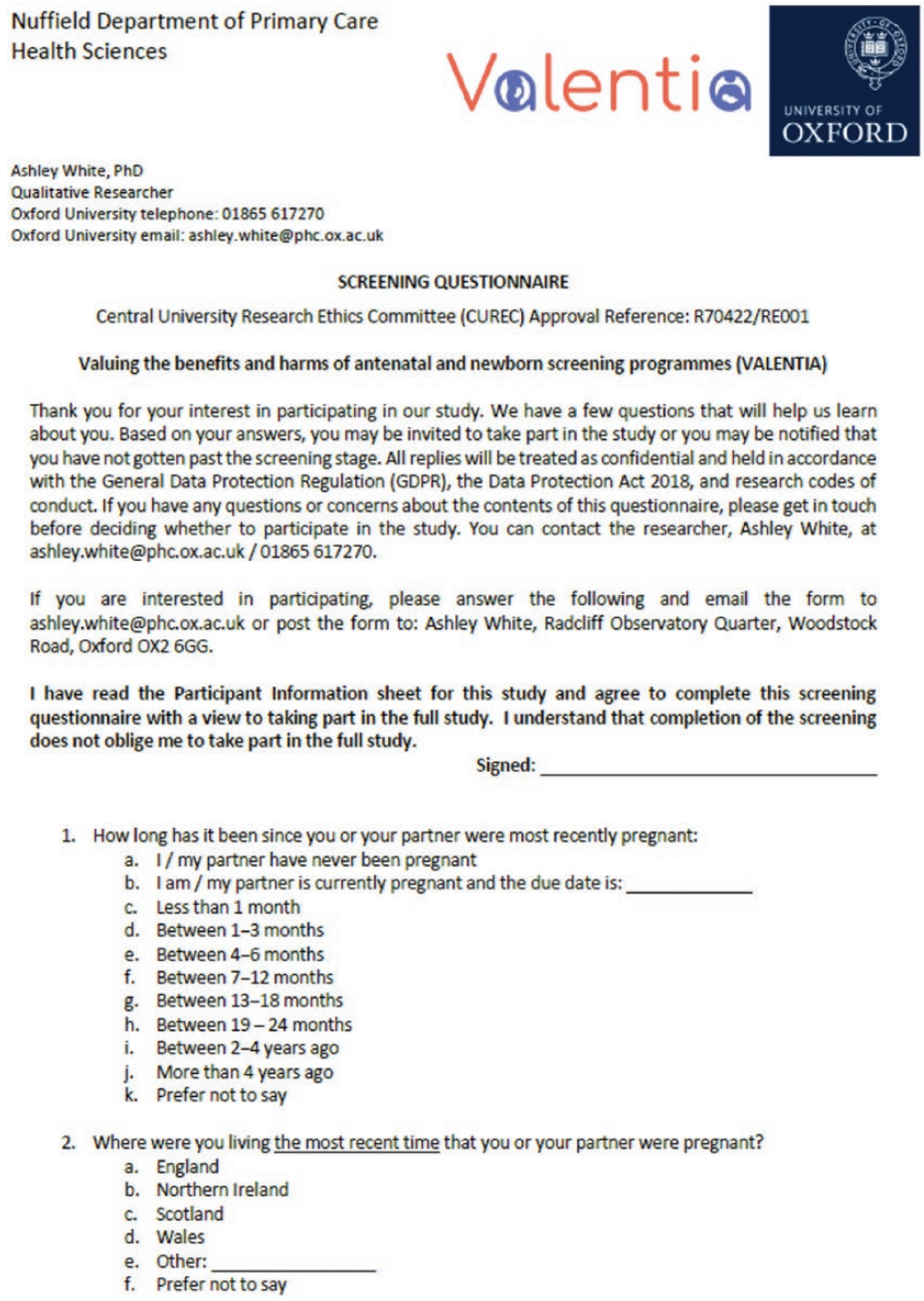
The University of Oxford is the data controller with respect to your personal data, and as such will determine how your personal data is used in the study. The University will process your personal data for the purpose of the research outlined above. Research is a task that is performed in the public interest. Further information about your rights with respect to your personal data is available from http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/.

14. ***Further Information and Contact Details***

If you would like to discuss the research with someone beforehand (or if you have questions afterwards), please contact:

Dr. Ashley White
Nuffield Department of Primary Care Health Sciences
Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG
University tel: 01865 617270
University email: ashley.white@phc.ox.ac.uk

FIGURE 9 Participant information sheet.



Nuffield Department of Primary Care
Health Sciences

Valentia

UNIVERSITY OF OXFORD

Ashley White, PhD
Qualitative Researcher
Oxford University telephone: 01865 617270
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SCREENING QUESTIONNAIRE

Central University Research Ethics Committee (CUREC) Approval Reference: R70422/RE001

Valuing the benefits and harms of antenatal and newborn screening programmes (VALENTIA)

Thank you for your interest in participating in our study. We have a few questions that will help us learn about you. Based on your answers, you may be invited to take part in the study or you may be notified that you have not gotten past the screening stage. All replies will be treated as confidential and held in accordance with the General Data Protection Regulation (GDPR), the Data Protection Act 2018, and research codes of conduct. If you have any questions or concerns about the contents of this questionnaire, please get in touch before deciding whether to participate in the study. You can contact the researcher, Ashley White, at ashley.white@phc.ox.ac.uk / 01865 617270.

If you are interested in participating, please answer the following and email the form to ashley.white@phc.ox.ac.uk or post the form to: Ashley White, Radcliff Observatory Quarter, Woodstock Road, Oxford OX2 6GG.

I have read the Participant Information sheet for this study and agree to complete this screening questionnaire with a view to taking part in the full study. I understand that completion of the screening does not oblige me to take part in the full study.

Signed: _____

1. How long has it been since you or your partner were most recently pregnant:
   a. I / my partner have never been pregnant
   b. I am / my partner is currently pregnant and the due date is: _____
   c. Less than 1 month
   d. Between 1–3 months
   e. Between 4–6 months
   f. Between 7–12 months
   g. Between 13–18 months
   h. Between 19 – 24 months
   i. Between 2–4 years ago
   j. More than 4 years ago
   k. Prefer not to say

2. Where were you living the most recent time that you or your partner were pregnant?
   a. England
   b. Northern Ireland
   c. Scotland
   d. Wales
   e. Other: _____
   f. Prefer not to say

FIGURE 10 Participant questionnaire. (*continued*)

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The following questions are about whether or not you have taken part in antenatal or newborn screening tests. You may find it helpful to look at the antenatal and newborn screening timeline we included. You can also learn about screening tests offered by the NHS here:
https://www.nhs.uk/conditions/pregnancy-and-baby/screening-tests-in-pregnancy/

3. You or your partner may have been offered **antenatal screening tests** in the past. Antenatal screening tests are used to see if your baby has a higher chance of having a health condition. Antenatal screening tests are shown in green and red on the screening timeline. Think about all the times you or your partner were pregnant. **Please mark all the boxes that apply to your experiences.**

	Yes, I / my partner experienced this.
Where you had care:	
I / my partner had antenatal care on the NHS.	
I / my partner had antenatal care at a private hospital, clinic, or office.	
Antenatal scans:	
I / my partner had some scans during pregnancy but I do not remember when.	
I / my partner had an early pregnancy / dating scan around 10–12 weeks.	
I / my partner had a mid-pregnancy / anomaly scan around 20 weeks.	
I / my partner had additional scans besides the early and mid-pregnancy scans.	
I / my partner declined to have any scans during pregnancy.	
I am unsure if I / my partner had scans during pregnancy.	
Antenatal tests:	
I / my partner had some tests during pregnancy but I do not remember what they were.	
I / my partner had some tests during pregnancy but I do not know what they were for.	
I / my partner had blood tests for infectious conditions like HIV, syphilis, and hepatitis B.	
I / my partner had blood tests to learn my / their rhesus status.	
I / my partner had blood tests to see if I / they had sickle cell disease or thalassaemia.	
I / my partner had a blood test and scan to see the chances of the baby having Down's syndrome (T21), Edwards' syndrome (T18), or Patau's syndrome (T13).	
I / my partner had a non-invasive prenatal test (NIPT) to see the chances of the baby having Down's syndrome (T21), Edwards' syndrome (T18), or Patau's syndrome (T13).	
I / my partner had a chorionic villus sample (CVS) test to confirm the chances of the baby having Down's syndrome (T21), Edwards' syndrome (T18), or Patau's syndrome (T13).	
I / my partner had an amniocentesis test to confirm the chances of the baby having Down's syndrome (T21), Edwards' syndrome (T18), or Patau's syndrome (T13).	
I / my partner were offered an amniocentesis or CVS test but did not want to do it.	
I / my partner declined to have any tests during pregnancy.	
I am unsure if I / my partner had tests like these during pregnancy.	

FIGURE 10 Participant questionnaire. (*continued*)

4. You or your partner may have been offered **newborn screening tests** in the past. These tests are offered in the days after a baby is born. Newborn screening tests are shown in blue and maroon on the screening timeline. **Please check all the boxes that apply to your experiences.**

	Yes, I / my partner experienced this.
Where you had care:	
I / my partner had newborn screening on the NHS.	
I / my partner had newborn screening through a private hospital, clinic, or office.	
Newborn screening:	
I / my partner have never had a child.	
I / my partner have not had a child live long enough to be offered newborn screening tests.	
My child(ren) had the 'heel-prick' newborn screening blood test.	
I / my partner do not remember being offered newborn screening tests for our child(ren).	
I / my partner declined to have newborn screening tests for our child(ren).	
I am unsure if I / my partner were offered newborn screening tests for our child(ren).	

5. If you are asked to take part in the study, would you be willing to discuss your experience in an online focus group? You would be given a fake name and no one besides the researchers would know your identity. Other details about the focus groups can be found in the participant information sheet you received.
    a. Yes
    b. No
    c. Unsure

We have some final questions about your background. We are asking these questions so that we can ensure we invite a diverse range of people to take part in the study.

6. Where do you currently live:
    a. England
    b. Northern Ireland
    c. Scotland
    d. Wales
    e. Other: _____

7. How old are you? _____

8. What is your current household income?
    a. Less than £10,000 per year
    b. £10,000 – 19,999 per year
    c. £20,000 – 29,999 per year
    d. £30,000 – 39,999 per year
    e. £40,000 – 49,999 per year
    f. £50,000 – 59,999 per year
    g. £60,000 – 69,999 per year
    h. £70,000 – 79,999 per year
    i. £80,000 – 89,999 per year
    j. £90,000 – 99,999 per year
    k. More than £100,000 per year
    l. Prefer not to say

FIGURE 10 Participant questionnaire. (*continued*)

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9. Would you consider yourself:
    a. Female
    b. Male
    c. Trans/transgender woman
    d. Trans/transgender man
    e. Non-binary
    f. Other (please describe: _____)
    g. Prefer not to say

10. How would you describe your current relationship status?
    a. Married or civil partnership
    b. Widowed
    c. Separated or divorced
    d. Living together with my partner but not married
    e. In a committed relationship but not living together
    f. Single
    g. Prefer not to say

11. How would you describe your race/ethnic group?
    a. Arab
    b. Asian / Asian British
    c. Black / African / Caribbean / Black British
    d. White
    e. Mixed / multiple (please describe: _____)
    f. Other (please describe: _____)
    g. Prefer not to say

12. What is the highest level of education you have completed?
    a. Secondary education / GCSEs / Scottish National Qualification
    b. Sixth form / A-levels / Scottish Highers / Vocational qualification
    c. Bachelor's / first / undergraduate university degree
    d. Master's or doctoral university degree
    e. Prefer not to say

13. How would you describe your religious, moral or spiritual beliefs?
    a. Atheist, agnostic, or non-religious
    b. Buddhist
    c. Christian
    d. Hindu
    e. Humanist
    f. Muslim
    g. Sikh
    h. Other (please describe: _____)
    i. Prefer not to say

14. Thank you for telling us a bit about your experiences with antenatal and newborn screening tests. If you would, **please tell us anything else that you think is important for us to know about your experiences.** This might be about the tests you had, the results of the tests, choices you made, conditions that your child had, etc. You can share as little or as much as you feel comfortable. Use as much room as you need below.

FIGURE 10 Participant questionnaire.

Appendix 9 Focus group guide

(A) Group 1 People's Experiences Focus Group Discussion Guide

INITIAL CHAT CONVERSATION

Hello and thank you everyone for joining us today. We will get started with some questions in just a moment but wanted to establish a few ground rules before we get into it.

1. ***Please be respectful of each other and the different opinions you may have**. We understand that people may have different views on certain topics we will discuss today, and we want to hear about those perspectives. However, we will not condone attacks on someone's ethnicity, religion, sexual orientation, political views, etc. Please try to remain civil.*
2. ***Please share your thoughts but also allow space for others to share, too**. We want to hear about everyone's experiences. If you have been taking over the conversation for a while, sit back for a moment to allow someone else a chance to join in.*
3. ***Anything you share is at your discretion**. Everyone has been assigned a fake name (except for the researchers). No other participants will know who you are. Please try not to use other people's real names (e.g. the name of your doctor). Also, be mindful of how much you share about your personal location, family, and/or experiences. For example, instead of saying, 'I am a 30-year-old married woman living in Reading with a 10-month-old daughter with cystic fibrosis and we see Dr. Smith', you could say, 'I am in my 30s, live in the southeast, and my daughter has cystic fibrosis. We see a specialist consultant'. However, it is up to you how much to disclose to the other participants.*

That's it – only three rules to follow.

So thank you everyone for joining us tonight. (We have XX people in the room. We understand that you all have XX experiences.)

We appreciate your time and look forward to what you have to share. We are going to ask some questions about what it has been like to be pregnant during these strange times. We are particularly interested to hear about the scans you might have had, the tests you might have been offered, and what you hope might happen in the future.

1. What kind of antenatal scans or screens did you/your partner have?

    - Probe: Where did participant and/or their partner receive antenatal care and why? (e.g. through the NHS, private care, combination).
    - Probe: Ask about specific tests by name

        - Blood for sickle cell and/or thalassaemia
        - Combined test or quadruple tests for T21/T18/T13
        - Dating, 20 week, other scans
        - Amnio or CVS
        - NIPT.

2. One of the things we want to learn more about is why people do or do not have screening tests. Can you tell me more about why you decided to (have/not have) (tests mentioned above)?

    - Probe: Whether participant was aware of screening and purposes.
    - Probe: Was it a choice, or something that 'just happened'?

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- Probe: What people or beliefs influenced their decisions?
- Probe: Explore why people might have had some and not others.

3. For those of you who had specific antenatal tests, can you tell me more about how you found out the results?

   - Probe: How and when results were delivered?
   - Probe: Who – if anyone – did they talk with after getting their results?
   - Probe: Solicit narrative about chain of decision-making processes (if applicable).

4. (Ask only if we have group where participants miscarried) I was wondering if you might be able to say a bit about your experience with miscarriage(s)? It is up to you how much you share. If you do not want answer, you can skip this question.

   - Probe: How do they feel about the experience?
   - Probe: Who – if anyone – did they talk with before/after?

5. (Ask only if we have group where participants terminated pregnancy) I was wondering if you might be able to tell me a bit about your experience with terminating a pregnancy(ies). Again, you do not need to answer if you do not want to.

   - Probe: How they/their partner made that decision?
   - Probe: Who – if anyone – did they talk with before/after?

6. (Ask only if we have group where participants gave birth but baby did not survive perinatal period) I was wondering if you might share a bit more about what that was like losing (baby/name)? It is okay if you do not want to talk about this.

   - Probe: Had screening pre-identified a condition? If so, was it better or worse to know in advance?
   - Probe: Who – if anyone – did they talk with before/after?
   - Probe: What – if any – funeral/memorial events unfolded?

7. (Ask only if we have group where participants gave birth and baby survived) Once your baby was born, do you remember having a heel prick test?

   - Probe: Circumstances around heel prick.
   - Probe: Circumstances around consent versus did it 'just happen'.
   - Probe: Whether participant was aware of screening and purposes.

8. (Ask only if we have group where participants gave birth and baby survived) Do you remember if you were notified about the results of the heel prick test?

   - Probe: How and when results were delivered?
   - Probe: Who – if anyone – did they talk with after getting their results?
   - Probe: Solicit narrative about chain of decision-making processes (if applicable).

9. (Ask only if we have group where participants' children have had positive newborn screen) Can you tell me more about what happened after you got the positive screen results?

   - Probe: Emotional responses to screening results.
   - Probe: What was the condition and how/if it was diagnosed?
   - Probe: Whether they gathered information on the condition and how?
   - Probe: Had child become symptomatic and impact result had at that point?
   - Probe: What their/their child's life is like living with the condition?
   - Probe: How the condition has been received by others and how that might change in the future?

Those are all of our prepared questions for today. Before we wrap up, is there anything that someone wants to ask about before we end our conversation? (Respond accordingly).

As a reminder, we will be posting three discussion questions for you to read and respond to in just a moment. You have until our next live chat to answer those. They are under the 'Forum' tab on the website. In the final discussion we will be asking you to think about the benefits and harms of screening.

Our next live chat will take place on (date and time).

Please let us know if you have any questions in the meantime by getting in touch at ashley.white@phc.ox.ac.uk.

That is it from us. Thank you for your time today everyone!

SECOND CHAT CONVERSATION

Hello and thank you everyone for joining us today.

Just like last time, we want to remind you that the same three ground rules apply. Please respect others, share the conversation, and remember that anything you share is at your discretion.

With that out of the way, we are going to ask you to think back again on your own experiences with antenatal and newborn screening.

Last time we chatted about your specific experiences with antenatal and newborn screening. We really appreciated your ideas about how to better communicate screening result! You have also had a chance to read and reflect on the vignettes. We appreciate you sharing your experiences and thoughts with us.

We have a few questions to wrap up everything today but I wanted to see if anyone had any reflections on the forum questions? Thank you again for taking time to answer those! (Transition to questions below).

1. Looking back at your overall journey, what were some of the benefits – or good things – about having had antenatal screening tests? Only antenatal.
2. Again, looking back at your overall journey, what were some of the harms – or bad or difficult things – about having had antenatal screening tests? Only antenatal.

    - For everyone – did antenatal screening feel like an end point? Or just a stop on the journey?

3. Looking back at your overall journey, what were some of the benefits – or good things – about having had newborn screening? Only newborn.
4. Again, looking back at your overall journey, what were some of the harms – or bad or difficult things – about having had newborn screening? Only newborn.
5. Thinking about your own experiences with the screening process overall, what could have been better?

    - Probe: What could have been better for partner and/or child?

6. Thinking about your own experiences with the screening process overall, what information or support do you wish you had beforehand?

    - Probe: What could have been communicated/how it could have been communicated?
    - Probe: Are there any people or sources of support you wished you had to consult?

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Those are all of our prepared questions for today. Before we wrap up, is there anything else that someone wants to talk about? (Respond accordingly).

As a reminder, our finance officer will be sending along electronic vouchers to thank you for your time. You should get those in the next few days. Please let me know if you have any questions by getting in touch at ashley.white@phc.ox.ac.uk.

That is it from us, thank you!

(B) Group 1 People's Experiences Focus Group Scenarios

The following questions are made up scenarios about how people might experience antenatal or newborn screening. Please imagine yourself living through these scenarios. What might you do if this happened to you? What might you want to know? Who might you want to speak to? There is no right or wrong answer.

SCENARIO 1

You and your partner Sam have been trying to have a baby for several years. You are 38 and Sam is 41. The first time you got pregnant you were 35, but you miscarried before 10 weeks. You got pregnant a second time a year later, and again had a miscarriage before 10 weeks. You and Sam worry that you are running out of time to conceive.

You are now pregnant for a third time and just had an early scan at 8 weeks. You hope that you do not experience another miscarriage as you really want to have a child.

You are being offered a blood test on the NHS to see if you are a 'carrier' for thalassaemia or sickle cell disease – two inherited blood conditions. People can be a 'carrier' of these conditions, which is also known as having the 'trait'. If you are a carrier, you generally will not have any health problems, but there is a chance that your child might inherit the condition.

People living with thalassaemia produce either no or too little haemoglobin, which is used by red blood cells to carry oxygen around the body. This can make them very anaemic (tired, short of breath and pale). There are several types of thalassaemia, each requiring varying degrees of treatment. Although the main health problems associated with thalassaemia can often be managed with treatment, it's still a serious health condition that can have a significant impact on a person's life. In the past, severe thalassaemia was often fatal by early adulthood. But with current treatments, people are likely to live into their 50s, 60s and beyond.

Sickle cell disease is the name for a group of inherited health conditions that affect the red blood cells. The most serious type is called sickle cell anaemia. People with sickle cell disease produce unusually shaped red blood cells that can cause problems because they do not live as long as healthy blood cells and can block blood vessels. Sickle cell disease varies between individuals from mild to serious. Most people with it lead happy and normal lives but the illness can be serious enough to have a significant effect on a person's life. Overall, the life expectancy for someone with sickle cell disease tends to be shorter than normal, but this can vary depending on the exact type of sickle cell disease they have, how it's treated and what problems they experience.

What might you do? What might you want to know? Who might you want to speak to?

SCENARIO 2

You recently gave birth to a little boy named Tyler. During pregnancy, you decided to have all the antenatal screens offered on the NHS. All your tests and scans came back with reassuring results and you had no concerns about your baby's health. Your labour and birth went smoothly and you were able to take your son home the next day.

A few days later, a midwife came to your house to check how Tyler was doing. You watched as the midwife did a heel prick test to check Tyler's blood. The midwife said everything seemed fine and then left shortly afterwards.

One week after the midwife came to your house, you received a phone call at 4 pm and were told that you need to come see the GP the next day. The person on the phone did not tell you much information but indicated that something happened with the heel prick test.

The next morning, you took Tyler to the GP. The GP told you that Tyler tested positive for a rare but potentially serious inherited condition called PKU. This condition means that Tyler will have a hard time digesting foods high in protein, such as meat, eggs and dairy products. Tyler will require a special diet and regular blood tests for the rest of his life. If the condition remains untreated, Tyler might develop an intellectual disability or seizures.

How might you feel at this moment? What might you want to know? Who might you want to speak to?

SCENARIO 3

You and your partner Mo have a 4-year-old daughter. You are pregnant again, and are 12 weeks along.

You were offered the 'combined test' as part of your antenatal care on the NHS. This is a screen that combines a blood test and scan to check the chances of a having a baby with Down syndrome (also known as Trisomy 21 or T21), Edwards syndrome (Trisomy 18/T18) or Patau syndrome (Trisomy 13/T13). You and Mo talked about it and decided that you wanted to do the screening test.

The screening test showed that there was a higher-than-average chance of having a baby with Down syndrome. Your midwife explains that there is a 1 in 90 chance of your baby having the condition. Your midwife explains that Down syndrome is a lifelong genetic condition that causes delays in learning and development. It may also cause medical conditions such as heart problems. However, it is a variable condition and some people are more seriously affected than others.

You and Mo would have to wait 1 week for further tests on the NHS, so you decided to have a further private screening test the next day. You had a NIPT at your local private hospital. NIPT is a blood test that can be used to assess the chance of having a baby with Down syndrome, Edwards syndrome or Patau syndrome (among others). It is a newer test than the 'combined test' you already had. NIPT is also more accurate than the 'combined test'.

The NIPT result tells you there is a > 9 in 10 chance your baby has Down syndrome. Put another way, the NIPT result tells you that there is a > 90% chance your baby has Down syndrome.

What might you do next? What might you want to know? Who might you want to speak to?

(C) Group 1 People's Experiences Interview Discussion Guide

(Interviewer script)

Thank you for taking time to speak with me about your experiences with antenatal and newborn screening programmes. We are going to start with a few questions about your background and then shift into talking about your experiences with screening programmes specifically. You have previously signed a consent form, but I want to be sure that you are happy to continue with the interview?

(Wait for affirmative)

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Great, thank you. As a reminder, we will remove any identifying details about you or your family members. We will only refer to you using a fake name to protect your anonymity. If I ask a question and you do not want to answer it, we can skip it, which is no problem. We can also end the interview at any point. It is entirely up to you. You can tell me as much or as little as you want. After the interview, I will send you a typed transcript of the conversation and you can change anything that you want to edit. Is that all okay?

(Wait for affirmative)

Is it okay for me to record our conversation so that I have an accurate record of what we talked about?

(If no, then proceed to question #2)

(If yes, then proceed with last statement)

I am going to start the recording in just a moment. The first thing I am going to ask is for you to confirm that you consent to having the conversation recorded. Then we will roll into the questions. Do you have any questions for me before we get going?

(If no, then proceed to question #1)

(If yes, then answer before starting question #1)

1. Okay, this is (interviewer) speaking with participant (number). Can you confirm that I have your permission to record this conversation?

Thank you for confirming. Now, I am going to ask you some questions about what it was like when (you/your partner) were pregnant. In particular, we are interested to hear about the scans you might have had, the tests you might have been offered, and what happened in your experience.

2. So, to start with, can you tell me a bit about your pregnancy(ies)? (Probe for each pregnancy).

    - Probe: How participant found out about their/their partner's pregnancy(ies)?
    - Probe: Overall picture of how pregnancy went: including time to conception, age, fertility treatments.
    - Probe: Where did participant and/or their partner receive antenatal care and why? (e.g. through the NHS, private care, combination).
    - Probe: What antenatal screens were they offered?

        - Blood for sickle cell and/or thalassaemia
        - Combined test or quadruple tests for T21/T18/T13
        - Dating, 20 week, other scans
        - Amnio or CVS
        - NIPT.

3. One of the things we want to learn more about is why people do or do not have screening tests. Can you tell me more about why you decided to (have/not have) (tests mentioned above)?

    - Probe: Whether participant was aware of screening and purposes.
    - Probe: Was it a choice, or something that 'just happened'?
    - Probe: What people or beliefs influenced their decisions?

4. (Skip if no tests at all) Can you tell me more about how you found out the results of (tests mentioned above)?

    - Probe: How and when results were delivered?
    - Probe: How the test results impacted the rest of pregnancy, if at all?
    - Probe: Who – if anyone – did they talk with after getting their results?
    - Probe: Solicit narrative about chain of decision-making processes (if applicable).

5. (Ask only if participant miscarried) I was wondering if you might be able to tell me a bit about your experience with miscarriage(s)? It is up to you how much you share, and we can skip this question if you want.

    - Probe: How do they feel about the experience?
    - Probe: Who – if anyone – did they talk with before/after?
    - (SKIP TO 12).

6. (Ask only if participant terminated pregnancy) I was wondering if you might be able to tell me a bit about your experience with terminating a pregnancy(ies). It is up to you how much you share and we can skip this question if you want.

    - Probe: How they/their partner made that decision?
    - Probe: Who – if anyone – did they talk with before/after?
    - (SKIP TO 12).

7. (Ask only if carried to term) Can you tell me about what your/your partner's labour and birth experience was like?

    - Probe: Who was involved in delivery (partner, midwife, specialists, etc.)?
    - Probe: What was it like for your partner (if applicable)?

8. (Ask only if participant gave birth but baby did not survive perinatal period) I was wondering if you might tell me a bit more about what that was like losing (baby/name)? It is okay if you do not want to talk about this, we can skip it.

    - Probe: Had screening pre-identified a condition? If so, was it better or worse to know in advance?
    - Probe: Who – if anyone – did they talk with before/after?
    - Probe: What – if any – funeral/memorial events unfolded?
    - (SKIP TO 12).

9. (Ask only if participant gave birth and baby survived) Once your baby was born, do you remember him/her having a heel prick test?

    - Probe: Circumstances around heel prick.
    - Probe: Circumstances around consent versus did it 'just happen'.
    - Probe: Whether participant was aware of screening and purposes.

10. (Ask only if participant's child had heel prick) Do you remember if you were notified about the results of the heel prick test?

    - Probe: How and when results were delivered?
    - Probe: Who – if anyone – did they talk with after getting their results?
    - Probe: Solicit narrative about chain of decision-making processes (if applicable).

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11. (Ask only if participant's child had positive newborn screen) Can you tell me more about what happened after you got the positive screen results?

    - Probe: Emotional responses to screening results.
    - Probe: Family communication around getting screening result/diagnosis – did they share it with others? When?
    - Probe: What was the condition and how/if it was diagnosed?
    - Probe: What did they know about the condition at the time it was first brought up?
    - Probe: Whether they gathered information on the condition and how.
    - Probe: Had child become symptomatic and impact result had at that point?
    - Probe: What their/their child's life is like living with the condition?
    - Probe: How the condition has been received by others and how that might change in the future?

(Ask all)

12. Thank you for telling me about your experiences. I have just a few more questions for you. Looking back at your overall experience, what were some of the benefits – or good things – about having had (specific antenatal/newborn) screening tests?

    - Probe: Do they believe this would be the case for other people?
    - Probe: What were the benefits of their own specific approach?

13. Again, looking back at your overall experience, what were some of the harms – or bad or difficult things– about having had (specific antenatal/newborn) screening tests?

    - Probe: Do they believe this would be the case for other people?

14. Thinking about your own experiences with the (specific antenatal/newborn) screen process, what could have been better?

    - Probe: What could have been better for partner and/or child?

15. Thinking about your own experiences with the (antenatal/newborn) screen process, what information or support do you wish you had beforehand, if any?

    - Probe: What could have been communicated/how it could have been communicated?
    - Probe: Specific services or people they could have consulted.

Those are all my prepared questions. Before we wrap up, is there anything that I have not asked about that you think is important to share?

(Respond accordingly)

Is there anything that you would like to ask me before we end our conversation?

(Respond accordingly)

A professional transcriber is going to type up our conversation. Once they are finished, I will send you a copy and you can take a look and make any changes, if you wish. Please feel free to get in touch with any other questions or concerns. Again, thank you very much for your time today!

(End recording)

(D) Group 2 Stakeholders Interview Discussion Guide

(Interviewer script)

Thank you for taking time to speak with me about your experiences with antenatal and newborn screening programmes. We are going to start with a few questions about your background and then shift into talking about your experiences with screening programmes specifically. You have previously signed a consent form, but I want to be sure that you are happy to continue with the interview?

(Wait for affirmative)

Great, thank you. As a reminder, we will remove any identifying details about you or your family members. We will only refer to you using a fake name, to protect your anonymity. If I ask a question and you do not want to answer it, we can skip it, which is no problem. We can also end the interview at any point. It is entirely up to you. You can tell me as much or as little as you want. After the interview, I will send you a typed transcript of the conversation and you can change anything that you want to edit. Is that all okay?

(Wait for affirmative)

Is it okay for me to record our conversation so that I have an accurate record of what we talked about? (and facilitate transcription)

(If no, then proceed to question #2)

(If yes, then proceed with last statement)

I am going to start the recording in just a moment. The first thing I am going to ask is for you to confirm that you consent to having the conversation recorded. Then we will roll into the questions. Do you have any questions for me before we get going?

(If no, then proceed to question #1)

(If yes, then answer before starting question #1)

1. Okay, this is (interviewer) speaking with participant (number). Can you confirm that I have your permission to record this conversation?
2. Great, thank you. Could you please tell me about how you are involved in antenatal and newborn screening?

    - Probe to understand their role, time devoted, who they typically interact with, their goals, route to involvement.

Thank you for that. I have some questions now specifically about antenatal screening. We will talk about newborn screening shortly but the focus for now is antenatal screening.

3. Based on your experiences, what are some potential benefits of antenatal screening?

    - Probe to determine how benefits might apply to specific people/groups/conditions/ pregnancy stage.

4. Based on your experiences, what are some potential harms of antenatal screening?

    - Probe to determine how harms might apply to specific people/groups/conditions/ pregnancy stage.

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5. Thinking about the antenatal screening system in (England), what about the process works well?
    - Probe to see about any variation based on specific people/groups/conditions.
6. What, if anything, could be improved about the current approach to antenatal screening?
    - Probe to see about any variation based on specific people/groups/conditions.

Thank you for that. I have some questions now specifically about newborn screening. So, as much as you can, think just about newborn screening for these next questions.

7. Based on your experiences, what are some potential benefits of newborn screening?
    - Probe to determine how benefits/positives might apply to specific people/groups/conditions.
8. Based on your experiences, what are some potential harms of newborn screening?
    - Probe to determine how harms/negatives might apply to specific people/groups/conditions.
9. Thinking about the newborn screening system in (England), what about the process works well?
    - Probe to see about any variation based on specific people/groups/conditions.
10. What, if anything, could be improved about the current approach to newborn screening?
    - Probe to see about any variation based on specific people/groups/conditions.

Okay, I have just a few more questions for you. We have been thinking about antenatal and newborn screening separately but now I want you to think about screening and testing programmes overall.

11. If you were given the opportunity, and the funding, what aspects of the current screening programmes might you change?
    - Probe around scope for training or other resources to support their work/role.

Those are all my prepared questions. Before we wrap up, is there anything that I have not asked about that you would like to share?

(Respond accordingly)

Is there anything that you would like to ask me before we end our conversation?

(Respond accordingly)

A professional transcriber is going to type up our conversation. Once they are finished, I will send you a copy and you can take a look and make any changes, if you wish. Please feel free to get in touch with any other questions or concerns. Again, thank you very much for your time today!

(End recording)

(E) Group 3 Midwives Focus Group Discussion Guide

(INTERVIEWER SCRIPT)

Thank you for joining us this evening. Before we get started, I wanted to remind everyone that we would like to record this session so we can revisit it and create an accurate transcript of the conversation. I have an audio recorder on my desk to do this, and will send this file to our typist. I would also like to do a video recording of my screen, just to be sure that I can accurately capture who is speaking at any given time. The video will only be used to check the accuracy of the written text transcript, and then will be destroyed. In any written reports or presentations, we will only refer to you using a fake name with experience as a midwife. If you prefer, you can turn your camera off during the conversation. Are there any questions before we start? Is it ok if I begin recording?

(BEGIN RECORDINGS)

As you know, this is a project assessing the benefits and harms of antenatal and newborn screening programmes here in the UK. This study has a few parts. One part involved speaking with nearly 50 people who were either pregnant or recently gave birth; or, in some cases their partners. Another part of the study involved conducting interviews with approximately 20 charity leaders or policy-making stakeholders. We have been working to make sense of the things these research participants have shared with us, and some of what they've shared will come up in our conversation this evening.

Now, we are turning to healthcare professionals like you to get an idea of whether we are missing anything. Everyone on the call this evening is a midwife. We are going to start with a few questions about your professional background and then shift into talking about screening programmes more specifically.

(INTRODUCTIONS)

1. Just to start, let's go around the call and have everyone introduce themselves. Could you please share a bit about your training and current position?

    - Probe: What type of patients do you typically work with in your role?
    - Probe: How are you involved in aspects of antenatal screening?
    - Probe: How are you involved in newborn screening?
    - Probe: What is the typical screening journey for a patient that you see?

(SENSE CHECKING)

As I mentioned earlier, we have also heard from a number of people who have gone through screening themselves and we are starting to make sense of their experiences. I have some questions about what they have shared, and want to see if it makes sense to you, as midwives.

2. One of the important things people have shared with us how important prior reproductive histories can be when it comes to making decisions about screening. For example, if someone had a very negative experience with a sonographer, they might feel quite anxious about going back for scans in the future.

    - Probe: How do you account for prior pregnancies in your practice?
    - Probe: Do you think other types of healthcare professionals approach prior reproductive experiences the same way?

3. Another important thing we keep hearing is how women might think of screening as both a positive and negative thing. For example, we had one participant who had multiple miscarriages, and because of her history she got weekly scans after 12 weeks. She described how she was terrified of going for her scans, because she was afraid the fetus would not have a heartbeat. But, once she was in the room and the sonographer found a heartbeat, she felt joy because, in that moment, everything was okay. She would have that feeling for about an hour afterwards but then doubt

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would creep back in, and then following week when she went in she was right back to being terrified. Does this sort of experience seem familiar to you?

- Probe: Are there other examples of where screening can be both beneficial and harmful?

4. We have also focused on how people get information about antenatal and newborn screening. Could you describe what you think the average woman knows prior to pregnancy?

- Probe: What might they know once pregnant about antenatal screening? Newborn screening?
- Probe: How do you handle providing information about screening tests? How much information is appropriate?
- Probe: Have you had training on this? What were you told?
- Probe: What have you amended during years of practice?
- Probe: Is it possible to ensure that pregnant people are fully informed about the screening tests?
- Probe: How do you handle a patient who does not want some of the standard screening tests? Ex – combined test? Heel prick?
- Probe: What would you say? What would you do?
- Probe: How might you involve partners in these conversations?

5. The implications of screening, or not screening, have also been on our minds. We've been thinking about how key decisions can have potentially long-term effects on individuals and their families. Could you describe what you think some of those long-term effects might be? Examples?

- Probe: Do women or their partners ever raise these with you?

(REFLECTIONS ON BENEFITS AND HARMS)

6. Thank you for everything you've shared with us so far. As we start to wrap up, I want you to think about antenatal and newborn screening overall.

- What, if anything, are some of the good things about the current approaches to antenatal screening?
- What, if anything, could be improved about the current approach to antenatal screening?
- What, if anything, are some of the good things about the current approaches to newborn screening?
- What, if anything, could be improved about the current approach to newborn screening?

Those are all our prepared questions. Before we wrap up, is there anything that we have not touched on that you would like to share?

(Respond accordingly)

Thank you all again for your time this evening. We really appreciate it. I'll be asking our finance team to send out vouchers to thank you for your time, so please keep an eye on your inbox for those in the next few days. Please feel free to get in touch with any other questions or concerns. Again, thank you very much for your time today!

(End recording)

Appendix 10 Group 1 participants' demographic characteristics (*n* = 49)

	No. or range	% or mean (SE)
Age	24–48	34.7 (0.75)
Gender		
Female	40	81.6
Male	9	18.4
Country		
England	40	81.6
Scotland	3	6.1
Wales	6	12.2
Time since last pregnancy		
I/my partner is currently pregnant	16	32.7
< 4 months	9	18.4
Between 4 and 6 months	6	12.2
Between 7 and 12 months	3	6.1
Between 13 and 18 months	3	6.1
Between 19 and 24 months	5	10.2
Between 2 and 4 years ago	7	14.3
Household income (£)		
10,000–19,999 per year	1	2.0
20,000–29,999 per year	1	2.0
30,000–39,999 per year	9	18.4
40,000–49,999 per year	5	10.2
50,000–59,999 per year	4	8.2
60,000–69,999 per year	4	8.2
70,000–79,999 per year	10	20.4
80,000–89,999 per year	6	12.2
90,000–99,999 per year	1	2.0
> 100,000 per year	5	10.2
Prefer not to say	3	6.1
Relationship		
Married	38	77.6
Cohabitating	10	20.4
Single	1	2.0

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	No. or range	% or mean (SE)
Ethnicity		
Arab	1	2.0
Asian/Asian British	1	2.0
White	47	95.9
Education		
Sixth form/vocational qualification	7	14.3
Bachelor's degree	19	38.8
Advanced university degree	23	46.9

SE, standard error.

EME
HSDR
HTA
PGfAR
PHR

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