Protocol – Acceptability of bloodspot screening and genome sequencing in newborns

Version 3 – 9 October 2023

Identification

This is the protocol for a systematic review of existing research on the acceptability of bloodspot screening and genome sequencing in newborns.

Registration

To be registered in the PROSPERO database following approval.

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Contributions

All authors contributed to the development of the protocol.

Amendments

Amendments to the protocol will be noted in the final report and via PROSPERO.

Funding:

This review is funded by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme.

Role of sponsor or funder:

The funder was involved in initial discussions regarding remit. The originator of the topic for the review was the UK National Screening Committee who provided comments at the pre-protocol and draft protocol stage and approved this version of the protocol.

INTRODUCTION

In the UK every baby is offered newborn blood spot screening, also known as the heel prick test, ideally when they are 5 days old. The UK Newborn Bloodspot Screening (NBS) programme enables early identification, referral and treatment of babies with 9 rare but serious conditions: sickle cell disease (SCD), cystic fibrosis (CF), congenital hypothyroidism (CHT), phenylketonuria (PKU), medium-chain acyl-CoA dehydrogenase deficiency (MCADD), maple syrup urine disease (MSUD), isovaleric acidaemia (IVA), glutaric aciduria type 1 (GA1) and homocystinuria (HCU).

There is interest in increasing the number of conditions included in the NBS panel. A focus on patient / family experience, preference and acceptability has become a feature of debates on newborn bloodspot screening and, in the absence of high quality evidence of screening's impact on health outcomes, has become a powerful driver to the expansion of international screening panels. It has recently become even more crucial to assess the health benefits and harms that such screening programmes have on the individuals and their families in light of Genomics England's plan to use Whole Genome sequencing to screen 100,000 newborns for rare diseases. One of the screening criteria used by the UK NSC to evaluate screening programmes is that 'The test should be clinically, socially and ethically acceptable to the population'.

Although the acceptability of these screening programmes and the practical and ethical (Brownsword and Joynson 2023) implications on families and babies when screening services are planned or reviewed should be taken into consideration when making recommendations, the issue of how 'acceptability' should be evaluated has not yet been considered by the UK NSC. Thus, a deeper comprehension of the available techniques utilised to assess "acceptability" in evaluations of newborn bloodspot screening programmes will be very helpful to progress the UK NSC capability to make recommendations in this area.

The Committee's immediate programme of work includes newborn screening for spinal muscular atrophy (SMA) and acceptability will need to be evaluated in the decision making process. It is anticipated that this review will also inform that process.

Research questions

Our research questions are:

1. What do we know about the quantity and quality of research that relates to acceptability of bloodspot screening and genome sequencing in newborns?
2. What are the currently available methods to evaluate acceptability of bloodspot screening and genome sequencing in newborns, and how robust are these?
3. How have existing theoretical frameworks been operationalised in research on bloodspot screening and genome sequencing in newborns, and which dimensions of acceptability have been studied in this body of literature?

Our aim is to address the research questions by carrying out a systematic review of published and 'grey' literature.

METHODS

We will carry out a systematic review of available literature on the acceptability of bloodspot screening and genome sequencing in newborns. We will include studies which meet our inclusion criteria listed below (Table 1).

Table 1. Parameters of the review

	Include	**Exclude**
Date	Evidence published from 1st January 2013 onwards	Studies published before 2013
Setting	UK and other high income countries, 38 members of the Organisation for Economic Co-operation and Development	Low and middle income countries
Population	Parents or other carers of babies in the first days of life who are eligible for or who have had bloodspot screening, and might be eligible for future genome sequencing. Includes parents of antenatal babies.	General population, adults who are not expecting a child or are parents of children older than infants in their first days of life, healthcare staff

Study type	Studies which report empirical data using the following designs: RCTs/non-randomised trials; Systematic reviews/meta-analyses; rapid reviews; scoping reviews; prospective/retrospective cohort studies; Case-control studies; Cross-sectional studies (including surveys); Qualitative studies	Articles with no full text available. Conference abstracts, case reports, and theses Website pages where there is no associated report Articles which are discussions, commentaries or provide discursive information rather than data, protocols for studies
Intervention	Newborn bloodspot screening or primary/initial/first tier newborn whole genome sequencing. As different countries vary in the conditions encompassed by newborn blood spot screening we will include any condition which currently forms part of the screening in any included country.	Other screening tests for infants or children including hearing tests. Use of genomic sequencing as a follow up diagnostic test for those who have already screened positive for a condition.
Outcomes	Any outcome related to acceptability in bloodspot screening or genome sequencing	Articles which do not include any measure of acceptability or relate to the effectiveness/value of acceptability measurement
Other	English Language papers	Papers published in other languages.

Information sources

A broad search to identify relevant literature will be conducted, including a search for relevant grey literature.

We will search from 2013 to current. The start date of 2013 has been selected as this will yield ten years of the most recent literature, given that views of acceptability and technology

changes over time, particularly in regard to genome sequencing. It includes the 2014 date when the NHS Newborn Blood Spot Screening programme was expanded to screen for homocystinuria (HCU), maple syrup urine disease (MSUD), glutaric aciduria type 1 (GA1) and isovaleric acidaemia (IVA) (UK Government, 2023).

We will search in the following databases: MEDLINE, Embase, PsycInfo, CINAHL, Cochrane Library, Social Science Citation Index (SSCI).

Targeted 'grey' literature searches will be carried out to identify relevant reports in websites such as: https://nationalscreening.blog.gov.uk, https://phescreening.blog.gov.uk, the National Institute for Health and Care Excellence, and relevant professional organisations.

We will also scrutinise the reference lists of studies meeting our inclusion criteria, and carry out citation searching on key included studies. We will draw on a previous review (Carlton et al. 2021) to cross check included/excluded studies and citation check.

We will also utilise the expertise of our UK NSC colleagues to suggest published articles and grey literature, and to identify any studies in progress that they or their contacts are aware of.

Search strategy

The search combines the concepts of newborn screening and acceptability. It is intentionally broad to attempt to retrieve all research on the acceptability of newborn blood spot screening. The search uses MeSH and free-text terms where appropriate. The MESH term for bloodspot screening is "neonatal screening". The only limit applied to the search is the date range 2013-Current. The search will be translated for the other databases.

See below for an example search strategy developed on Medline to be used to identify published and peer reviewed literature:

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to June 29, 2023>

Search	**Strategy:**
1 Neonatal Screening/	(11887)
2 Dried Blood Spot Testing/	(2070)
3 NBS.ab,ti.	(6662)
4 "blood spot screen*".ab,ti.	(84)
5 "blood spot test*".ab,ti.	(170)

6 "bloodspot screen*".ab,ti. (115)
7 "blood spot screen*".ab,ti. (84)
8 or/1-7 (19605)
9 exp Infant, Newborn/ (672895)
10 (newborn* or new-born* or neonate* or neo-nate*).ab,ti. (270579)
11 9 or 10 (774946)
12 "screen*".ab,ti. (961233)
13 11 and 12 (40581)
14 8 or 13 (50275)
15 ((screen* or test* or diagnos*) adj2 (attitude* or knowledge or awareness or accept* or perspective* or perception* or participat* or consent or understanding or view*)).ab,ti. (37331)
16 attitude to health/ or health knowledge, attitudes, practice/ (204648)
17 15 or 16 (237662)
18 14 and 17 (873)
19 limit 18 to yr="2014 -Current" (394)

Search string 1 is the MeSH term (The Medical Subject Headings (MeSH) thesaurus is a controlled and hierarchically-organised vocabulary produced by the National Library of Medicine. MeSH includes the subject headings appearing in MEDLINE/PubMed, the NLM Catalog, and other NLM databases) that newborn blood spot screening maps to.
Search sting 2 is a MeSH covering the dried blood spot testing for any condition in any population
Search string 3 is NBS an acronym for newborn blood spot screening searched as free-text
Search strings 4-7 are free-text terms for bloodspot screening truncated as appropriate
Search string 8 combines all the terms for bloodspot screening using Boolean operator OR
Search string 9 is the MeSH term for newborn
Search string 10 is free-text terms for newborn
Search string 11 combines all the terms for newborn using Boolean operator OR
Search string 12 is the free-text term screen truncated
Search string 13 combines the newborn and screen term using Boolean operator AND
to retrieve research about screening in newborns
Search string 14 combines the different terms for newborn screening using Boolean operator OR
Search string 15 is free-text terms for screen and acceptability (from Carlton review)
Search string 16 is MeSH terms for acceptability
Search string 17 combines terms for acceptability using Boolean operator OR

Search string 18 combines the terms for bloodspot screening and acceptability using Boolean operator AND
Search string 19 limits the search to research published from 2013-Current (on Medline when the search was run (03/07/2023) this was **June 29, 2023**).

Data management / data selection
Search results will be downloaded to Covidence for systematic screening.

Selection process

Title/abstract review and full-text review will be carried out by two independent reviewers using Covidence. Disagreements will be resolved by consensus or, in cases of persistent difference, by reference to a third reviewer.

Data collection process

Data extraction will be carried out by a team of reviewers using Covidence. Each extraction will be completed by a first reviewer and checked by a second for accuracy and consistency.

Data items
Data to be extracted will include:

- Year and place of study
- Details of the study population and type of screening
- Study design and outcomes measured
- Methods of assessing acceptability - categorisation
- Methods of assessing acceptability - textual description
- Elements of acceptability being assessed (from Carlton et al, 2021)
- Instruments/Tools used (where appropriate)
- Main findings
- Frameworks or theories used (where appropriate)
- Limitations/applicability to a UK context
- Recommendations/implications

Data synthesis

It is expected that due to the types of study designs which explore acceptability, statistical pooling of results (meta-analysis) will not be appropriate. Therefore synthesis of quantitative studies will primarily take the form of narrative approaches – such as textual, tabular and graphical presentation. We will use thematic synthesis to report key recurring themes within

the qualitative literature. If the literature allows, we will compare and contrast findings from the two types of data, using the Matrix Method (Candy et al, 2011), to explore similarities, differences and gaps.

The literature may use diverse ways to consider the concept of acceptability. We will note where studies use theories or frameworks within their reporting, for example the framework outlined by Sekhon et al. (2017) and used by Carlton et al. (2021) which describes elements of acceptability as:

1. Acceptability of Informing/Consent process about procedure
2. Acceptability of Informing/Consent process about possible outcomes
3. Acceptability of the sample collection procedure
4. Acceptability of the communication of the outcomes (immediate)
5. Acceptability of ongoing support following communication of outcomes (short term).

We will note where other key theories or concepts which are not included in this framework are outlined, for example, 'living with' aspects, identity, stigma and social acceptability.

Quality assessment

We will assess the quality of each included study using appropriate checklists such as the Joanna Briggs Institute checklists for quantitative studies, the Mixed Methods Appraisal Tool (MMAT), and the CASP tool to assess qualitative studies. We will summarise the quality of the individual studies and the literature as a whole.

Robustness of tools used to measure acceptability

In addition to evaluating the methodological quality of the conduct of the studies, we will also aim to provide an indication of the robustness of the methods that have been used within the studies to evaluate acceptability. In order to do this we will develop a checklist to assess robustness of measurement tools, including but not limited to: was there potential for additional biases in the tool (e.g. measurement bias, interview bias, response bias); how was the tool developed and tested; was the tool based on theory or other underpinning empirical framework; how comprehensive are the included items.

Patient, public and stakeholder involvement

We will seek input from experts and advisors in the field including colleagues within the University of Sheffield and NHS. We will also liaise with the UK National Screening Committee to identify key stakeholders and possible contacts for example via the Bloodspot Task Group.

We will establish a patient and public advisory group specific to this topic. We will advertise the opportunity for people to join this group widely including via research advisor websites, third sector organisations, online communities, and via our established database of people interested in advising on research projects. We will consider all responses and purposively select from them to recruit a diverse range of people in terms of age, gender, location, background and experiences. We will aim for 8-10 group members. It is anticipated that the group will meet at three points during the review - initial stage to discuss parameters and inform understanding of the topic, during analysis of findings to assist with interpretation, and at the end to input into identifying key messages and developing outputs. Our public co-applicant will assist with the recruitment process, and offer mentoring if required. We will offer training in the form of a video session and reimburse people for their time.

Equity, diversity and inclusion (EDI)

We will report on EDI both in the review process and in the included studies. We will draw on existing tools including the PROGRESS-Plus framework, Preferred Reporting Items for Systematic Reviews and Meta-Analysis for equity-focused systematic reviews (PRISMA-Equity) guideline, and Sex and Gender Equity in Research (SAGER) guidelines for initial coding but will particularly look for intersectionality characteristics (e.g. for populations with social deprivation, religious characteristics and ethnicity) where they may define a particular response in terms of acceptability.

Project timetable

	July 23	Aug 23	Sept 23	Oct 23	Nov 23	Dec 23	Jan 24	Feb 24	March 24	April 24
Scoping and protocol development	x	x	x							
Evidence identification			x	x	x	x				
Data extraction					x	x	x	x		
Quality assessment							x	x		
Analysis and report writing								x	x	
Draft final report									x	
Peer review and production of other outputs									x	x

References

Brownsword, R., Joynson, C. Good governance and the development of an ethical framework for the UK National Screening Committee. *Medical Law International* (2023).

Candy, B., King, M., Jones, L. *et al.* Using qualitative synthesis to explore heterogeneity of complex interventions. *BMC Med Res Methodol* 11, 124 (2011). https://doi.org/10.1186/1471-2288-11-124

Carlton, J., Griffiths, H.J., Horwood, A.M. et al. (2021) Acceptability of childhood screening: a systematic narrative review. Public Health, 193. pp. 126-138. ISSN 0033-3506.

Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res. 2017 Jan 26;17(1):88. doi: 10.1186/s12913-017-2031-8. PMID: 28126032; PMCID: PMC5267473.

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