UK National Screening Committee

UK National Screening Committee (UK NSC)

EquipoISE - A multi-disease in-service evaluation within the UK newborn blood spot screening programme: Extended bloodspot ISE

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Contents

Aim

To ask the UK National Screening Committee (UK NSC) to note the work currently being undertaken with the following aims:

1. The primary purpose of EquipoISE is to answer policy-relevant research questions that would allow the UK National Screening Committee to make recommendations on the addition of new conditions to the UK newborn blood spot screening programme. This includes:
   (a) assessing whether and how genetic-based screening tests could be incorporated into the programme.
   (b) generating more evidence on how the outcomes of children are changed through screening for different conditions.

Recommendation

The Committee is asked to note the ongoing work and to receive further updates with regard to the works' progress.

A multi-disease in-service evaluation within the UK newborn blood spot screening programme: Extended bloodspot ISE (EquipoISE)

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1. Summary

Rare diseases affect 1 in 17 people during their lifetime, amounting to over 3.5 million people in the UK, with 75% of rare disease affecting children of whom 30% die before the age of 5 years [1]. Presymptomatic screening detection soon after birth can prevent disease development and severe disability and death. However, we do not understand the early natural history of these conditions, and risk incorrectly labelling healthy babies with diseases in our search for presymptomatic detection of early disease. We have a unique opportunity in the UK to revolutionise research in this space, with the recent 10 Year Health Plan setting out ambitions for earlier diagnosis, leveraging advances in genomic sequencing, and increasing access to specialist treatment at the core of the strategy [2].

We have had a uniform newborn bloodspot screening programme for over 50 years since the introduction of screening for phenylketonuria in 1969, now screening for 10 of the circa 100 conditions which can be routinely tested for. The stored dried blood spots (DBS) from this create the potential for a unique DBS-Biobank, enabling retrospective testing of the stored blood spots and investigation of subsequent outcomes in linked datasets to establish the early natural history, in particular linking test results to those who later developed disease, and measuring the frequency of similar results in those in whom disease did not develop. The most promising candidates can be examined in prospective studies, and if successful, rolled out nationally. This DBS-Biobank underpins the proposed development of EquipoISE, a rolling multi-condition in-service evaluation within the NHS NBS programme that would allow new conditions to be assessed rigorously and sustainably, enabling the UK NSC to make timely and principled decisions as new tests and treatments emerge.

This document sets out a proposed framework for EquipoISE for generating the evidence needed to support safe, timely and sustainable expansion of the UK newborn blood spot screening programme. Its aims are to describe how EquipoISE would work, to include its five phases for implementation, case examples, and a prospective comparative study design that exemplifies how new conditions could be evaluated within the programme.

Crucially, this work will support the Government's goal of radically shifting the NHS from focusing on sickness to focusing on prevention, enabling it to "raise the healthiest generation of children ever"[3]. It will also capitalise on the value of UK data and help the UK to meet its target to become, by 2030, one of the "top three fastest places in Europe for patient access to medicines and MedTech"[4]. **The NSC is now considering with partners, ways in which to take this proposal forward.**

[1] https://www.gov.uk/government/publications/uk-rare-diseases-framework/the-uk-rare-diseases-framework
[2] https://www.gov.uk/government/publications/10-year-health-plan-for-england-fit-for-the-future
[3] https://www.gov.uk/government/publications/uk-rare-diseases-framework/the-uk-rare-diseases-framework
[4] https://www.gov.uk/government/publications/life-sciences-sector-plan

1.1. Aims of EquipoISE

The primary purpose of EquipoISE is to answer policy-relevant research questions that would allow the UK National Screening Committee to make recommendations on the addition of new conditions to the UK newborn blood spot screening programme. This includes:
(a) assessing whether and how genetic-based screening tests could be incorporated into the programme.
(b) generating more evidence on how the outcomes of children are changed through screening for different conditions.

2. Contents

3. Abbreviations

DBS	Dried blood spot
EquipoISE	Extended blood spot ISE
HDRS	Health Data Research Service
HRA	Health Research Agency
HTA	Human Tissue Act
ISE	In-service evaluation
MLD	Metachromatic Leukodystrophy
MS	Mass spectrometry
NBS	Newborn blood spot
NDRS	National Disease Registration Service
NHS	National Health Service
NIHR	National Institute for Health and Care Research
REC	Research ethics committee
SMA	Spinal muscular atrophy
UK NSC	UK National Screening Committee

4. Purpose of EquipoISE

Rare diseases collectively affect a substantial proportion of the population—around 1 in 17 people—and the majority manifest in childhood. Many of these conditions are treatable only if identified before or at the earliest stages of symptom onset, creating a compelling clinical rationale for presymptomatic detection in the newborn period. More than 100 conditions are now technically detectable using dried blood spot (DBS) or emerging genomic methodologies, and the number of potentially actionable conditions is growing rapidly.

Despite this, there remains a critical evidence gap preventing the safe and principled expansion of the newborn blood spot (NBS) screening programme. For most rare conditions, we lack robust data describing the early natural history, true population prevalence, age of onset, and clinical significance of early biochemical or genetic markers. This means we do not yet know which biomarkers reliably predict disease in the newborn period, which abnormalities represent benign variation, or how many children labelled "positive" would ever have gone on to develop symptoms. Without these data, expanding screening risks incorrectly labelling healthy babies, exposing families to unnecessary anxiety and interventions, and placing pressure on systems already supporting children with confirmed disease.

At the same time, the UK is uniquely positioned to generate the evidence required for safe, evidence-based expansion. The UK's uniform, long-standing national NBS screening programme, combined with systematic retention of DBS samples and the existence of national clinical outcome datasets, creates a natural "whole-population" research infrastructure. These features allow for both retrospective testing of stored DBS and prospective in-service evaluations, enabling robust estimation of test performance, penetrance, and real-world outcomes at scale.

In combination, the growing therapeutic landscape, the potential harms of premature expansion, and the unique UK data environment create a clear imperative: to establish a national, structured, and ongoing approach to generating the evidence needed for principled newborn screening decisions. This is the purpose of EquipoISE.

5. Background

5.1. Current NHS Newborn Blood Spot Programme

The NHS NBS screening programme screens for ten conditions[5] and there is clinical imperative in further expansion to include additional conditions[6]. However, there are fundamental gaps in the evidence the UK National Screening Committee (NSC) requires to recommend modification of the NHS NBS screening programme. Previous UK NSC processes have evaluated a range of disorders, with multiple conditions potentially detectable via DBS testing currently "not recommended" for screening[7].

Nine of the conditions included in current NBS screening are monogenic inherited disorders, the exception being congenital hypothyroidism. The screening tests used in the NBS screening programme are based on disease-relevant biomarkers, e.g. assessment of haemoglobin fractions for sickle cell disease, and specific metabolites for the inherited metabolic disorders. Confirmatory testing includes assessment of the disease-specific genes, however "genetic-test-first" approaches to NBS screening are being evaluated (see below on genomic NBS screening).

Disorder	**Genetic Basis**	**Screening test**
Cystic fibrosis	Autosomal recessive *CFTR*	Immunoreactive trypsinogen; DNA analysis (4 gene panel) second tier pre-notification test
Sickle cell disease	Autosomal recessive *HBB*	Haemoglobin fractions
Congenital hypothyroidism	Most not monogenic	Thyroid stimulating hormone (TSH)
Phenylketonuria	Autosomal recessive *PAH*	Phenylalanine and tyrosine
Medium chain acylCoA dehydrogenase	Autosomal recessive *ACADM*	C8- and C10-acylcarnitines
Maple syrup urine disease	Autosomal recessive *BCKDHA, BCKDHB, DBT, DLD* and others	Leucine, isoleucine, alloisoleucine
Isovaleric acidaemia	Autosomal recessive *IVD*	C5-acylcarnitine
Glutaric aciduria type 1	Autosomal recessive *GCDH*	C5-DC-acylcarnitine
Homocystinuria	Autosomal recessive *CBS*	Methionine (homocysteine second tier pre-notification test)
Hereditary tyrosinaemia type 1	Autosomal recessive *FAH*	Succinylacetone

[5] Cystic fibrosis, sickle cell disease, congenital hypothyroidism, along with seven inherited metabolic conditions (phenylketonuria (PKU), medium-chain acyl-CoA dehydrogenase deficiency (MCADD), maple syrup urine disease (MSUD), isovaleric acidaemia (IVA), glutaric aciduria type 1 (GA1), homocystinuria (pyridoxine unresponsive) (HCU) and hereditary tyrosinaemia type 1 (HT1).

[6] Jones, S.A.; Cheillan, D.; Chakrapani, A.; Church, H.J.; Heales, S.;Wu, T.H.Y.; Morton, G.; Roberts, P.; Sluys, E.F.; Burlina, A. Application of a Novel Algorithm for Expanding Newborn Screening for Inherited Metabolic Disorders across Europe. Int. J. Neonatal Screen. **2022**, 8, 20. https://doi.org/10.3390/ijns8010020

[7] https://view-health-screening-recommendations.service.gov.uk/?name=&affects=newborn&screen=no. These include X-linked adrenoleukodystrophy, amino acid metabolism disorders, biotinidase deficiency, congenital adrenal hyperplasia, Duchenne muscular dystrophy, fatty-acid oxidation disorders, galactosaemia, Gaucher disease, long chain 3-hydroxyacyl-CoA dehydrogenase deficiency , metachromatic leukodystrophy, mucopolysaccharidosis type 1, organic acid oxidation disorders, severe combined immunodeficiency disorders, and spinal muscular atrophy.

5.2. Drivers to Expansion

Many conditions could be included in a newborn bloodspot screening programme; more than 35 are routinely recommended in the USA and Italy. Most of these conditions are considered relatively rare, though collectively at a population level the numbers of individuals and families impacted are substantial[8,9].

Across peer countries in Europe, North America, and Australasia, newborn screening programmes vary substantially[10]. Yet, few of the policy decisions appear to have been based on rigorous analysis of the relative benefits and harms of including new conditions[11]. This renders their translation to a UK setting far from straightforward. Indeed, in 2007 Pollitt commented that "the current variations in screening practice across the developed world suggest that rational policy is hard to make"[12]. Today there is some but certainly incomplete overlap between newborn screening programmes.

A key challenge is the relative absence of relevant research that would allow for systematic assessment of the benefits and harms of potential screening. Generating such data is difficult due to the cost and complexity of repeatedly setting up large, long-term, research studies to answer questions about individual rare conditions.

Over the last 20 years, in response to technological advances, many high-income countries have rapidly expanded newborn screening. However assessment of the effectiveness before and after introduction of new programmes across Northern Europe is limited, and we still do not have good, published, data on which to base many newborn screening decisions. Also, differences in screening programmes, such as the day on which the dried blood spot is collected, impact how easily findings can be generalised from one setting to another.

The development of **novel disease-modifying treatments** including gene therapies is an important imperative for the expansion of newborn screening, especially for disorders where treatment must be instigated in the pre-symptomatic phase, for example metachromatic leukodystrophy which is the subject of a recent UK NSC consultation[13].

While biomarker/ metabolite-based screening continues to be the mainstay of NBS screening programmes, **genomic methodologies** as a primary means for screening are also rapidly expanding, with numerous ongoing research programmes globally evaluating genomic newborn screening including the Genomics England Generation Study[14]. The Generation Study aims to recruit 100,000 newborns in England and is evaluating over 200 actionable gene-conditions; babies in whom a condition is suspected are referred to NHS services. The Generation Study conditions list includes

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[8] HM Government. The UK Rare Diseases Framework. Available: https://www.gov.uk/government/publications/uk-rare-diseases-framework/the-uk-rare-diseases-framework

[9] Ferreira CR. The burden of rare diseases. Am J Med Genet A. 2019;179: 885–892. doi:10.1002/ajmg.a.61124

[10] Sikonja, J.; Groselj, U.; Scarpa, M.; la Marca, G.; Cheillan, D.; Kölker, S.; Zetterström, R.H.; Kožich, V.; Le Cam, Y.; Gumus, G.; et al. Towards Achieving Equity and Innovation in Newborn Screening across Europe. Int. J. Neonatal Screen. **2022**, 8, 31. https://doi.org/10.3390/ ijns8020031

[11] Taylor-Phillips S, Stinton C, Ferrante di Ruffano L, Seedat F, Clarke A, Deeks JJ. Association between use of systematic reviews and national policy recommendations on screening newborn babies for rare diseases: systematic review and meta-analysis. BMJ. 2018;361: k1612. doi:10.1136/bmj.k1612

[12] Pollitt. Introducing new screens: Why are we all doing different things? J Inherit Metab Dis (2007) 30:423-429.

[13] https://view-health-screening-recommendations.service.gov.uk/metachromatic-leukodystrophy/

[14] Tuff-Lacey A., et al. The Generation Study Protocol: Version 4, 3 November 2023. Genomics England Ltd.

disorders already part of routine newborn screening but has expanded this significantly to include a further ~80 inherited metabolic disorders, a range of hormonal conditions, immune system conditions, and importantly extending to conditions under specialities (e.g. gastroenterology) not traditionally including in newborn screening[15]. This is likely to translate into further differences in future newborn screening programmes worldwide. **There is a need to evaluate how genomic and biomarker/ metabolite-based methodologies are best combined and integrated in clinically effective newborn screening programmes.**

Currently the Generation Study requires collection of a separate blood sample (umbilical cord blood, heel prick or venous blood sample) to allow for DNA extraction. Consideration of the potential for DNA extraction from DBS sample, or ongoing need for parallel sample collection, is required.

5.3. Potential Analyses to support evaluation of NBS expansion

Retrospective analysis of stored DBS samples from "DBS-Biobank"	**Prospective** analysis of newly acquired routine DBS samples
• Assay evaluation • Population-level epidemiology	• Assay evaluation • Population-level epidemiology
• Testing "offline" by partner research groups • Assumption there would be no clinical notification of "screen positive" results • Linkage with clinical outcome data	• Testing "inline" in current NBS service laboratories, with/without clinical notification of "screen positive" results • Testing "offline" by partner groups using residual sample after routine NBS testing, with/without clinical notification of "screen positive" results • Linkage with clinical outcome data
• Biomarker/ metabolite -based assays • DNA based testing	• Biomarker/ metabolite -based assays • DNA based testing
• Potential expansion of current storage capabilities and protocols to increase the quality of the DBS-Biobank	• Potential expansion into a research platform to reduce cost and increase speed of research

5.3.1. Retrospective analyses

Retrospective analysis of stored, historic DBS samples is required as part of the research process to generate data needed in assay development and evaluation, as well as generating population-level evidence on disease epidemiology. The current NHS NBS screening programme retains DBS samples for a period of at least five years; some laboratories may store for considerably longer than this. This provides a *de facto* biobank of samples. However, there is a need to standardise processes around DBS storage and retention to optimise the quality and utility of this **DBS-Biobank**. Collaboration with

[15] https://www.generationstudy.co.uk/conditions-we-test-for

key stakeholders would provide access to research groups to access this DBS-Biobank of samples to facilitate assay development and evaluation.

5.3.2. Prospective analyses

Prospective analysis of DBS samples within the live NBS screening programme will form another component of the proposal. This would result in generation of population level data on assay performance and disease epidemiology, and depending on individual disorder characteristics would include the option for clinical notification and actionability whereby "condition suspected" results would lead to clinical contact with the affected individual and treatment initiation. Accordingly, this requires review of current **consent processes** and language to ensure it sufficiently encompasses the planned activities and fully informs families of how their data and samples could be used.

Analysis of DBS samples in this prospective phase for agreed additional conditions could be integrated "inline" into current NBS screening service laboratory processes. It is notable that the recent introduction of routine screening for hereditary tyrosinaemia type 1 (HT1)[16] required all NBS laboratories in the UK moving to use of a single-source commercial test kit. The commercial test kit includes >50 analytes/metabolites, although only the required 9 analytes are currently analysed for the seven target inherited metabolic disorders. This could permit expansion to analysis of additional analytes, although this does not include all analytes that would be required for all possible inherited metabolic disorders considered for NBS screening, particularly the lysosomal diseases. However, any expansion in the "live" system would need to be evaluated for any detrimental impact on workflows and processes that could have an effect on turnaround times for current NBS screening disorders.

Prospective analysis of DBS samples for other conditions could also be undertaken "offline" as a separate process following the routine live NBS laboratory analysis, using residual samples. This would be undertaken separate to current NBS service laboratories, for example by specific research groups.

5.4. Development of a DBS-Biobank

In the UK routine NBS samples are stored for clinical purposes under current policy, allowing for future analysis if the child develops specific clinical problems. There are, however, several factors that can impact on sample stability, including storage temperature, humidity and light exposure.

The UK is well positioned to develop a national dried blood spot biobank (DBS-Biobank), building on the long-standing newborn bloodspot screening programme. Standardisation of storage conditions would be one component in formalising this resource as a research-accessible biobank. The development of a UK DBS-Biobank would also align with international recommendations. In particular, Principle 10 of EURORDIS recommendations emphasises that "blood spot samples should be stored in national biobanks for quality control and research purposes while ensuring appropriate measures for data access as well as robust safeguards for data protection and privacy are in place."[17] Establishing a national DBS-Biobank would ensure that the UK remains aligned with evolving best practice, while providing a foundational resource for evaluating new conditions for screening.

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[16] https://www.england.nhs.uk/2025/10/nhs-to-screen-all-newborn-babies-for-life-threatening-metabolic-disorder/#:~:text=Newborn%20babies%20will%20now%20be,per%20year%20in%20the%20UK.

[17] https://www.eurordis.org/our-priorities/diagnosis/newborn-screening/

There may be a possibility to expand to store other sample types with consent from parents, which could be used retrospectively top determine what results of follow up tests on those samples would have been.

5.5. Clinical Outcome Data

The key policy question is "does screening for a disease do more good than harm at reasonable cost". To understand the benefit part of this we must measure the benefit of earlier detection at screening in comparison to later symptomatic detection. This requires comparative data which can be obtained in several ways such as: adding conditions (where we do not know the balance of benefit and harm) in some geographical areas or time periods and not others, and comparing disease prevalence and outcomes to without screening; comparing outcomes in children by time point of diagnosis (with appropriate consideration of confounding); or comparing treated and untreated children diagnosed at newborn screening (for example before and after new treatments become available). This also requires measurement of harms. False positive test results can be quickly and readily measured using follow up confirmatory testing prospectively, and thus the number of families affected by the adverse psychological outcomes measured.

A critically important harm emerges from our lack of understanding of natural history of early disease (as medical evidence is mostly in symptomatic infants) and the potential to label infants with a disease and treat them for it when it actually would never have become clinically significant. There are examples of this throughout screening, in babies, infants and adults. One of the clearest examples was infants receiving unnecessary cancer treatment after screen detection for neuroblastoma in Japan, because the medical evidence was centred around using the test in symptomatic babies, and as we often find in screening, those test results do not have the same meaning in asymptomatic infants. This can be measured through triangulation of several approaches such as looking retrospectively at the disease marker in previous dried blood spots or adult biobanks to ascertain the marker prevalence in healthy people or prospectively revealing the marker (of unknown clinical significance) in a subset of people.

There is also a need to generate more evidence on the outcomes of children screened, including assessment of the efficacy of the NBS screening programme in detecting (not missing) affected children, and the health improvements generated by early detection and treatment. Capturing long-term outcome data for rare diseases is challenging. The NHS **National Disease Registration Service (NDRS)** aims to achieve comprehensive registration of rare diseases and thus has the potential to be a valuable central resource for long-term outcomes monitoring [18].

The potential to link data from retrospective analysis of DBS-Biobank samples to later clinical outcomes captured by mechanisms such as the NDRS system would allow evaluation of screening assay performance. Further, the NHS 10 Year Plan will establish a new **Health Data Research Service (HDRS)** aiming to be a world-leader in using technology innovation to accelerate transformation[19].

[18] https://digital.nhs.uk/ndrs

[19] https://www.gov.uk/government/publications/10-year-health-plan-for-england-fit-for-the-future

5.6. UK Government Policy Context

Crucially, this work aligns with UK Government's recently announced plans to transform both the NHS and the UK Industry Strategy.

1. By generating the evidence on the effectiveness and safety and long-term health outcomes of potential new additions to the NBS, EquipoISE will support the Government's planned shift of the NHS, from its focus on sickness to focus on prevention, and its aim to "raise the healthiest generation of children ever."[20] ("Fit for the Future: 10 Year Health Plan for England.")
2. EquipoISE will accomplish this by linking the DBS-Biobank and long-term outcome health data sets, capitalising on the value of UK data, and in particular, leveraging the combined strengths of the UK's health data and genomic potential[21]
3. Finally, by enabling in-service evaluations to identify new tests to integrate into the NBS screening programme and generate high-quality evidence of the outcomes of the children screened, EquipoISE will contribute to meeting the UK Government's target to become by 2030 one of the "top three fastest places in Europe for patient access to medicines and MedTech"[22]

6. What is EquipoISE?

EquipoISE is a proposed rolling multi-condition in-service evaluation within the NHS NBS screening programme.

In-service evaluations (ISE) involve adapting real-world screening programmes to answer operational or effectiveness questions necessary to make formal screening policy recommendations [23]. They are designed to combine methodological rigour with real-world conditions and provide a unique avenue for sustainably generating the evidence needed for further modifications to the UK NBS programme.

EquipoISE' purpose is to generate the ongoing evidence required for the UK NSC to make principled decisions on the inclusion of multiple new conditions for newborn screening. In its initial phase, this screening is anticipated to be via biochemical assays but will expand to encompass genomic approaches to screening as proposed in the 10 Year Plan, exemplified by the current ongoing evaluation of screening for spinal muscular atrophy (SMA), and by the Generation Study.

For a condition that is already on the NBS screening panel, if a new test becomes available, analysis of the DBS-Biobank stored DBS cards using the new test would facilitate comparison with the current test. Additionally, use of the DBS-Biobank would enable analysis of adjustment to screening cut-off values on test performance.

For a condition not on the screening panel, using the DBS-Biobank will enable very large sample size analysis in a much shorter time than in a prospective analysis. This analysis would facilitate test

[20] https://www.gov.uk/government/publications/10-year-health-plan-for-england-fit-for-the-future
[21] https://www.gov.uk/government/publications/life-sciences-sector-plan
[22] https://www.gov.uk/government/publications/life-sciences-sector-plan
[23] UK National Screening Committee. Seminar explains process of planning and running an in-service evaluation. 22 Nov 2023. Available: https://nationalscreening.blog.gov.uk/2023/11/22/seminar-explains-process-of-planning-and-running-an-in-service-evaluation/

performance evaluation and also provide information on population distribution of the test result values as well as indication of disease prevalence.

6.1. How EquipoISE could work

Collaboration with key stakeholders is necessary to refine the plan for EquipoISE, here we outline a possible strategy (figure 1), and consider possible study designs.

We could implement in four phases, followed by a fifth phase of ongoing monitoring. Identification of potential conditions in step 1 would be broad and pragmatic but would have clear rules such as there being a test and an effective treatment. The ISE element could be broader in evaluating conditions in the retrospective analysis, but narrower in the prospective analysis where results are reported to parents to ensure only conditions in which screening is reasonably probable to improve outcomes.

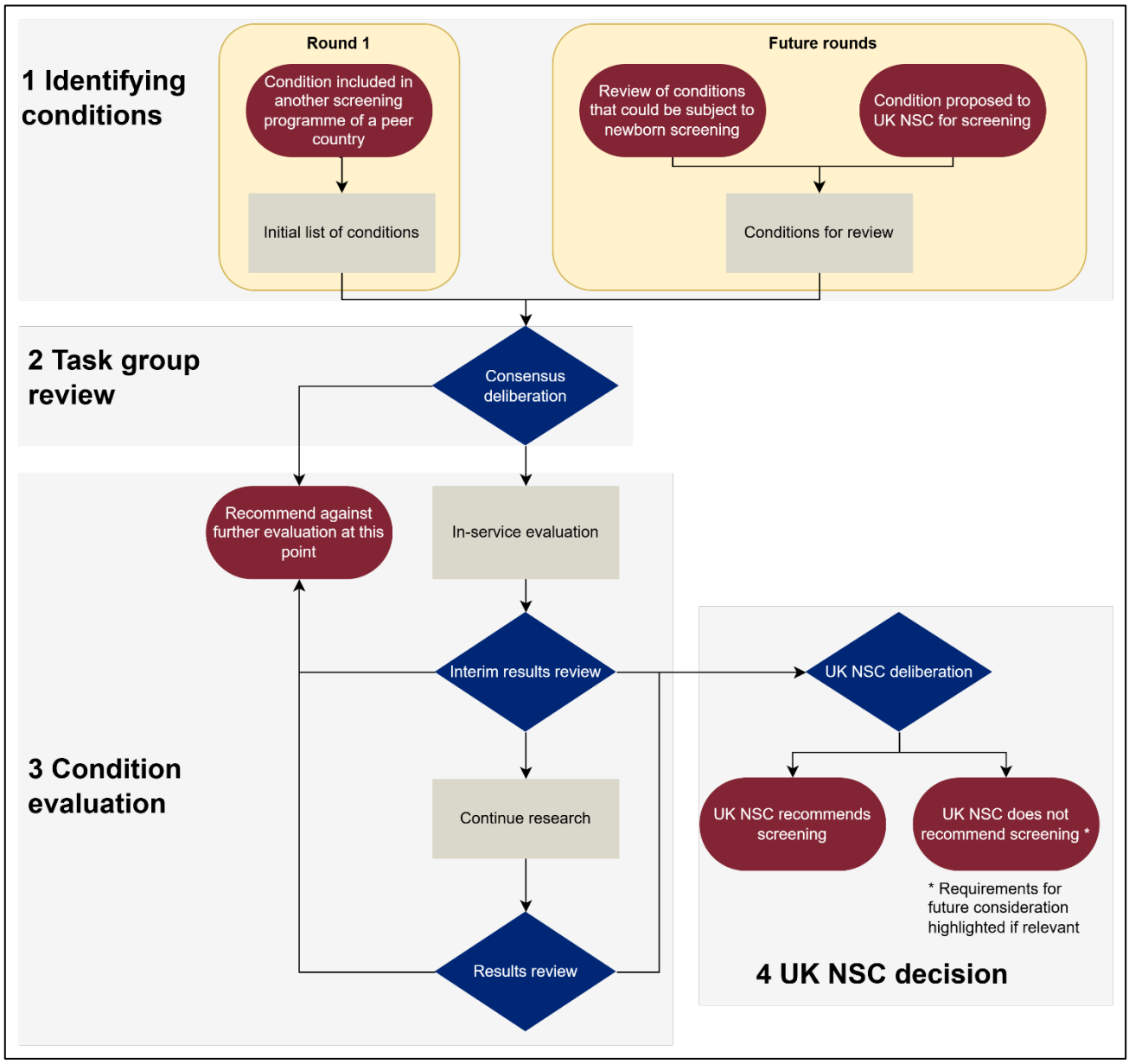

Figure 1: A potential protocol for delivering EquipoISE

6.1.1. *Phase 1: Longlisting conditions.*

In the initial round of EquipoISE, a longlist of conditions will be put forward for consensus deliberation.

Creating a longlist: To build on the experience of other countries, the longlist will consist of conditions that are already included in the routine nationally-recommended NBS screening programme of a European country.

In future, new conditions would be considered at regular intervals based on reviews of conditions that could be screened for using available technology including cross-reference to the conditions being screened for in the Generation Study. Other candidate conditions would be identified through stakeholder engagement and the UK NSC open call for topics.

6.1.2. *Phase 2: Shortlisting conditions and finalising conditions for inclusion in first round of prospective ISE*

Shortlisting process:

UK NSC and relevant partners and external expert stakeholders will assess each condition using set criteria (see section 10). Targeted evidence reviews will be conducted for shortlisted conditions to inform the appropriate further analysis within EquipoISE, which would include:

- No further evaluation at this time
- Further retrospective DBS-Biobank based data gathering
- Prospective in-service evaluation
- UK NSC decision to recommend screening if the level of evidence is considered sufficient prior to an ISE.

6.1.3. *Phase 3: Condition evaluation.*

After review and recommendation, an analysis plan for each condition is put into action.

This process would entail collaboration through NIHR of methodologists with rare-condition expertise working with UK NSC (particularly the blood spot task group) and frontline NHS staff with disease expertise, together with other stakeholders, to evaluate for each shortlisted condition:

- Appropriate screening test to be used (including appropriate testing platforms, laboratory facilities, and considering screening cutoff thresholds for the specific test)
- Power analysis to determine sample size required to give appropriate evaluation of the efficacy of the screening test including clinical outcomes
- Determine require follow-up time to determine useful clinical outcomes, relating to knowledge of the natural history of each disorder and expected age of presentation
- Determine key outcome measures specific to that disorder (e.g. survival status, developmental milestones, need for specific intervention such as organ transplantation)
- Agree data items to be assessed and collected, and agree mechanism for capturing the data with linkage between assay results and clinical outcome data

- Confirmed methodology of analysis for each disorder including geographic scope (part or whole-country)
- Establish comparator/control data set (which could include non-screened population, comparison with other UK countries, comparison with international data, comparison with retrospective NBS samples from DBS-Biobank from specified time period (e.g. previous 12 months).
- The commissioned team would agree to assess the data at regular interim intervals and, along with feasibility assessment by NHS England, to revert to UK NSC for further decision to adopt as a formal programme, continue evaluation, or discontinue if there is evidence of lack of efficacy or feasibility.

6.1.4. Phase 4: UK NSC recommendation.

Following on from evaluation, the condition can be brought to the UK NSC for a decision on whether it should be formally recommended for the national NBS screening programme.

6.1.5. Phase 5: Ongoing monitoring.

Ongoing, long-term, monitoring of process and outcomes for conditions within the national NBS screening programme.

7. Case Examples

Four disorders are included to exemplify potential utility of the EquipoISE programme. All four are included in other international screening programmes, have been previously evaluated by UK NSC via the evidence review process using standardised review criteria [24], and currently not recommended for UK screening.

Disorder	Phenotypes	Gene	Generation Study?	Screening test	On current NBS lab test kits?	Previously evaluated by UK NSC?	Treatment available?
Primary systemic carnitine deficiency OMIM #212140	Dilated cardiomyopathy Hepatomegaly Hypoketotic hypoglycaemia, hyperammonaemia Neurological manifestations	*SLC22 A5*	Yes	C0 (free carnitine) level	Yes	Yes (not recommended)[25]	Yes (oral carnitine replacement)
Early treatment can prevent severe sequelae and can prevent development of fatal dilated cardiomyopathy. Treatment very low burden, high efficacy.							
Evidence Gaps/ Uncertainties[26]: The clinical course of primary systemic carnitine deficiency, also known as carnitine transporter deficiency (CTD) and carnitine uptake defect (CUD), is variable, and there is no reliable way to predict phenotype/prognosis There is uncertainty over the accuracy of the screening test as most screening studies have not performed extensive follow-up, and therefore false-negatives could have been missed Screening can identify heterozygotes, and the natural history of heterozygotes is not well understood Although there is an accepted treatment, there is uncertainty over whether all cases identified through screening will require treatment							
Potential good candidate for prospective ISE with live actioning of screen positive cases							

[24] https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes
[25] https://view-health-screening-recommendations.service.gov.uk/fatty-acid-oxidation-disorders/
[26] Screening for Carnitine Transporter Deficiency External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). 2014

Biotinidase deficiency OMIM #253260	Seizures Developmental delay Skin rash, alopecia Optic atrophy Lactic acidosis	*BTD*	Yes	Biotinidase activity	No	Yes (not recommended)[27]	Yes (oral biotin replacement)
Early treatment can prevent all manifestations of disease. Treatment very low burden, high efficacy. Would require introduction of biotinidase enzyme assay as new screening test. Included in many national screening programmes							
Evidence Gaps: Limited evidence on the prevalence and/or incidence in the UK Limited number of studies currently available, the heterogeneity in the index tests examined, and the lack of consistency in the outcomes reported limits comparability of the evidence Potential to detect "partial deficiency" that may not require treatment.							
Potential candidate for initial use of retrospective DBS-biobank to establish screening assay.							

Metachromatic leukodystrophy (MLD) OMIM #250100	Progressive childhood dementia and neurodegeneration	*ARSA*	Yes	C16: Sulfatide (first tier) Arylsulfatase enzyme activity (second tier) *ARSA* mutation analysis (third tier)	No	Yes (not recommended). Recent consultation exercise.[28]	Yes (gene therapy HSCT)[29]
Only pre-symptomatic treatment effective for late infantile phenotype, necessity to detect via screening. Further evidence requirement suggested following UK NSC consultation.							
Evidence Gaps: (from UK NSC Consultation) • Further analysis of robustness of proposed multi-tier screening assay							
Potential candidate for prospective off-line evaluation of screening assay, potentially with clinical notification							

[27] https://view-health-screening-recommendations.service.gov.uk/biotinidase-deficiency/
[28] https://view-health-screening-recommendations.service.gov.uk/metachromatic-leukodystrophy/
[29] https://www.nice.org.uk/guidance/hst18

X-linked Adreno-leukodystrophy OMIM #300100	Manifestations in males Adrenal insufficiency (80% lifetime risk) Progressive cerebral leukodystrophy (cALD, ~ 35-40% boys, and risk into adulthood) Myeloneuropathy (AMN, later adult-onset spinal cord disease, ~90% males)	*ABCD1*	Yes (males)	lysoC26 phosphatidylcholine (first tier)	Yes	Yes (not recommended)[30]	Yes (adrenal replacement therapy; haematopoietic stem cell transplant for early stage cerebral disease (cALD)). No current disease modifying treatment for AMN
Screening programme introduced recently in Netherlands[31] Presymptomatic diagnosis via screening facilitates monitoring and treatment for adrenal insufficiency Presymptomatic diagnosis via screening facilitates monitoring via MRI surveillance for cerebral leukodystrophy and treatment with haematopoietic stem cell transplant [32].							
Evidence Gaps: • Validation of multi-tier screening algorithm: Requires sex-specific screening and development of second/third tier testing. • Potential detection via NBS of pedigrees without clinical manifestation, and potential utility of lysoC26PC level to detect only target condition pedigrees.[33]							
Potential candidate for retrospective analysis of lysoC26PC levels in DBS-Biobank sample, and prospective offline evaluation of screening algorithm.							

[30] https://view-health-screening-recommendations.service.gov.uk/ald/

[31] Alberson M et al. J Inherit Metab Dis 2023;46:116-128. DOI: 10.1002/jimd.12571

[32] Chiesa R et al. Blood Adv 2022;6:1512-1524. DOI 10.1182/bloodadvances.2021005294

[33] Billington, C.J., Jr., et al., *Prognostication and Biomarker Potential of C26:0 Lysophosphatidylcholine in Adrenoleukodystrophy.* JAMA Pediatr, 2025. **179**(4): p. 465-467.

8. Potential prospective study designs for phase 3

To answer the key policy question is does screening for a disease do more good than harm, the combination of prospective and retrospective data should provide measurement of the benefit of earlier screen detection over late, and the harms of screening (as outlined in section 5.5 (Clinical outcome data)). For conditions where a diagnosis can be made using the newborn blood spot test (no follow up tests required) then more evidence can be ascertained from retrospective testing of dried blood spots, and less evidence is required from the prospective study. In this case the retrospective study can examine all babies who would have been test positive (and therefore diagnosed with the disease) and follow up to ascertain whether they became symptomatic. If they all became symptomatic within 5 years, then there is no overdiagnosis and all test positives are going to develop symptomatic disease. For conditions where after the NBS test confirmatory tests are required, retrospective analysis is less helpful because it is difficult to distinguish between a false positive test result and overdiagnosis. Here retrospective studies provide important data, but more extensive prospective analysis is required. Overall, the assessment of balance of good and harm can be made by triangulating published research alongside new retrospective and prospective studies, but research requirements are unlikely to be identical for different conditions.

There are many possible study designs for the prospective research, which require iterative design between multiple stakeholders, here we propose one to give an exemplar:

8.1. Comparative prospective study design using geographical clusters that could be implemented within EquipoISE

In addition to the case examples, we outline a potential prospective comparative study design to exemplify the potential utility of the EquipoISE programme further. We propose a pragmatic design that uses prospectively collected DBS samples with geographical area clusters. A subset of conditions is evaluated through live prospective screening, while the remainder are evaluated through deferred testing of prospectively banked samples.

8.1.1. Prospective screening arm

The country is divided into clusters which get one of two approaches (Approach 1 and Approach 2), each continuing routine NBS screening.

In Approach 1 clusters, the NBS screening laboratories:

- Integrate additional screening for Conditions 1-5 into the live NBS screening workflow.
- Prospectively collect and store DBS for the potential evaluation of conditions 6-10 later

In Approach 2 clusters, the NBS screening laboratories:

- Integrate additional screening for Conditions 6-10 into the live NBS screening workflow.
- Prospectively collect and store extra DBS for the potential evaluation of conditions 1-5 later

Clinical follow-up:

Babies who screen positive for live-tested conditions are managed according to agreed clinical pathways, and outcome data are captured via routine datasets and/or condition-specific registries. where all newborns are tested with the candidate assay and subsequent clinical outcomes.

8.1.2. Deferred-testing evaluation arm (comparator)

Some children in each area will later present clinically with conditions that were not included in that area's extended live screening (e.g. a child in Area 1 later diagnosed with Condition 7, which was only live-tested in Area 2). For these children:

- The prospectively banked DBS stored at birth is tested for the relevant condition(s). This determines whether the newborn would have screened positive at birth had that condition have been included

To estimate false-positive and overdiagnosis rates:

- A sample of banked DBS from unaffected babies in the non-live screening area is tested using the same assays. These samples will be linked to clinical outcome data, and any babies with a recorded diagnosis of the target condition will be excluded. The remaining samples (i.e. those with no subsequent diagnosis) will be treated as presumed unaffected and so if screened would either have been false positives or overdiagnosis. (and false positive rates would be available from the clusters with follow up tests)

All babies receive the full standard of care, and no proven or recommended screening test is withheld. The variation between areas relates only to experimental conditions that are not yet part of the national programme. Importantly, all babies continue to receive equivalent clinical care, as only unproven screening tests are being evaluated and no established actionable findings are delayed or withheld.

Cross-area comparisons:

- For Conditions 1–5, Area 1 provides prospective screening data, while Area 2 provides deferred-testing comparator.
- For Conditions 6–10, the roles are reversed.

8.1.3. What this design allows

- **Estimation of real-world test accuracy metrics:** combining prospective live testing (for sensitivity and predictive value) with deferred testing of stored samples (for specificity and false-positive rates) enables estimation of test accuracy under real-world service conditions.
- **Estimation of number of test positives who would not have developed disease**: by following screen-positive infants over time, the design can determine the proportion who later manifest clinically important disease.
- **Spectrum of disease detected**: Comparing spectrum of disease detected through prospective screening with those presenting clinically identifies spectrum differences (e.g., milder, atypical, or later-onset forms) and helps quantify the likelihood of detecting low-severity or uncertain disease

- **Evaluation of screening effectiveness:** comparing outcomes between babies screened prospectively in one area and those diagnosed through usual clinical presentation allows assessment of whether screening leads to earlier detection and improved health outcomes, including reductions in morbidity or mortality where relevant.

All study designs have challenges because of the nature of rare diseases, but iterations of this type of approach considering multiple conditions at once can deliver the most robust data available internationally with only one set of research and setup costs and critically accelerating evidence production for many conditions at once.

9. Consent Considerations

The current consent language for the NHS NBS screening programme makes allowances for research using non-identifiable data

Presently, research on existing DBS cards is permitted, provided the research has been approved by a research ethics committee (REC). The following information is given to parents about the use of their child's personal data after newborn screening[34]. While the wording differs slightly across England, Wales, Scotland, and Northern Ireland, all four regions communicate the following:

- After screening, blood spot cards are stored for at least five years and may be used:
  1. to check the result or for other tests recommended by your doctor (if the results could affect the health of your baby, you will be contacted);
  2. to help improve the screening programme or testing methods for conditions already approved for screening in England (if the results could affect the health of your baby, you will be contacted); or
  3. for research to help improve the health of babies and their families in the UK (this will not identify your baby, and you will not be contacted).
- In addition, there is a small chance that researchers may want to invite you or your child to take part in information gathering linked to the newborn blood spot screening programme. Researchers undertaking any additional studies would explain what is being done and you would then be asked if you wish to take part in that study. Please let your midwife know if you do not want to be contacted to discuss taking part in any additional information gathering.

The Newborn Blood Spot Screening Programme Code of Practice[35] sets out the conditions for DBS retention and storage, including further use of the samples. This Code of Practice applies to England, Wales, and Northern Ireland and states that:

- **Retention:** DBS should be stored for five years beginning from date of receipt of the sample in the laboratory. They should then be destroyed within 12 months. However, the guidance states that retention policy is 'under review' and that 'screening laboratories are requested not to destroy any residual newborn blood spot cards and shall be notified directly when the outcome of the review has been reached.'

[34] Screening for You and Your Baby: Newborn Blood Spot (last updated 11 Aug 2025)
[35] NHS Newborn Blood Spot Screening Programme: Code of practice for the retention and storage of residual newborn blood spots

- **Storage:** Stored residual DBS should be physically separated from personal information (e.g. NHS number) but kept with laboratory identification. Linkage of residual DBS to personal information will only be possible through the laboratory identification or card serial number and carried out only by individuals authorised by the Directors of Newborn Screening Laboratories.
- **Uses:**
    - May be tested with parental consent at the request of the child's clinician should the need arise.
    - May be used for audit, training, improvement and development of laboratory methods relevant to screening, public health monitoring and other uses as allowed under the provisions of the Human Tissue Act 2004.
    - Residual DBS or screening data may be used for research, without seeking individual consent, if the identifiers have been removed from samples and data before they are given to researchers and if the research has research ethics committee approval, is compliant with relevant legislation, and is compliant with any research requirements of the HTA and HRA.
    - Very occasionally, research may involve contacting parents or their children, inviting them to take part. In these circumstances, parents and/or their children will be informed about this research and given time to consider their participation.

In Scotland, the NHS Inform website states that: *'leftover blood samples may be used for research, education and training. If this happens we'll remove your baby's personal details. If we ever need to use samples that are not anonymous, we'll always ask you for your consent first.'*[36]

The HTA Code of Practice for Research provides further advice on interpreting consent

Additional advice was sought from the Health Research Authority (HRA), in interpreting the existing consent language, considering what research questions may be explored through an ISE of the NBS screening programme, and where additional consent might be required.

The HRA emphasised the importance of *reasonable expectations*. In exploring a particular research question and whether data use for that project required additional consent, the HRA advised considering whether, under the current consent language, a participant might reasonably expect their data to be used in that particular way.

They provided further advice from the Human Tissue Authority (HTA), relating to genetic testing. Paragraph 76 of the HTA Code of Practice: E states:

- *If appropriate consent has previously been obtained to use samples for research under the HT Act, and there is a subsequent intention for the research to include the analysis of DNA, as long as the consent does not rule-out DNA analysis, then the original consent will suffice as 'qualifying' consent for use in England, Wales and Northern Ireland. However, where samples are being prospectively collected for research involving DNA analysis, it should be made clear to the donor that their bodily material will be used for this purpose.*

This advice is intended to reflect that new methodologies (like genetic testing) may develop after consent is initially sought and therefore existing consent should pragmatically suffice. However, this

[36] NHS Inform Screening: blood spot test

would be very unlikely to license exploration of new conditions not previously screened for, where the results may affect clinical management (as the principle of reasonable expectation is unlikely to be upheld).

The Human Tissue Act also allows for the use of DNA material without qualifying consent in certain 'excepted purposes.' This applies to all four of the devolved nations.[37]

- Medical diagnosis or treatment.
- Where the bodily material is from a living person and used for: **clinical audit**, educational training relating to human health, **performance assessment**, public health monitoring or **quality assurance**.
- Where the bodily material is from a living person (i.e. living at the time the sample was taken); AND '**anonymous**' to the researcher; AND to be used in **research** with/pending project-specific ethical approval (from an NHS REC).

To summarise advice received, existing guidance, and current consent language, we suggest the following considerations

1) **No additional consent likely to be required:**
   a) Improvements to existing screening programmes, such as evaluating the impact of a new screening test compared to the reference standard. This would fall under QA/QI, not research[38],[39].
   b) Screening historic DBS to compare genetic to biochemical screening test results for a condition already within the NBS screening programme [40].
   c) Linking anonymised or pseudonymised screening data with health outcomes data.[41,42]

2) **Case-by-case discussion with the HRA:**
   a) Using historic DBS as a control group, screening their samples for new conditions.

3) **New, explicit consent required:**
   a) Introducing screening for a new condition into a live screening programme (e.g., through an ISE), either all at once, to select areas, or through a stepped-wedge approach.

Note: the above are suggestions only. ISEs (including EquipoISE) are expected to involve NIHR and therefore an REC, who will have final say over the particulars of any research project approved.

[37] Section 45, Human Tissue Act (2004). https://www.legislation.gov.uk/ukpga/2004/30/contents
[38] Screening for You and Your Baby: Newborn Blood Spot (last updated 11 Aug 2025)
[39] Section 45, Human Tissue Act (2004). https://www.legislation.gov.uk/ukpga/2004/30/contents
[40] HTA Code E: Research
[41] NHS Newborn Blood Spot Screening Programme: Code of practice for the retention and storage of residual newborn blood spots
[42] NHS Inform Screening: blood spot test

10. Shortlisting Criteria

The aim of phase 2 of EquipoISE is to *choose conditions for research* (in-service evaluation) by the UK NSC, research and NHS partners.

These criteria are not intended to be used in lieu of the UK NSC criteria for recommendation for a routine screening programme.

10.1. Rule-out questions

If the answer is no (*possible answers: yes, no, unsure)* to any of these questions, do not consider this condition further for EquipoISE.

1. Can the condition be identified in a pre-symptomatic individual?
2. Is there an effective intervention for this condition that is already routinely available via the NHS, or realistically expected to become available subject to evaluation?
3. Does pre-symptomatic intervention improve outcomes for the individual with this condition in comparison with initiating intervention after symptoms emerge?
4. Is there a group of clinicians who care for babies with this condition (who will agree a clear case definition) and create national guidelines for their diagnosis and care before the ISE of the condition starts?

10.2. Criteria

	Question	Options*	Certainty of response
The condition *The ISE process is burdensome and will put pressure on services already being delivered so a heuristic assessment of likely benefit (number of babies and severity) will be an important consideration.*			
1.	The condition is an important health problem judged by its frequency when presenting clinically^. ^ Presenting clinically means symptomatic presentation rather than the frequency of the condition under screening conditions.	1: >1:100,000 2: >1:75,000 3: >1:50,000 4: >1:25,000 5: >1:5000	Scale from 1-5, where 1 means very low and 5 very high.
2.	The condition is an important health problem judged by its severity in its clinically presenting form^. ^ Presenting clinically means symptomatic presentation rather than the severity when detected through screening.	Scale from 1-5, where 1 means very low severity and 5 very high severity.	Scale from 1-5, where 1 means very low and 5 very high.
The test			
3.	There is a precise and validated screening test^ ^Include second tier testing if required. Second tier tests are confirmatory tests used when an initial screening test produces equivocal or unclear results.	Yes, No, Unsure	Scale from 1-5, where 1 means very low and 5 very high.
4.	This validated test methodology is already being used in a screening programme somewhere in the world?	Yes, No, Unsure	Scale from 1-5, where 1 means very low and 5 very high.
5.	How clearly does a true positive result link to the need for clinical intervention?^	Scale from 1-5, where 1 means very low likelihood of needing clinical intervention and 5 very high	Scale from 1-5, where 1 means very low and 5 very high.

	^A true positive is someone who has a positive screening test who has the condition in question. If an individual is identified with this screening test, how likely are they to need intervention?	likelihood of needing clinical intervention.	
6.	There is an agreed pathway of further confirmatory investigation of individuals with a positive test result	Yes, No, Unsure	Scale from 1-5, where 1 means very low and 5 very high.
6	The test methodology can be easily adopted in the UK context.	Yes, No, Unsure	Scale from 1-5, where 1 means very low and 5 very high.
The intervention			
7.	Intervention in the pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care.	Scale from 1-5, where 1 means limited additional benefits and 5 good additional benefit for all forms of the condition.	Scale from 1-5, where 1 means very low and 5 very high.
8.	Harms accruing to screening and treating are potentially significant, including harms from false positive test results, harms from detection of disease of uncertain significance and direct harms of testing and treatment.	Scale from 1-5, where 1 means insignificant harms and 5 very significant harms.	Scale from 1-5, where 1 means very low and 5 very high.
Feasibility criteria			
9.	There is an established, functioning, method of collecting data on longitudinal outcomes for babies with this condition.	Yes, No, Unsure	Scale from 1-5, where 1 means very low and 5 very high.
10.	Would screening for this condition require a change to the existing practice of day (day 5) DBS collection for newborn screening?	Yes, No, Unsure	Scale from 1-5, where 1 means very low and 5 very high.
11.	Is a commercially available test already in use elsewhere or is it feasible, without extensive work, to	Yes, No, Unsure	Scale from 1-5, where 1 means very low and 5 very high.

	create a robust and straightforward laboratory developed test?		
12.	Can this condition be included in the ISE without an unreasonable risk to the performance of the current newborn programme within the NHS?	Yes, No, Unsure	Scale from 1-5, where 1 means very low and 5 very high.
13.	Does this condition fit within a broader group that might be efficiently screened for together, for example as part of a combined test or clinical network?	Yes, No, Unsure	Scale from 1-5, where 1 means very low and 5 very high.

*****It is important to remember that the answers will not be known – if they were then we wouldn't need research – so an estimate and the certainty of your response is what is required.

11. Example Condition longlist

The table below is intended to provide an example of an initial longlist of conditions that might be considered for an ISE. Conditions are included in the national programmes (not only pilots) of another European nation and then reviewed by members of the NSC. Source for condition lists are Therrell (2024)[43] and Loeber (2021)[44] coupled with primary review of Italian legislation[45]. Conditions either in the UK NBS programme or subject to an ISE were removed.

	Group	Abbreviation	Full Name
1	Endocrine	CAH	Congenital adrenal hyperplasia
2	Miscellaneous	BIO	Biotinidase deficiency
3	Miscellaneous	G6PD	Glucose-6-phosphate dehydrogenase
4	Miscellaneous	RMD	Remethylation disorders (methylenetetrahydrofolate reductase, methylcobalamin deficiencies)
5	Miscellaneous	UDP	UDP-galactose-4-epimerase deficiency
6	Amino Acid	ASA	Argininosuccinic acidemia
7	Amino Acid	MAT I/III	Methionine adenosyl transferase I/III deficiency
8	Amino Acid	ARG	Argininaemia
9	Fatty Acid Oxidation	CUD	Carnitine uptake defect
10	Fatty Acid Oxidation	CACT	Carnitine acylcarnitine translocase deficiency
11	Fatty Acid Oxidation	LCHAD/TFP	Long-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency
12	Fatty Acid Oxidation	SCAD	Short-chain acyl-CoA dehydrogenase deficiency

[43] Therrell, B. L., Padilla, C. D., Borrajo, G. J. C., Khneisser, I., Schielen, P. C. J. I., Knight-Madden, J., Malherbe, H. L., & Kase, M. (2024). Current status of newborn bloodspot screening worldwide 2024: A comprehensive review of recent activities (2020–2023). *International Journal of Neonatal Screening*, *10*(2), 38. https://doi.org/10.3390/ijns10020038

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13	Fatty Acid Oxidation	CPT-I/CPT-II	Carnitine palmitoyl transferase deficiency Type 1 (or Type 1A) (or Type 2)
14	Fatty Acid Oxidation	GA-2	Glutaric acidaemia Type 2
15	Peroxisomal	ALD	X-linked Adrenoleukodystrophy
16	Organic Acid	MMA (MUT)/(CBL)	Methylmalonic acidaemia (non-specific term describing the disease see CBL [Cobalamin A or B or C or D (Methylmalonic acidaemia)], MUT; [Methylmalonic acidaemia (mutase deficiency)])
17	Organic Acid	PA	Propionic acidaemia
18	Organic Acid	MCD	Multiple carboxylase deficiency
19	Organic Acid	BKT	β-Ketothiolase deficiency
20	Organic Acid	3-HMG	3-Hydroxy 3-methyl glutaric aciduria
21	Organic Acid	3-MCC	3-Methylcrotonyl-CoA carboxylase deficiency
22	Organic Acid	HCSD	Holocarboxylase synthetase deficiency
23	Organic Acid	2-MBG	2-Methylbutyryl-CoA dehydrogenase deficiency
24	Lysosomal disease	MLD	Metachromatic leukodystrophy

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