



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Feasibility study into expanding *the neonatal heel prick screening test*





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Synopsis

Feasibility study into expanding neonatal heel prick test

In the first week after birth, a few drops of blood are taken from the heel of the baby and examined for a number of severe and rare congenital diseases. In 2015 the Health Council of the Netherlands advised the Minister of Health, Welfare and Sport to expand the heel prick test to include another fourteen disorders. The National Institute for Public Health and the Environment (RIVM) has carried out a so-called feasibility study to see if this is achievable. It appears that it is, as long as the expansion is implemented in phases.

However, it also appears that this expansion can only take place under a number of conditions including adequate staffing levels and financial means, the availability of flexible IT amenities, and a good interface with the health services. In 2017, the first two of the fourteen conditions - alpha and beta thalassemia - have already been added to the programme.

The expansion is a complex process due, amongst other things, to the large number of disorders, the logistics and organisation of laboratories, the availability and quality of testing methods, the follow-up investigations that will be necessary, and the interface with the health services. Furthermore, the test will cover rare disorders that are not yet included in the screening test in many countries. This means that only very limited knowledge is available at an international level.

After each of the investigations there is a go/no-go moment at which time the Minister must decide whether the condition can enter the implementation phase or further research is needed first. There is also the possibility that the condition cannot realistically be included in the heel prick screening test (at that time).

There is enough support for further expansion from professional bodies, patient organisations and other interested stakeholders. However, the current neonatal heel prick test must not come under pressure from the planned expansion and its associated preparations.

Keywords: feasibility study, heel prick screening test, population screening, neonatal screening, rare disorders, implementation

Publiekssamenvatting

Uitvoeringstoets uitbreiding neonatale hielprikscreening

In de eerste week na de geboorte worden enkele druppels bloed uit de hiel van het kind onderzocht op een aantal ernstige, zeldzame aangeboren ziektes. In 2015 heeft de Gezondheidsraad de minister van VWS geadviseerd om de hielprik met veertien aandoeningen uit te breiden. Het RIVM heeft in een zogeheten uitvoeringstoets onderzocht of deze uitbreiding haalbaar is. Dit blijkt het geval te zijn, mits de uitbreiding gefaseerd wordt doorgevoerd.

Ook blijkt dat de uitbreiding alleen onder een aantal randvoorwaarden kan plaatsvinden, zoals voldoende personeel en financiële middelen, beschikbaarheid van flexibele ICT-functionaliteiten, en een goede aansluiting op de zorg. In 2017 zijn inmiddels de eerste twee (alfa- en bèta-thalassemie) van de veertien aandoeningen toegevoegd aan het programma.

De uitbreiding is een complex proces, onder meer vanwege het grote aantal aandoeningen, de logistiek en organisatie in de laboratoria, de beschikbaarheid en kwaliteit van testmethodes, de aanvullende onderzoeken die nog moeten plaatsvinden, en de aansluiting op de zorg. Het betreft bovendien zeldzame aandoeningen die nog niet door veel landen zijn opgenomen in het screeningspakket. Hierdoor is ook op internationaal niveau slechts beperkte kennis beschikbaar.

Na elk van de onderzoeken is sprake van een go/no go-moment. Dan moet de minister besluiten of de aandoening de implementatiefase in kan gaan of dat eerst verder onderzoek nodig is. Ook kan het zijn dat het nog niet haalbaar is om de aandoening (op dat moment) toe te voegen aan de hielprikscreening.

Onder de betrokken beroepsgroepen, patiëntenorganisaties en andere stakeholders bestaat voldoende draagvlak voor de verdere uitbreiding. De huidige neonatale hielprikscreening mag echter niet onder druk komen te staan door de (voorbereidingen voor de) uitbreiding.

Kernwoorden: uitvoeringstoets, hielprikscreening, bevolkingsonderzoek, neonatale screening, zeldzame aandoeningen, implementatie

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Summary

On 8 April 2015, the Health Council (HC) recommended adding fourteen additional disorders to the heel prick screening programme in its advice entitled 'Neonatal screening: new recommendations'.

On the instructions of the Minister of Health, Welfare and Sport (VWS), the National Institute for Public Health and the Environment (RIVM) commissioned the Centre for Population Screening (CvB) to carry out a feasibility study. The feasibility study was designed to shed light on the feasibility of implementing the screening for fourteen new disorders as part of the neonatal heel prick screening programme, and the framework within which this expansion could take place. Based on the results of the feasibility study, the Minister for Health, Welfare and Sport will make a decision regarding the expansion of the neonatal heel prick screening programme.

The content of the advisory report of the Health Council, the response of the Minister of Health, Welfare and Sport, and the letter commissioning the feasibility study were all grounds for conducting a number of preliminary studies according to the CvB. The purpose of these preliminary studies was to gather additional information regarding feasibility and the parameters for including the new disorders in the neonatal heel prick screening programme. These preliminary studies were conducted in close collaboration with the parties represented in the programme committee, individual experts and patient organisations.

Groups of external experts were established for each disorder or group of disorders for the preliminary studies. Based on the evaluation framework developed and the (international) literature reviewed, the expert groups advised the CvB whether and when each disorder could be added to the heel prick screening programme, and which actions and possible follow-up research would be needed.

The preliminary study did not include alpha and beta thalassaemia or SCID. Screening for alpha and beta thalassaemia has already been implemented, on 1 January 2017. A pilot study will be launched for SCID in 2018 by ZonMw.

Outcome of preliminary studies

The disorders proposed for inclusion in the neonatal heel prick screening are rare, and in some cases extremely rare. Between 20 and 40 children with one of these disorders are expected to be identified annually, in total.

A primary or first-tier screening test is available for all conditions. For almost all the disorders, the implementation of the first-tier test alone would lead to a significant number of false positive referrals. False positive referrals are undesirable because they lead to unnecessary anxiety for parents and because of the pressure they place on the capacity of referrers and care providers.

For most of the disorders a second-tier test would be necessary, and possibly even a third-tier test, in order to reduce the number of false positive referrals. The use of post-analytical tools may reduce the number of false-positive test results. Research will need to be carried out to establish whether the use of these tools can be implemented effectively, efficiently and legally.

Some of the first-tier tests may require changes to logistical and laboratory organisation, which still require further study. For a number of disorders, there will also be consequences for the purchase of equipment and internal organisation of the laboratories. It is expected that most second and third-tier tests can be carried out using the existing infrastructure of the screening laboratories.

In relation to all disorders, further research is required before the introduction of screening can proceed. The expert groups have formulated research questions that relate to validation studies, the implications for laboratory logistics and supplementary studies (including some pilots). The validation studies concern research regarding the normal values and cut-off points for the test parameters to be used; sometimes research will be required in relation to the optimum test parameters. Close involvement will be required from the screening laboratories.

The supplementary research concerns more scientific questions, such as effectivity. The involvement of ZonMw is preferable in order to carry out four of the research studies.

The conclusion of the cost-effectiveness analysis (CEAs) is that the costs per Quality Adjusted Life Year (QALY) gained almost correspond with the limit set for prevention in the Netherlands.

Timeline

After each validation or supplementary study, there will be a 'go/no-go' decision. At these points, a decision will be made on whether the relevant disorder can proceed to the implementation phase, whether further research is required, or whether the condition is not yet ready to be added to the heel prick screening programme.

The various disorders will be added in phases, following a 'go' decision. Implementation at the end of 2019 now seems feasible for CPT1, MMA and PA. MPS I and GALK will follow at the end of 2020. And by the end of 2021 the introduction of CACT, CPT2 and BKT is planned, as well as OCTN2, SCID and X-ALD. Finally, this will be followed by GAMT at the end of 2022.

Parameters and focus areas

In order to realise the potential health benefits of screening, good integration with care and adequate capacity for diagnostics and good-quality treatment will be required. Before screening for a certain condition can be introduced, there must be clarity on the period within which referral and admission to a hospital should occur. Policy must also be developed regarding diagnosis and treatment, preferably in the form of guidelines and protocols proposed by the relevant professional group.

The role of the centres of expertise designated by the minister will need to be defined.

For almost all the organisations involved in the heel prick screening programme and their respective responsibilities, adding a new condition, or starting a pilot study for a new condition, will mean additional workload. The most significant effects will be on the reference laboratory, screening laboratories, the DVP (implementing organisation), the Centre for Population Screening in its coordinating role.

Changes to the quality assurance measures, put in place by the parties involved, will also be required as a result of the expansion.

The professionals involved will be offered a professional training programme prior to the start of pilot studies and prior to the phased addition of the various disorders involved.

Almost all information and communication resources will need to be adapted. Additionally, new material will need to be developed to include disorder-specific information regarding the conditions to be added to the programme.

For the renewal of the data systems used in the neonatal heel prick screening programme, the Praeventis renewal programme (PvP) and the laboratory reference system (NHS-LIMS) project have already been launched in preparation for the expansion.

The timetable for the introduction of screening for the new disorders and the associated testing methods, validation studies and other studies will need to be monitored closely, and it will be necessary to decide whether the new Praeventis and NHS-LIMS systems can be made available for each disorder/study, whether to adapt the existing Praeventis and/or LIMS, or whether to explore other alternatives.

When a new condition is added to the programme, ICT must be able to handle the necessary process steps with regard to the heel prick card, add new letters to the system, set up short-cycle monitoring and log new indicators.

This will require a great deal of flexibility from the ICT functionality, which must be available in good time before the addition of a new disorder.

Due to the low prevalence of these disorders and the uncertainty due to false positive results, the number of referrals and the number of repeated first heel pricks will be subject to short-cycle monitoring. The outcomes of diagnostics and the timeliness of diagnostics will also need to be closely monitored. It will be necessary to develop new indicators. New target and signal values will need to be developed for the disorders to be added to the programme.

The main focus points for the Caribbean Netherlands (CN) are the question of whether it is necessary to send test shipments from heel prick cards from CN to the Netherlands to discover whether particular disorders can be reliably analysed for new-borns from the CN. Furthermore, the development of specific follow-up protocols for diagnostics and care for children with abnormal results merits extra attention.

Tenders for new testing methods and possible equipment will need to be carried out. Furthermore, the part of Praeventis that is required for the heel prick screening programme is expected to be held for tender in 2017. In 2018, preparations for the tendering process will be made for the screening laboratories.

In brief, there are many focus points and matters to be arranged. The turnaround times and timeline set out above have been significantly influenced by factors relating to the implementation of the current programme and external factors, and will most likely continue to be subject to change (faster or slower for different disorders) in the coming years.

Risks

The phased expansion of the heel prick programme will be an extensive undertaking. It will involve the expansion of an existing programme through the addition of a large number of complex, rare disorders. Risks include: insufficient availability and capacity on the part of the parties involved, discontinuity in the regular screening programme, inadequate coordination with the care system, the inadequate (or late) funding of research, delays in the necessary changes to data management systems.

Costs

The one-off costs during the preparatory phase and during the phased introduction will amount to around €14 million over a five-year period. Structural annual costs of the heel prick screening programme are expected to rise from approximately €19.1 million in 2017 to €19.9 million in 2019 and €27.0 million in 2022.

1 Introduction

In the Netherlands, almost all new-born babies (approximately 175,000 per year) are currently screened using the heel prick for cystic fibrosis, sickle cell disease, adrenogenital syndrome, congenital hypothyroidism and thirteen metabolic disorders. These disorders cannot be cured, but they can be treated. Around 200 sick children are identified every year within this group; around 800 new-borns are referred due to abnormalities revealed by the heel prick test. In addition, some 800 new-borns each year are identified as carriers of sickle cell anaemia. Since 2015, the heel prick screening has also been implemented on the islands of Bonaire, Sint Eustatius and Saba, which together form the Caribbean Netherlands (CN).

On 8 April 2015, the Health Council (HC) recommended adding fourteen further diseases to the screening programme in its advice 'Neonatal screening: new recommendations'. On 30 October 2015, the Minister of Health, Welfare and Sport (VWS) commissioned the Centre for Population Screening (CvB) of the National Institute for Public Health and the Environment (RIVM) to perform a feasibility study (see Appendix 1).

This feasibility study is meant to shed light on the feasibility of implementing the screening for fourteen new diseases in the neonatal heel prick screening, and the framework within which this expansion could take place. Based on the results of the feasibility study, the Minister of Health, Welfare and Sport will decide on the expansion of the neonatal heel prick screening programme.

The background to the existing neonatal heel prick screening programme is briefly discussed in section 1.1. In section 1.2, a summary of the advice of the HC on the extension of the heel prick screening programme is presented. Section 1.3 describes the response of the Minister of Health, Welfare and Sport to this advice. Subsequently, in section 1.4, the way in which the feasibility study was to be carried out (as specified by the ministry) is explained. The approach taken to the feasibility study is described in section 1.5. Finally, section 1.6 contains a reading guide for this report.

1.1 The existing neonatal heel prick screening programme

Nineteen diseases and disorders are currently screened for.¹ Screening for phenylketonuria (PKU) using heel prick blood has been in place in the Netherlands since 1974. Since 1981, the blood has also been checked for congenital hypothyroidism (CH) and since 2000 for adrenogenital

¹These include the following disorders: Adrenogenital syndrome (AGS), Biotinidase deficiency (BIO), Congenital hypothyroidism (CH), Cystic fibrosis (CF), Galactosemia (GAL), Glutaric acidemia type 1 (GA-1), HMG-CoA lyase deficiency (HMG), Isovaleric aciduria (IVA), Long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHADD), Maple syrup urine disease (MSUD), Medium-chain acyl CoA dehydrogenase deficiency (MCADD), 3-Methylcrotonyl-CoA carboxylase deficiency (3-MCC), Multiple CoA carboxylase deficiency (MCD), Phenylketonuria (PKU), Sickle cell anaemia (SZ), Alpha thalassaemia (HbH), Beta thalassaemia (TM), Tyrosinemia type 1 (TYR-1), Very long-chain acylCoA dehydrogenase deficiency (VLCADD).

syndrome (AGS). Since 1 January 2007, fourteen additional diseases and disorders have been screened for: thirteen metabolic disorders and sickle cell anaemia.

Screening for sickle cell anaemia can also reveal carrier status. Parents can opt not to receive information about carrier status.

With effect from 1 May 2011, cystic fibrosis (CF) was added to the screening.

The testing method for homocystinuria (HCY) is inadequate, and screening for this disease was discontinued on 1 April 2016.

As a first step towards the further expansion of heel prick screening, alpha (HbH) and beta thalassaemia (TM) were added to the programme on 1 January 2017.

A neonatal hearing check is mostly performed at the same time as the heel prick blood is taken.

The goal of the neonatal heel prick screening is the early detection of a number of rare, serious and often hereditary diseases, for which intervention shortly after birth has clear advantages over intervention that would otherwise only take place at a later stage, or not at all. According to the HC, possible interventions include treatment using medicine or a special diet, but also preventive measures such as avoiding fasting with certain fatty acid metabolism disorders.

One important advantage of the neonatal heel prick screening is the health benefit for the new-born, due to the extent to which the disorders detected are treatable. In addition, a lengthy diagnostic process can be avoided.

Screening also has disadvantages. In suspected cases of a health issue, the child usually needs to be seen by a paediatrician quickly. This leads to anxiety for the family involved. It may ultimately turn out that nothing is wrong (this is the case in around 600 of the 800 children referred annually). Some children with disorders are also missed (which is the case in a handful of cases annually).

A detailed description of the screening can be found on the website (http://www.rivm.nl/Onderwerpen/Onderwerpen/H/Hielprik/Voor_professionals). The programme organisation and guidelines for the neonatal heel prick screening can also be consulted there. For a brief summary of the neonatal heel prick screening in the Netherlands, we refer to the neonatal heel prick screening fact sheet, which can also be found on the website.

1.2 The advice of the HC

On 8 April 2015, the HC issued its advice 'Neonatal screening: new recommendations' to the Minister of Health, Welfare and Sport on the basis of her request for advice dated 28 June 2012.

The HC still considers the existing criteria for inclusion in neonatal heel prick screening to be adequate. The goal of the screening should remain: a health benefit for the new-born, operationalised as health gain or the prevention of health issues, through early intervention in the

case of serious diseases or disorders for which the natural course is known. The Committee considered whether screening for non-treatable diseases should also have a place within the programme, but believes that this is currently not appropriate in the majority of cases.

Based on an evaluation framework, the HC recommends adding fourteen diseases to the screening programme. This includes eleven metabolic disorders, namely:

- Carnitine acylcarnitine translocase deficiency (CACT);
- Carnitine palmitoyltransferase deficiency type 1 (CPT1);
- Carnitine palmitoyltransferase deficiency type 2 (CPT2);
- Galactokinase deficiency (GALK);
- Guanidinoacetate methyltransferase deficiency (GAMT);
- Methyl acetoacetyl-CoA thiolase deficiency; beta-ketothiolase deficiency (MAT, referred to as BKT in this feasibility study);²
- Methylmalonic acidemia (MMA);
- Mucopolysaccharidosis type 1 (MPS I);
- Organic cation transporter 2 deficiency (OCTN2);
- Propion Acidemia (PA);
- X-linked adrenoleukodystrophy (X-ALD);
- two haemoglobinopathies:
 - Beta thalassaemia major (TM);
 - HbH disease (HbH);

and one severe immune deficiency (Severe combined immune deficiency (SCID)).

In the view of the HC, adding diseases to the heel prick screening in a responsible way is not possible without a proper pilot study. For all diseases other than those already detected as secondary findings in 2015 (TM, HbH and OCTN2), the HC advises carrying out a more extensive pilot study.

Secondary findings and carrier status

The neonatal heel prick screening may already result in secondary findings: findings other than those intended. The HC focuses mainly on clinically relevant secondary findings. A distinction has been drawn between two different situations: manageable and non-manageable diseases. In the first case, there are options for prevention or treatment, while in the second case there are not. The HC takes the view that manageable diseases that are identified through secondary findings must always be reported to the parents because this is in the interest of the child. Non-manageable diseases should in principle not be reported, because this may affect the child's right to an open future. One exception to this could be made if the disease manifests itself early and the child can be spared a lengthy diagnostic process.

One particular clinically relevant secondary finding is when the child is a carrier of certain diseases. A majority of the Committee of the HC recommends not reporting the carrier status of the child to the parents.

² At the expert meetings, it was indicated that it is preferable to use the term beta-ketothiolase deficiency (BKT) rather than methyl-acetoacetyl-CoA thiolase deficiency (MAT). This is to avoid confusion with another metabolic disorder with the abbreviation 'MAT'. Only the name beta-ketothiolase deficiency and the abbreviation BKT are therefore used in this feasibility study.

The Committee takes the view that neonatal screening should not become a carrier status screening in disguise, and that a neonatal screening is an inappropriate moment at which to report carrier status. Carrier status for sickle cell anaemia should no longer be reported to parents, even if this has been happening in recent years.

1.3 The response of the Minister of Health, Welfare and Sport

On 9 July 2015, the Minister of Health, Welfare and Sport responded to the recommendation of the HC (Appendix 2). The minister indicated that she intended to adopt the proposals for the inclusion of fourteen diseases in the neonatal heel prick screening. At the same time, she announced that due to the large number of diseases involved, she would be forced to make choices about the speed with which these would be added to the population screening. The minister stated careful implementation would be necessary, but she wants to ensure that rapid progress is achieved where this could happen. The minister then divided the fourteen diseases into three groups.

Shorter preparation time

First of all, she identified three diseases that are expected to require a short preparation time before they can be added to the programme. This group consists of the secondary findings (OCTN2, TM, HbH) that were already being reported to parents in 2015. It should be noted that these diseases would require changes to information management, information provision, the promotion of expertise and possibly the method of testing, according to the minister. These adjustments would involve some preparation time.

Medium preparation time

The minister then named six diseases which, in terms of screening methods, closely resemble the current range of metabolic disorders (MA, PA, CACT, CPT1, CPT2 and BKT). She stated that she wanted research to begin on the implementation of screening for these diseases, which can be detected using existing equipment. However, a proper pilot scheme would still be needed to make the step from the research setting to population screening. Expansion to include these diseases will require many changes, for example with regard to an adequate definition of the parameters for the testing methods, the provision of information and the promotion of expertise and integration with care, wrote the Minister.

Longer preparation time

For the other five diseases (GALK, GAMT, MPS I, SCID, X-ALD), a much longer preparation time and more robust pilot schemes will be needed before they can be included in the screening. The long preparation time is due to several factors.

For some diseases, completely new testing methods will need to be applied, and these will need to be tested/validated before their addition to the neonatal heel prick screening programme. For X-ALD, a distinction must be made between male and female babies. This distinction has not previously been made in the programme and has implications for the entire process, from completing the heel prick card and identifying the disease through to archiving the cards.

Non-treatable diseases

The minister acknowledged the disadvantages identified by the HC and the risks of including non-treatable diseases in the neonatal heel prick screening. At the same time, she recognised that more knowledge regarding non-treatable diseases may lead to treatment options with the potential to reduce suffering. She therefore opted to set up a neonatal heel prick screening for non-treatable diseases, which parents can opt into. The minister said she would look at how this can be organised effectively and responsibly.

Secondary findings

The minister agreed with the GR that secondary findings should be avoided wherever possible. She also made the distinction between manageable and non-manageable secondary findings.

Manageable secondary findings should, in her opinion, be reported to the parents, in the interest of the baby. Frequently recurring manageable secondary findings should, like OCTN2, TM and HbH, be considered for future inclusion in the programme as diseases that are officially screened for.

Secondary findings that cannot be managed should not be reported. The minister made an exception for diseases that manifest themselves early and where a lengthy diagnostic process can be avoided.

Carrier status

Regarding the reporting of carrier status for sickle cell anaemia, the minister indicated that there was a dilemma. In practice, we know that reporting carrier status involves considerable work for those carrying out the screening, particularly at the screening laboratories, the implementing organisation and among the general practitioners involved. In addition, it is questionable whether, in the event of informed consent, it is desirable to devote considerable attention to what is, strictly speaking, a secondary issue within the screening programme. However, the minister sees no alternative for the time being. She wanted to consider how this dilemma could be resolved, for example by asking the parents about their wishes in advance. Until that time, the policy will remain unchanged within the neonatal heel prick screening programme and carrier status of sickle cell anaemia will be reported to the general practitioner and the parents concerned.³

Future developments

The Minister observed that at the technological and scientific level, innovation will continue to ensure that better treatment methods are developed and better detection methods are found. This will mean significant health benefits for babies following treatment. When it comes to the neonatal heel prick screening, she wants to ensure that there is a rapid response to these innovations in order to achieve the optimum health benefit. For this reason, she will be asking the HC more often than previously whether new developments may have an impact on

³ About 800 children per year are involved in such cases. Carriers of other haemoglobinopathies, such as HbAC, HbAE, HbAD (also about 800 cases per year), are not reported to general practitioners and parents. Parents are not informed of these forms of carrier status, even though this is visible using the current testing method and there is a risk of a subsequent child with sickle cell anaemia if one of the parents is a carrier.

candidate diseases for the neonatal heel prick screening or on ethical aspects.

1.4 Instructions for the implementation trial

The Minister of Health, Welfare and Sport instructed the Centre for Population Screening to carry out a feasibility study, on 30 October 2015, in order to shed light on the feasibility of implementing screening for fourteen new diseases in the neonatal heel prick screening, and the framework within which this expansion could take place. The minister anticipated a minimum lead time for the implementation trial of eighteen months.

The minister wished to see the following areas included in the feasibility study: primary process, organisation, tasks and responsibilities, communication, information and expertise promotion, quality assurance, monitoring and evaluation, information management, capacity of and integration with care and financing.

The Minister asked the Centre for Population Screening to prioritise the changes required in the areas of information management, information provision, expertise promotion and (possibly) the testing method for the three diseases with a potentially shorter preparation time (OCTN2, TM and HbH), which were already being reported as secondary findings in 2015.

For the category of diseases that require a longer preparation time, the Minister asked the Centre for Population Screening to prioritise SCID. She also asked for a cost-benefit analysis for the addition of screening for this disease to the heel prick screening. The reason for this request was that this screening test is more complex and costly than the other neonatal screening test methods.

Furthermore, the Minister asked the Centre for Population Screening to identify which secondary findings can be expected using the testing methods chosen. She also requested an indication of whether these secondary findings are communicated to the target group and to the parents directly involved, and if so in which way.

Current developments in the existing heel prick programme will affect the future expansion of the programme and vice versa. This relates specifically to the tender for the Laboratory Information Management System (LIMS), the replacement of laboratory equipment (for example, the LC-MS/MS), the tender for the work carried out by the screening laboratories and the renewal of the Praeventis information system. The Minister asked the Centre for Population Screening to focus on coordination and alignment in the feasibility study.

1.5 The approach taken in the feasibility study

In November 2015, the Centre for Population Screening began the feasibility study. In addition to the points that the minister mentioned in relation to the feasibility study, the following principles were important for the Centre for Population Screening:

- Improvements to the regular programme were, in principle, not to be part of the feasibility study.
- The broad public acceptance of the neonatal heel prick screening should not be undermined by (preparations for) the expansion of the programme.
- The organisational structure of the regular programme was used wherever possible in the feasibility study and will be used as well in the implementation phase of the extended screening.
- The report describes how the expansion can best be arranged in relation to each domain separately, and overall including all domains.
- General starting point: public values. The public values established by the Centre for Population Screening - those of quality, accessibility and affordability (see 6.1) - are also important here.

The involvement of all relevant professional associations, patient organisations and implementing organisations was essential in this feasibility study. These parties were involved through the existing programme committee and the existing working groups, through the temporary addition of a working group on finances, and by setting up an RIVM working group for the expansion of the screening programme. An RIVM Knowledge Platform was also used, having been set up specifically for the expansion.

Appendix 3 provides a summary of the parties involved in setting up the feasibility study. Appendix 4 describes the composition of the newly established working groups and the existing programme structure.

This report has been drawn up on the basis of the principles described above, input from the parties concerned and with the help of the information collected.

1.6 Reading guide

This report presents the results of the feasibility study. Chapter 2 describes how the preliminary study was carried out, and the inventory of the support and its various components. Chapter 3 summarises the main conclusions of the expert groups (also see Section 2 and Appendix 5) for each of the (clusters of) diseases. Chapter 4 focuses specifically on SCID. Chapter 5 to 10 describe the principles and starting points of the existing programme, and outlines which changes will be required in order to introduce the desired expansion in the various domains identified.

Chapter 11 focuses on the expansion of the neonatal heel prick screening programme in the Caribbean Netherlands.

The domain of implementation is discussed in chapter 12. This section describes how the expansion of the programme can best be implemented. Due to the complexity of the proposed expansion to the programme, the feasibility study focused particularly on the risks involved. These are also covered in chapter 12.

Section 13 relates to the expected costs of the preparation phase and the implementation of the extended screening programme. Calculations are presented that describe developments in relation to the capacity of the various parties involved in the screening programme.

Finally, chapter 14 summarises the key points of this feasibility study and advice regarding to the introduction of the expansion of the neonatal heel prick screening programme.

2 Preliminary studies and support base

The content of the advisory report of the HC (April 2015), the response of the Minister of Health, Welfare and Sport (July 2015), the Plan of Action for the implementation trial for the expansion of neonatal heel prick screening (October 2015) and the letter commissioning the implementation trial (October 2015) were all grounds to conduct a number of preliminary studies. The purpose of these preliminary studies was to gather additional information regarding feasibility and the parameters for including the new disorders in neonatal heel prick screening programme. These preliminary studies were conducted in close collaboration with the parties represented in the programme committee, individual experts and patient organizations.

This section describes those preliminary studies into feasibility and the timeframe for the introduction of screening for the new disorders (2.1), the initial exploration of the expertise and capacity required for the inclusion of metabolic disorders in the heel prick (2.2), the financial structure of the heel prick screening programme (2.3), and an evaluation of certain issues during international congresses (2.4). The final section provides an explanation of the support base for the expansion of the heel prick screening programme and the implementation trial (2.5).

2.1 Preliminary research into feasibility and timeframe for introduction

A preliminary study into feasibility and the timeframe for introduction was necessary to acquire further insight into the availability, quality (clinical validity), reliability and practical applicability of the testing method, and follow-up in healthcare practice.

The preliminary study did not include alpha and beta thalassaemia or SCID.

Screening for alpha and beta thalassaemia has already been implemented, on 1 January 2017. An abbreviated implementation trial was set up for this, on the basis of which the minister decided to add these disorders to the current screening programme in November 2016. Also see Appendix 9.

The abbreviated implementation trial indicated that the rapid introduction of screening for OCTN2 was not desirable.

A pilot study will soon be underway for SCID via ZonMw. This pilot is being prepared by the national Working Group on Immune Deficiency (WID).

As a first step in the preliminary study into the feasibility and timeframe for introduction, a number of experts from the Centre for Health Protection (GZB) at RIVM developed an evaluation framework (also see Appendix 6) that could be used by external expert groups to evaluate the disorders.

The evaluation framework was confirmed by the Centre for Population Screening after being discussed by the programme committee for the neonatal heel prick screening and with the ministry.

Subsequently, groups of external experts were established for each disorder or group of disorders. For the composition of these groups, see Appendix 5. The expert groups met once for each disorder or group of disorders between June 2016 and October 2016.

Based on the evaluation framework and the (international) literature collected, the expert groups advised RIVM whether and when each disorder could be added to the heel prick screening programme, and which actions and possible follow-up research would be needed.

The main thrust of the (draft) recommendations and an initial impression of the consequences for implementation were presented and discussed at a national meeting held on 13 February 2017. The members of the expert groups, the programme committee and the working group on finance (also see 2.3) were all invited to this meeting.

The final recommendations of the expert groups and the evaluation framework for each (group of) disorder(s) can be viewed in full in Appendix 8.

The expert groups and other parties involved gathered additional information regarding, among other things, the quality and availability of testing methods and integration with care. This concerned the aspects that received limited attention in the HC report.

Looking back at the work done by the expert groups, it yielded a great deal of additional information, but there was insufficient time for further research to address all the components of the evaluation frameworks.

2.2 Initial exploration of expertise and capacity for the inclusion of metabolic disorders in the heel prick

The expansion of the heel prick screening programme to include fourteen additional disorders includes eleven metabolic disorders. The current heel prick screening already includes thirteen metabolic disorders. The expansion will require specific expertise in care for metabolic disorders. It is essential that the academic hospitals have sufficient expertise and capacity available.

At the beginning of March 2017, representatives of metabolic paediatricians, the Capacity Unit, the patient organization VKS, the National Plan for Rare Diseases, NFU, NVK, ZonMw, the Ministry of Health Welfare and Sport and the academic hospitals discussed the anticipated bottlenecks, as well as ideas on how to address these bottlenecks (see section 12).

2.3 Study of financial issues relating to heel prick screening

Financial issues relating to the extension of the heel prick screening programme were discussed within a dedicated finance group. The main stakeholders in the programme were represented in this working group (see Appendix 4).

At the end of 2016, the working group presented a proposal for a fee structure for the implementation of the heel prick screening and for laboratory analyses. The working group also advised the Centre for Population Screening on the initial estimates of the cost of implementing the expansion, and structural costs after the expansion of the programme.

2.4 Evaluation of issues during international conferences

Two international conferences were attended in 2016: the APHL (Association of Public Health Laboratories) in St. Louis (USA) and the ISNS (International Society for Neonatal Screening) in The Hague. At these conferences, international experts discussed the forthcoming expansion of heel prick screening in the Netherlands. Themes addressed during these discussions included: experiences in other countries with testing methods for the disorders to be added, information systems and communication and public information.

2.5 Support base

Support base for expansion

There is support among the general public, patient organizations and professionals for the expansion of the heel prick screening programme to include fourteen additional disorders.

This support was evaluated in May 2015, one month after the publication of the HC's advice, at an extra meeting of the programme committee (also attended by a number of SCID experts). The basic principles of the screening programme were discussed in relation to the proposed expansion, the new disorders, SCID, carrier status and secondary findings, and screening for non-treatable conditions. By the end of the session, it was clear that the parties supported the expansion of the screening programme.

Support among professionals is also evident from the great commitment and effort that they have demonstrated through their participation in the expert groups, the preparation of the recommendations and the evaluation framework (see 2.1), their participation in additional meetings and discussions during the programme committee, the research working group and the working group for information and expertise promotion. However, questions were asked about the order in which the disorders should be added and the turnaround time involved.

The same applies to the patient organisations⁴. They are also in favour of the expansion of screening to include fourteen additional disorders. However, from the point of view of future patients with these disorders, they also explicitly asked for rapid implementation: as far as they are concerned, this should occur more quickly than the timeframe that has currently been proposed. The number of disorders to be added is also too limited, in the view of the patient organisations. Other conditions should be considered for inclusion in the screening, and it was asked that further attention be given to the HC's advice to set up screening for

⁴ VSOP and VKS are members of the PNHS.

untreatable conditions. Media coverage mainly related to the desirability of further expansion.

Public support for the expansion was not evaluated.

The expansion to include fourteen disorders is not expected to have any negative consequences for participation in the screening.

This expectation is based on the fact that earlier expansions of the heel prick screening (the addition of fourteen disorders in 2007, the addition of CF in 2011 and the addition of alpha and beta thalassaemia in 2017), and coverage of the proposed new expansion to include fourteen additional disorders did not lead to public opposition.

Support for the content of the implementation trial

The Centre for Population Screening asked the parties represented in the national programme committee for their response to the implementation trial. Their formal written responses were added to this implementation trial.

3 Results of preliminary studies and reflections of the Centre for Population Screening

3.1 Introduction

The Centre for Population Screening has conducted preliminary studies into the feasibility, parameters and timeframe for introduction of the expansion of the neonatal heel prick screening programme.

This section presents the most important results of these preliminary studies, focusing in particular on the testing method and laboratory equipment. For the reasons outlined in section 2.1, this section does not address alpha and beta thalassaemia and SCID.⁵

Section 3.2 presents the annual expected numbers of patients. Section 3.3 discusses the screening tests required and the consequences for laboratory equipment and logistics. This section also discusses false positive and false negative test results. Section 3.4 considers the issue of secondary findings. Section 3.5 discusses the collection of blood and the timing of this. Section 3.6 discusses (referrals to) diagnostics and treatment. Section 3.7 identifies the research that is required before the screening of the various disorders can be implemented, and section 3.8 presents the minimum time required for the forthcoming expansion on the basis of the research questions to be answered. Section 3.9 summarises the main conclusions of the preliminary studies. Finally, in section 3.10, the Centre for Population Screening provides a reflection on the timeframe (phasing) proposed by the experts. It also considers the complexity of implementation.

For a short description of the different disorders, see Appendix 7.

3.2 Expected numbers of sick children per year

The disorders proposed for inclusion in the neonatal heel prick screening are rare; some are extremely rare. Table 1 shows the expected numbers of sick children per year for each disorder. Between 20 and 40 children with one of these disorders are expected to be identified annually, in total. CACT, CPT1 and BKT are extremely rare. The discovery of these conditions in children can take years. For the other disorders, one or only a few cases are expected to be identified annually.

⁵ For the sake of completeness, SCID is included in a number of the tables in this chapter.

Table 1: Expected numbers of sick children per year

Disorder	Expected numbers of sick children per year ^{1, 2}	
CACT	0-1	Less than 1 patient every 5 years
CPT1	0-1	Less than 1 patient every 5 years
CPT2	2-16	
GALK	0-2	
GAMT	0-2	
BKT	0-1	Around 1 patient every 1 to 5 years
MPS I	1-4	
MMA	1-2	
OCTN2	1-9	
PA	0-1	Around 1 patient every 1 to 2 years
X-ALD	6-7	Number relates to boys detected
SCID	2-4	

¹ Based on an estimated number of births of 175,000 per year

² The sources used are listed in Appendix 10

3.3 Screening tests and laboratory equipment

This section describes screening tests that are available to make the forthcoming expansion of the heel prick screening programme possible, and the consequences for laboratory equipment⁶. Table 2 provides an overview of the tests available and the analytes that are tested for. In addition to the primary test (first-tier test), additional tests are also included that are necessary to reduce the number of false positive test results (second and third-tier tests).

⁶ In section 5, Primary process, table 7 provides an overview of the equipment currently available in the laboratories.

Table 2: Available screening tests

Disorder	First-tier test	Second-tier test	Third-tier test
CACT	MS/MS acylcarnitine profile; (C16 + C18:1)/C2 most informative *		
CPT1	MS/MS acylcarnitines (C0/C16 + C18)		
CPT2	MS/MS acylcarnitine profile; (C16 + C18:1)/C2 most informative *		
GALK	Total galactose (TGAL) assay on GSP or other equipment	Galactokinase assay (currently only on whole blood)	
GAMT	MS/MS Guanidine acetate (GA) and GA/creatinine ratio	LC-MS/MS ⁷ on the same analytes as first-tier test	DNA (optional)
BKT	MS/MS acylcarnitines C5:1, C5-OH (,C4-OH)	LC-MS/MS on the same analytes as first-tier test	
MPS I	MS/MS iduronidase (IUDA) activity; alternative available	Glycosaminoglycans (GAG) assay (currently only on whole blood)	DNA (optional)
MMA	MS/MS C3 carnitine and/or C3/C2 ratio	LC-MS/MS; methyl malonic acid (MMA) and methylcitric acid (MCA)	
OCTN2	MS/MS C0 carnitine		
PA	MS/MS C3 carnitine and/or C3/C2 ratio	LC-MS/MS; various analytes in research	
X-ALD	MS/MS C26: 0-lyso-phosphatidylcholine (LPC)	LC-MS/MS on the same analytes as first-tier test	DNA (optional)
SCID	T-cell receptor excision circles (TREC) assay	DNA (optional)	

*) of the carnitine profile, (C16+C18:1)/C2 is the ratio that discriminates best, but still insufficient for an adequate test

⁷ This report refers to LC-MS/MS when the LC function is used in the test. If the LC function is not used in the test, the term MS/MS is used.

Primary tests

A primary or first-tier screening test is available for all conditions.

For CACT, CPT1, CPT2, BKT, MMA, OCTN2, PA and X-ALD, these tests can be run on the existing Liquid Chromatography tandem Mass Spectrometry (LC-MS/MS) equipment, using the MS/MS assay and kit used in the current screening.

The first-tier test for CACT is identical to that for CPT2 and therefore cannot distinguish between these two disorders. The same applies to MMA and PA.

One specific challenge when screening for X-ALD is implementing the HC's advice to screen only boys. Currently, the sex of the child being tested is not known when the laboratory tests are carried out, because in the regular programme all children are screened for all conditions. It is advisable to look at whether it would be possible to select boys in the laboratory by recording sex on the heel prick card before the laboratory test is carried out.

It is also unclear whether it is feasible, in terms of laboratory logistics, to test boys and girls in different ways. This requires further investigation.

In principle, the first-tier tests for GAMT and MPS I can also be performed on existing LC-MS/MS equipment.

However, the test for MPS I is not part of the kit currently used. The use of another kit would require an extra run and therefore the purchase of an additional LC-MS/MS device in the five screening laboratories. The alternative - carrying out this test on the existing equipment overnight - is less practical, given the logistical and personnel challenges that this would involve.

No commercial assay is yet available for GAMT. However, a test is in use at VUmc that could be further developed into an in-house testing method. In-house tests are testing methods that are not commercially available (not usually CE-marked), but have been developed independently by the laboratory. In in-house testing, quality is guaranteed through ISO15189 certification of the laboratory. All the laboratories involved in heel pricking screening are soon expected to be ISO15189 certified. The use of an in-house test would also require additional LC-MS/MS equipment, would be new for the existing NHS laboratories and would require further study with regard to scaling up and quality assurance. One option would be to have a central laboratory perform all GAMT analyses using this testing method. This would save on equipment, but would create a logistical challenge and would need to be assessed for feasibility, timeliness and reliability.

The first-tier test for GALK can be automated with the equipment already available in the laboratories. The screening test for GALK measures galactose, an analyte that is measured in the current screening in a small number of the heel prick samples using a manually performed test to screen for galactose-1-phosphate uridylyltransferase deficiency (GALT). For the latter screening, consideration could be given to replacing the current manual TGAL test with the automated test. However, this would require laboratory validation.

Second and third-tier tests

For almost all the disorders, the implementation of the first-tier test alone would lead to a significant number of false positive referrals. However, a full understanding of the numbers involved is lacking. False-positive referrals are undesirable because they lead to unnecessary anxiety for parents and because of the pressure they place on the capacity of the referrers and care providers.

With the exception of CPT1 and OCTN2, a second-tier test is necessary, and possibly even a third-tier test, to reduce the number of false positive referrals.⁸ The available second and third-tier tests are also shown in Table 2. The number of second and third-tier tests that would need to be carried out by laboratories per day is limited.

Good second-tier tests are available for GAMT, BKT and X-ALD. In principle, these tests can be performed on the existing or additional LC-MS/MS equipment. In practice, however, it may prove that this would still lead to implementation problems that necessitate the purchase of additional equipment.

Potential second-tier tests are also available for GALK and MPS I. These can currently only be performed on whole blood, and therefore not using dried blood from heel prick cards. It remains to be proven whether application on the blood from the heel prick card is possible. For MPS I, this seems more likely than for GALK. Based on data from the current screening for galactosaemia, it is expected that the number of false positive results that the first-tier GALK test produces will be very small (1-2 per year). The need for a good second-tier test therefore seems limited, but this has yet to be confirmed definitively.

For MPS I, research is underway regarding whether testing for an additional heel prick taken later could reduce the number of false positive results.

For CACT/CPT2 and MMA/PA, good second-tier testing has yet to be developed. For MMA, there is currently a good second-tier test, but without a good test for PA this would not reduce the number of false positive results. Internationally, several second-tier tests for PA are being researched. Here, too, research is required regarding whether testing an additional heel prick taken later could provide a solution.⁹ This is because in some children, C3 and the C3/C2 ratio have normalised by that point. The disadvantage is that a second visit to the child and parents would be needed, as well as an explanation of the interim findings. The development of good second-tier tests for CACT/CPT2 has, as yet, been relatively unsuccessful.

False positive test results can also occur in relation to OCTN2 deficiency. Low carnitine concentrations in heel prick samples do not occur only in babies with OCTN2 deficiency; in most cases they are caused by an

⁸ The primary test for CACT is identical to that for CPT2 and therefore cannot distinguish between these two disorders. The same applies to MMA and PA. This issue could also be resolved through the use of second-tier tests.

⁹ This extra heel prick would need to be distinguished from the repeated first heel prick if the quality of the blood spots on the heel prick card and the second heel prick (THP) are not satisfactory in the case of a non-conclusive result. If this additional heel prick is introduced at some point, clear and unequivocal terminology would be established in consultation with the field.

(asymptomatic) OCTN2 deficiency in the mother. A second-tier test would be of little help in this respect. However, blood collection at a later point (approximately fourteen days after birth) would ensure that the carnitine concentration measured reflects the concentration of the child rather than of the mother. The ideal time for determining the carnitine concentration of the child has yet to be identified.

A (third-tier) DNA test is available as an option for GAMT, MPS I and X-ALD. Specific genes are being investigated in this regard. If the need for this is demonstrated, it would need to be ascertained in relation to each disease whether DNA analysis should be carried out in the screening laboratory or in a clinical genetic laboratory. For the current screening for Cystic Fibrosis (CF), for example, agreements have been made with the clinical genetic laboratories in Tilburg, Zwolle and Amsterdam (VUmc).

In addition to reducing the number of false positives, DNA analysis at X-ALD also offers the opportunity to distinguish boys, who benefit from rapid diagnosis, from girls, for whom there is no such advantage. However, this would only become relevant if the preferred scenario of gender selection prior to laboratory analysis proves unfeasible.

False positive test results

Table 3 shows whether false positives are an issue that requires further research and/or development for each disorder.

Table 3: Persisting false positives and false negatives issue

Disorder	False positive issue	False negative issue
CACT	Second-tier not yet available	
CPT1		
CPT2	Second-tier not yet available	
GALK		
GAMT		
BKT		First-tier only positive with crisis
MPS I	Second-tier only on full blood	
MMA	Second-tier PA still under development	
OCTN2	First heel prick must be done later	First heel prick must be done later
PA	Second-tier still under development	
SCID	Second-tier DNA test possible?	
X-ALD		

In addition to developing good second and possibly third-tier tests, another interesting option for a number of disorders would be to reduce the number of false positive screening results.

A number of expert groups (CACT/CPT2, BKT, MPS 1, MMA/PA and OCTN2) as well as the programme committee for the neonatal heel prick screening programme have advised using Region 4 Stork (R4S) and Collaborative Laboratory Integrated Reports (CLIR) post-analytical tools. For this, the results for different analytes are included in a probability calculation, which results in a more accurate estimate of the probability of a disorder than at the current cut-off limits based on one or a small number of analytes.

Before these post-analytical tools can be used for the neonatal heel prick screening, however, a number of important questions would need to be answered regarding effectiveness, efficiency, continuity and privacy and so on. Further study would be required for this.

The section on Primary process discusses extensively the potential use of these post-analytical tools.

False negative test results

In addition to the issue of false positive results, false negative test results are another issue for a number of disorders that will be added to heel prick screening (see Table 3). This relates to BKT and OCTN2. For BKT, false negatives occur because blood counts are only abnormal during a ketoacidotic crisis. False negatives are therefore inevitable using the current test. Although the relative number of false-negative results for this condition is high (50%), given the low prevalence of BKT, less than one case per year will be missed.

The number of false-negative results for OCTN2 is unknown. If the heel prick were conducted at a later point, not only would the number of false positive results be lower, but also the number of false negative results.

The occurrence of false-negative test results will have to be included in the information provided to the parents, as is the case in the regular programme.

Summary

First-tier tests are available for all conditions that are part of the forthcoming expansion of the heel prick screening programme. Except for the CPT1 test, the available first-tier tests also lead to false positive test results in addition to accurate positive results.

Some of these tests may require adjustments to logistical and laboratory organization that still require further study (in-house test GAMT, sex-specific screening X-ALD, possibility of extra heel prick for OCTN2). For a number of disorders, there are also consequences for the purchase of equipment and equipment for the laboratories (extra LC-MS / MS equipment for GAMT and MPS I).

In particular, the adjustments required for the use of an in-house test for GAMT and for the screening of boys only for X-ALD require extensive research and the impact and scope cannot yet be fully evaluated.

For most of the disorders, second and third-tier tests are available that can reduce the numbers of false positive screening results. This is not (yet) the case for CACT and CPT2. Neither can all of these tests be used in a screening setting (GALK and MPS I only on whole blood). For MMA

and PA, problems around the second and third-tier tests have yet to be resolved.

The second-tier tests for GAMT, BKT and X-ALD are assumed to be adequate. It is still uncertain whether new equipment will also need to be purchased for these tests.

For CACT, CPT2, BKT, MPS 1, MMA, PA and OCTN2, post-analytical tools are also an option for reducing the number of false positives. However, the effectiveness and feasibility of these tools requires further investigation.

Finally, false negative results occur for BKT and OCTN2.

The occurrence of false-positive and false-negative test results will have to be included in the information provided to the parents.

3.4 Secondary findings

By secondary findings, we refer to findings that emerge during the screening other than those being sought. In the forthcoming expansion of the heel prick screening, the screenings for BKT, MMA, OCTN2, PA and X-ALD may produce secondary findings (see Table 4).

Table 4: Conditions involving secondary findings

Disorder	Secondary findings	Comments
BKT	2-Methyl-3-Hydroxybutyryl-CoA dehydrogenase (MHBD) deficiency	Very rare; can be prevented by also testing for C4-OH
MMA	Sucla2 deficiency and methylmalonylCoA epimerase	Rare, newly discovered disorders which we know little about
	Neonatal vitamin B12 deficiency due to maternal vitamin B12 deficiency	Treatable with vitamin B12
OCTN2	Maternal OCTN2 deficiency	Many of the mothers identified are asymptomatic
PA	Sucla2 deficiency and methylmalonylCoA epimerase	Rare, newly discovered disorders which we know little about
	Neonatal vitamin B12 deficiency due to maternal vitamin B12 deficiency	Treatable with vitamin B12
X-ALD	Peroxisomal biogenesis defects (e.g. Zellweger syndrome, ACOX1 deficiency and D-bifunctional protein deficiency) Carrier status of mother/sisters	80% of female carriers become seriously ill as adults (adrenomyeloneuropathy); the condition is untreatable.

When screening for BKT, the C5-OH, C5:1 method detects the very rare and untreatable condition 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency (MHBD); ten patients are known to have this condition in the world. An alternative test algorithm with the addition of C4-OH can prevent this secondary finding.

When screening for MMA and PA, two (very) rare and recently discovered diseases can be detected, which we know little about as yet (succinate dehydrogenase deficiency and methylmalonyl-CoA epimerase). Neonatal vitamin B12 deficiency due to maternal vitamin B12 deficiency can also be detected. Neonatal and maternal vitamin B12 deficiency can be treated with vitamin B12 (hydroxycobalamin).

Screening for OCTN2 also detects OCTN2-deficient mothers. Many of these women are asymptomatic, and it is not clear whether the treatment of these women is always necessary. Treatment consists of lifelong carnitine supplementation. One adverse effect of supplementation is that urine, breath and body smell unpleasant.

Finally, screening for X-ALD also leads to the detection of other mostly untreatable peroxisomal biogenesis defects, including Zellweger syndrome, ACOX1 deficiency and D-bifunctional protein deficiency. The introduction of a third-tier DNA test (ABCD gene) makes it possible to distinguish between X-ALD and these disorders. Incidentally, many children with peroxisomal biogenesis defects are already symptomatic at birth.

The diagnosis of X-ALD implies carrier status of the mother and possible carrier status of sisters. Some 80% of female carriers become seriously ill as adults. This late-onset condition cannot be treated. For X-ALD, knowledge of carrier status can therefore be an issue. It requires proper medical guidance and care.

In all cases involving non-treatable secondary findings, the HC has prioritised the health benefit of screening for the condition for the child concerned over the disadvantages for the child (and the parents), in the event of a secondary finding. This also applies in the case of a secondary finding in relation to a participant who has not been screened (in the case of X-ALD, the sister or mother of a boy with X-ALD). This prioritisation was accepted by the expert groups, with the exception of OCTN2. For OCTN2, it was found that many asymptomatic mothers are also identified. For this group, as well as for some of the children identified, it is unclear whether treatment would be necessary. The experts took the opinion that further research should be carried out into the genotype-phenotype relationship for this disorder before a decision can be made about the definitive introduction of screening for OCTN2.

For all incidental findings, it is important to inform the parents properly and to check the consequences for informed consent.

3.5 Blood sampling and timing

Blood sampling

The proposed expansion of the neonatal heel prick screening programme will result in more blood being required. The current programme requires seven pricks for the first-tier tests and up to six pricks for any follow-up tests. The expansion of the programme would involve four extra pricks for the extra first-tier tests and between two and four additional pricks for the follow-up tests. As long as the quality of the blood spots on the heel prick card is adequate, this is feasible. Hence it

is important that the quality of the blood spots on the heel prick card is as high as possible.

Timing of blood sampling

Another question with regard to blood collection is the timing of the first heel prick and the possible need for an extra heel prick at a later point in time. With regard to CPT1 and OCTN2, the first heel prick should preferably be taken at a later point in time. However, this would be problematic for a number of other disorders in the current programme and is therefore not a realistic option. Another option is to carry out an extra heel prick at a later time, as has also been proposed for MPS I, MMA and PA. However, children with a false negative OCTN2 result would then not be detected.

3.6 Referral, diagnostics and treatment

In order to realise the potential health benefits of screening, good integration with care and diagnostics will be required, as well as good-quality treatment.

Children who have tested positive for one of the new disorders are referred by the medical advisors of the Vaccine Provision and Prevention Programmes (DVP) at RIVM to the academic centre in their region, via their general practitioner. An important point here is the time within which referral, admission, diagnostics and treatment should take place at the hospital. Before screening for a certain condition can be introduced, the time within which referrals must take place must be defined, in consultation with the parties involved, and communicated to referrers and paediatricians.

In order to guarantee the quality of diagnosis and treatment, this policy must be set down before the introduction of screening for a disorder, preferably in guidelines and protocols established by the relevant professional group. One issue to be addressed when developing these guidelines and protocols is the very limited number of children involved, as well as the workload for the paediatricians responsible.

An important development in relation to quality of care is the development of centres of expertise for rare diseases, and their recognition by the Ministry of Health, Welfare and Sport. The basis for this recognition is a review by a committee, headed by the Dutch Federation of University Medical Centres (NFU), which both medical specialists and patient organizations participate in. The purpose of recognising these centres is to accelerate the diagnosis of rare diseases and to improve care and treatment for patients with a rare condition. The development of these centres of expertise will need to be addressed in the guidelines and protocols to be produced by the various professional groups.

Communication with parents and the care providers involved in the screening and referrals will also need to address the role of these centres of expertise.

3.7 Required research

The various expert groups formulated research questions relating to each disorder (see Table 5). The questions relating to each condition have been linked to validation research and supplementary research.

Table 5: Research required, including research questions

Disorder	Validation study	Supplementary research
CACT	Screening parameters Normal values and cut-off point Numbers of FP	Effects of use of post-analytical tools
CPT1	Screening parameters Normal values and cut-off point Numbers of FP	Effect of extra heel prick at later point for second-tier test
CPT2	Screening parameters Normal values and cut-off point Numbers of FP	Effects of use of post-analytical tools
GALK	Automated TGAL testing Normal values and cut-off point Cut-off point (possibly on whole blood)	Second-tier possible using heel prick cards? Adaptation of GAL screening Δ manual TGAL test switching of first-tier and second-tier tests
GAMT	Commercial test? Second or third-tier test required?	Logistical and financial consequences of using in-house method including KEA
BKT	Screening parameters (avoid secondary finding for MHBD) Normal values and cut-off point Numbers for FN (enrich panel with TP)	Effects of use of post-analytical tools Long-term follow-up and care needs related to asymptomatic and mild variants
MPS I	Choice of testing method Normal values and cut-off point National validation concerning numbers of referrals, pseudo-deficiencies and carriers	Effects of use of post-analytical tools Possibility of second-tier GAG test on blood spot to reduce pseudo-deficiencies Effect of extra heel prick at later point for second-tier test Long-term follow-up and care needs related to mild variants
MMA	Screening parameters Normal values and cut-off point Numbers of FP Possibility of second-tier test	Effects of use of post-analytical tools Effect of extra heel prick at later point for second-tier test Long-term follow-up and need for and/or type of treatment for mild variants

OCTN2		Effects of use of post-analytical tools Effect of extra heel prick at later point for second-tier test Genotype-phenotype relationship of children and mothers Health measures for mothers Health effects, impact and costs (cost-effectiveness)
PA	Screening parameters Normal values and cut-off point Numbers of FP Possibility of second-tier test	Effects of use of post-analytical tools Effect of extra heel prick at later point for second-tier test Long-term follow-up and need for and/or type of treatment for mild variants
X-ALD	Clinical validation through case-control study with study size on guided US data Need for and effects of third-tier DNA test	(Effects) of scenarios with sex selection Evaluation of carrier status issue

The validation studies are primarily aimed at answering research questions that are closely related to the test(s) for the relevant condition in the heel prick screening. They require close involvement by the screening laboratories.

The supplementary research concerns more scientific questions. Other parties also need to be involved in these, and the role of screening laboratories is less clear.

On the basis of the results of the research, a decision will need to be made on whether screening is possible or not. This decision is an important go/no-go moment, based on the results of these studies. It would be advisable to formulate criteria for this decision in advance.

The expert groups noted that further research is necessary in relation to all disorders before the introduction of screening can take place. Supplementary research is required in addition to, or in combination with, the validation studies.

No validation study is planned for OCTN2. OCTN2 is reported to the parents of children screened as an incidental finding within the current programme. It is recommended to continue to include this condition in the heel prick screening as a secondary finding, and to research the effectiveness and health benefits of testing for and reporting OCTN2 in the coming years. Based on the results of this research, a decision can be made regarding follow-up action; discontinuing this particular screening is one of the options.

The experts also recommended conducting research into the psychosocial consequences of the (expansion of the) neonatal heel prick screening programme. We do not know enough about the stress of false positive results and secondary findings for parents, in the opinion of these experts.

It is necessary to estimate the turnaround times for these various studies as quickly and accurately as possible. In addition, the costs of the research and the financial resources available must also be estimated as quickly as possible. In addition to the validation studies, the research relates to post-analytical tools and the effect of an extra heel prick at a later point in time.

For four lines of research, it would seem sensible to ask ZonMw to carry out this work (evaluation of the relevance and quality of the specific research questions; supervision of research projects). These are:

1. Study of the effectiveness and the logistical and financial consequences of the use of the in-house method for GAMT.
2. Research into the feasibility and potential health benefits of screening for OCTN2.
3. Expanded pilot study into screening for X-ALD (comparable to the SCID pilot).
4. Research into the psychosocial consequences of the (expansion of the) neonatal heel prick screening programme.

A rapid assessment is also required in relation to the personnel capacity required and available in screening laboratories. Only then can a definitive assessment be made of whether the timeframe outlined by the expert groups (see section 3.8) is actually feasible.

Finally, a number of expert groups drew attention to the importance of conducting a structural evaluation study on the new screenings (and those already introduced) to assess whether the effectiveness of the screening is adequate.

3.8 Timeframe for introduction

Based on the questions yet to be answered and the research that will be required to do so, the various expert meetings estimated the timeframe to be followed in order to introduce screening for the various additional disorders.

It should be noted that this does not yet take account of contingent aspects of implementation, such as information management, capacity issues, quality aspects, expertise improvement processes, and adjustments required in the primary process.

For SCID, the estimate made by RIVM was based on the HC's advice and the pilot study for SCID developed by the field and to be launched in 2018 (also see section 4).

Implementation in the period 2018-2019 for the screening of CPT1, GALK, MPS I, MMA, PA and X-ALD is currently considered feasible by the experts. For the other disorders, more time will be needed for responsible implementation. The introduction of the screening for these disorders (CACT, CPT2, GAMT, BKT, OCTN2, SCID) is considered feasible for the period 2019-2021 (see Table 6), although the introduction of OCTN2 screening would depend on the results of the study into the effectiveness and potential health benefits of testing and reporting for OCTN2.

Table 6: Planned timeframe for expansion of the heel prick

Disorder	2018-2019	2019-2021	Comment
CACT			Introduction together with CPT2
CPT1			
CPT2			Introduction together with CACT
GALK			
GAMT			Due to use of in-house test
BKT			
MPS I			
MMA			Introduction together with PA
OCTN2			Due to genotype-phenotype relationship
PA			Introduction together with MMA
SCID			Due to time required for pilot
X-ALD			

The screenings for CACT and CPT2 use the same first-tier test. This means that these screenings cannot be introduced separately. This also applies to the screenings for MMA and PA.

3.9 Conclusions of preliminary studies

The preliminary studies produced the following conclusions:

- The conditions to be added are rare or very rare. Between 20 and 40 children with one of these disorders are expected to be identified annually, in total.
- A primary or first-tier screening test is available for all conditions. Some of the tests may require adjustments to logistical and laboratory organization, which still require further study (in-house test GAMT, sex-specific screening X-ALD). For some disorders, there will also be implications for the purchase of equipment and equipment for the laboratories (extra LC-MS/MS equipment for GAMT and MPS I).
- For almost all the disorders, the implementation of the first-tier test alone would lead to a significant number of false positive referrals. However, a full understanding of the numbers involved is lacking. For most of the disorders, a second-tier test, and possibly even a third-tier test, would be necessary and possible to reduce the number of false positive referrals. This is not (yet) the case for CACT and CPT2. Neither can all of the tests be applied in a screening setting (GALK and MPS I only on whole blood). For MMA and PA, problems concerning the second and third-tier tests have yet to be resolved. It is expected that most second and third-tier tests can be carried out using the existing infrastructure of the screening laboratories. For GAMT, BKT and X-ALD this has yet to be determined definitively, however.
- In addition to the issue of false positive results, false negative test results are another issue for a number of the disorders that will be added to heel prick screening. This concerns BKT and OCTN2.

- In addition to developing good second and, where necessary, third-tier tests, another potential option for a number of disorders would be to reduce the number of false positive screening results. A number of expert groups (CACT/CPT2, BKT, MPS I, MMA/PA and OCTN2) as well as the programme committee for the neonatal heel prick screening programme have advised using Region 4 Stork (R4S) and Collaborative Laboratory Integrated Reports (CLIR) post-analytical tools. Before these post-analytical tools can be used for the neonatal heel prick screening, however, a number of important questions will need to be answered regarding effectiveness, efficiency, continuity and privacy and so on.
- In all cases involving non-treatable secondary findings, the HC has prioritised the health benefit of screening for the condition for the child concerned over the disadvantages for the child (and the parents), in the event of a secondary finding. This prioritisation was not questioned by the expert groups, with the exception of OCTN2.
- In order to realise the potential health benefits of screening, good integration with care and adequate capacity for diagnostics and good-quality treatment will be required. Before screening for a certain condition can be introduced, there must be clarity on the period within which referral and admission to a hospital should occur. Policy must also be developed regarding diagnosis and treatment, preferably in the form of guidelines and protocols proposed by the relevant professional group. An important development in relation to quality of care is the development of centres of expertise for rare diseases.
- The expert groups noted that further research is necessary in relation to all disorders before the introduction of screening can proceed. The various expert groups formulated research questions in relation to each disorder. These relate to validation studies and/or supplementary studies and the implications for laboratory logistics. The validation studies are primarily aimed at answering research questions that are directly related to the test(s) for the relevant condition in a screening context. This includes research into the normal values and cut-off points for the test parameters to be used; sometimes research is required in relation to the optimum test parameters. Close involvement is required from the screening laboratories. The supplementary research concerns more scientific questions. Other parties also need to be involved in these studies. ZonMw should be commissioned to carry out four of the research studies.
- A number of expert groups also drew attention to the importance of conducting a structural evaluation study on the new screenings (and those already introduced) to assess whether the effectiveness of the screening is adequate.
- Based on these questions that have yet to be answered and the research that will be required to do this, the various expert meetings estimated a timeframe for the introduction of screening for the various additional disorders. Introduction in the period 2018-2019 for the screening of CPT1, GALK, MPS I, MMA, PA and X-ALD is currently considered feasible by the experts. For the other disorders, more time will be needed for responsible

implementation. The introduction of the screening for these disorders (CACT, CPT2, GAMT, BKT, OCTN2, SCID) is considered feasible for the period 2019-2021.

3.10 Reflection of the Centre for Population Screening

Timing of blood sampling

Another question is the possible need for an extra heel prick at a later point in time (see 3.5). Introducing an extra heel prick for all children would, in the view of the Centre for Population Screening, place a heavier burden on parents, could adversely affect support for the programme, would cost around €4.3 million annually and would only produce limited health benefits.

Timeframe for introduction

The advice of the expert groups differs in some respects from the HC's advice and the ministry's classification based on it. The reason for this is the possibility of changing insights in the light of the results of additional studies and developments occurring since the publication of the HC's advice in 2015. The introduction of screenings for CACT, CPT2, BKT and OCTN2 should occur later according to the experts' advice than under the classification in the Minister's response to the HC's advice. By contrast, the timing of the introduction of the screenings for GALK, MPS I and X-ALD was brought forward by the experts.

The Centre for Population Screening wishes to make a number of comments regarding implementation according to the proposed timeframe.

When drafting the proposed timeframe, the experts did not take into account the personnel capacity required in the screening laboratories to carry out multiple validation studies simultaneously. Neither was the available capacity of metabolic paediatricians taken into account. The experts also assumed that there would be no financial limitations with regard to the implementation of the validation studies and the supplementary research required. The proposed timeframe is therefore subject to sufficient personnel capacity and funding availability.

It is therefore necessary to estimate the turnaround times for the various simultaneous studies as accurately as possible. In addition, the costs of the research and the financial resources available must also be estimated as quickly as possible. The same applies to the personnel capacity required and available in screening laboratories. Only then can a definitive assessment be made of whether the timeframe outlined by the expert groups is actually feasible.

The expansion of the heel prick screening is also taking place in the context of the optimisation of the current screening. This includes, for example, improving the quality of the blood spots, tightening referral periods and preparing various tenders such as for the screening equipment, the laboratory information management system and the laboratories themselves. The existing information system, Praeventis from DVP, which handles (among other things) the execution of the heel prick screening, must also be replaced. These changes to the heel prick screening programme are, to a large extent, conditional on the proper

implementation of the expansion of the programme and may affect the expansion in a positive or negative way.

Finally, the proposed timeframe is, of course, dependent on the outcomes of the various research projects. If the results of a study are inadequate, this may lead to the postponement or even the abandonment of screening for the relevant condition.

In section 12, Implementation, the Centre for Population Screening presents a timeline for the studies required, the subsequent go/no go decisions, and the timing of the introduction of the various disorders to the heel prick screening programme, as things currently stand.

Complexity of introduction

Based on the preliminary study and its own knowledge and experience, the Centre for Population Screening is of the opinion that the intended expansion of the heel prick screening is a complex undertaking, due to the number of disorders, logistics and organisation in the laboratories, testing methods, validation studies and supplementary research that all need to be completed, and the required integration with the care system.

All this implies that the expansion will have consequences for information and communication, the acquisition of expertise and information management in the current screening programme. The small changes required in relation to these and other aspects may also prove complex and time-consuming.

4 SCID

4.1 Introduction

Within the group of disorders which the neonatal heel prick screening is expected to be expanded to include, SCID occupies a special position. In her response to the GR's advice, the minister requested a particular focus on a number of points in relation to this condition (see below). These points require further detail on this condition, which will be provided in this section. In section 4.6, we will focus on the consequences of possibly adding this particular disorder to the heel prick screening in relation to a number of areas of the pilot scheme.

4.2 The advice of the Health Council of the Netherlands (GR) and the response of the minister

One of the fourteen disorders which the GR recommended adding to the heel prick screening is SCID. Just like the other disorders, the GR recommends that a proper pilot study be carried out for SCID. In her response to the GR's recommendation, the minister indicated that this is a condition that will require a longer preparatory period, with a more robust pilot scheme, before it can be added to the programme. She also noted the need for a thorough cost-benefit analysis (CBA) in relation to implementation, as this screening test is more complex and costly than the other neonatal screening test methods. Within the category of disorders that require a longer preparatory period, the Minister wishes to prioritise SCID, because the inclusion of this disorder has the potential to produce the biggest health gains. It would be the first disorder in neonatal screening that can be completely cured (using stem cell transplantation), said the minister.

4.3 Number of sick children, screening tests, secondary findings

The number of sick children with SCID per year is expected to be between two and four.

A good first-tier test (T-cell receptor excision circles (TREC) assay) is available. This TREC assay has a PCR analysis step. This implies specific requirements with regard to laboratory equipment. In specific terms, this would involve two separate and isolated laboratory areas, and the layout of these areas would also need to meet specific requirements. Four of the five of the screening laboratories currently meet these requirements.

For SCID, a second-tier test is needed to reduce the number of false positive results. The flow *cytometry* used in healthcare can only be applied to whole blood and is not suitable as a second-tier test. Second-tier DNA testing can be done using heel prick blood.

There is a possibility of secondary findings with SCID. Screening for SCID also results in the discovery of other (congenital) T-cell defects, including DiGeorge syndrome, for which there is no curative treatment, although symptomatic treatment is available. The pilot scheme for SCID that is currently being prepared will focus on follow-up healthcare,

including the prevention of secondary findings and the consequences for children, parents and care.

4.4 Pilot study by ZonMw.

The Ministry of Health, Welfare and Sport has decided to begin a pilot study for SCID at ZonMw. This pilot is being prepared by a project group consisting of the national Working Group on Immune Deficiency (WID), which will also call on RIVM's expertise from the screening programme. The aim of this prospective pilot study is to gain an insight into aspects relevant to (the decision on) the inclusion of SCID screening in the neonatal heel prick screening programme. The study should focus on the practical implications, test qualities (including secondary findings), costs and the perspectives of end users and professionals.

For further details on the research questions, reference can be made to the project plan for the SCID pilot scheme (see Appendix 11). It is expected that the lead time for the pilot will be two years.

4.5 Cost-benefit analysis (CBA) and cost-effectiveness analysis (CEA)

A cost-benefit and cost-effectiveness analysis was performed in relation to SCID by the Netherlands Organisation for Applied Scientific Research (TNO), commissioned by the Centre for Population Screening. In addition to the results of the CBA and CEA, TNO also included a summary in the report on the results of CBAs and CEAs with regard to SCID screening carried out elsewhere in the world (see Appendix 12).

The costs and effects/benefits of SCID screening in the Netherlands were determined on the basis of the model formulated and basic estimates for the model parameters. The scenario with SCID screening was compared with the scenario without SCID screening for an annual cohort of 170,000 children. Sensitivity analyses were also carried out, whereby the values for the uncertain parameters were varied. An additional sensitivity analysis also included the cost of sick leave for SCID patients as a proxy for costs outside the healthcare system, producing an estimate of the social costs.

The calculation model used by TNO as the basis for the calculations was expanded, so that the effectiveness of the screening could be expressed not only in terms of years of life gained, but also in QALYs (quality-adjusted life years). Furthermore, the time horizon for the calculations was extended to a lifetime, and the model was adapted to the plans for a pilot study in the Netherlands. The values for the model parameters were based on literature research and expert opinion.

CEA

The total costs of screening and diagnostics are €990,200 higher when screening for SCID is included, compared to a scenario without screening for SCID, see Table 7.

Table 7: Cost of screening and diagnostics for SCID (in €)

Costs	With screening	Without screening
Lab testing, possible re-testing	806,900	n/a
Second heel prick	12,300	n/a
Flow cytometry and genetic testing	224,700	53,800
Total	1,044,000	53,800

The total cost of treating children with SCID is €257,600 lower when screening is included compared to a scenario without screening (see Table 8). This is because fewer children would die before they can receive a transplant, so the treatment cost for children who die before treatment are lower with screening (€23,700 vs. €74,400 per year). This means that more children would undergo a transplant, but because in a scenario with screening children are detected earlier, the costs per transplant are lower than in a scenario without screening. The resulting total costs of transplantation are also lower with screening (€248,000 versus €424,500 per year). Finally, the long-term treatment costs for SCID-related issues are also lower, because earlier transplantation yields more health benefits in a scenario with screening than in a scenario without screening (€29,700 versus €60,100). In total, screening for SCID will lead to a saving of €257,600 per year in the treatment costs for SCID.

Table 8: Annual treatment costs for SCID (in €)

Costs	With screening	Without screening
Treatment costs for SCID patients who die before treatment	23,700	74,400
Transplant costs for SCID	248,000	424,500
Long-term costs of SCID	29,700	60,100
Total	301,400	559,000

Added together, the costs of screening, diagnostics and treatment are €1,417,200¹⁰ in a scenario with screening and €684,600 in a scenario without screening, a difference of €732,600 (€990,200 minus €257,600).

The difference between the scenarios with and without screening in the Netherlands is 35.1 QALYs. The costs per QALY gained therefore amount to €20,900 (€732,600/35.1). This is almost the same as the cost limit that is usually applied in the Netherlands (€20,000 per QALY).

Sensitivity of CEA

In a univariate sensitivity analysis (where one parameter is varied between an assumed minimum and maximum value) the costs per QALY gained vary between €8,100 and €31,700.

The cost-effectiveness ratio does not change in the specific sensitivity analysis which includes the additional costs of the sick leave of SCID patients in comparison with the general population.

¹⁰Includes €71,800 in non-SCID treatment costs, in both scenarios.

In addition to the univariate sensitivity analysis, in which the effect of adjusting one parameter at a time was investigated, a multivariate sensitivity analysis was also performed, in which several parameters were varied simultaneously. An analysis was carried out in which all the parameters in the sensitivity analysis were set at the least favourable value in terms of cost-effectiveness, and another analysis in which the parameters were set at the most favourable value.

In the least favourable scenario, the cost of screening for SCID compared to a scenario without screening was €108,000 per QALY. In the most favourable scenario, screening yields both health gains and cost savings of, respectively, 73.8 QALYs and €384,900 per year. The range of possible cost-effectiveness ratios therefore remains very wide due to the current uncertainty regarding a number of parameter values. Important parameters that would have a major influence on the cost-effectiveness ratio include the prevalence of SCID among new-borns, the costs of the screening test and the costs of late transplantation. The researchers recommend conducting further research into these parameters in order to derive a more accurate estimate of their value, for example in the pilot study on SCID screening.

CEAs from other countries

Cost-effectiveness ratios in studies from other countries vary between €31,930 and €67,290 per QALY. In addition to the higher treatment costs assumed in these studies from other countries, this difference is also a result of the model expansions that the researchers used. In addition to preventing death from SCID through screening, they also expected that in cases of early discovery, the treatment would have better outcomes and lead to more life years and better quality of life.

CBA

To determine the cost-benefit ratio, TNO compared the total value of the deaths prevented (€2,297,500) and the savings in the treatment costs (€257,600) with the extra cost of screening and diagnostics incurred through the introduction of SCID screening (€990,200). This results in a cost/benefit ratio of 2.58; this would mean that every euro invested in SCID screening would yield €2.58.

When varying the assumed financial value of a statistical life, the cost/benefit ratio varies between 1.39 and 4.87.

4.6 Consequences of pilot and addition of SCID to programme

The pilot scheme and the subsequent addition of SCID to the neonatal heel prick screening programme are expected to have consequences for a range of areas. These are briefly discussed below.

General

In order to participate in the SCID screening pilot, separate informed consent would need to be requested from the participants, for whom separate information material about SCID should be designed.

Professional training

The inclusion of SCID in the screening package would have a limited impact on the content of the information provided by the obstetric care

provider: a new category would be added to the different categories of disorders, namely immune system disorders. The obstetric care provider or screener can mention this category and refer to the general information leaflet, but she/he would not provide disorder-specific information about this. Practice has shown (for example when CF was added to the screening) that when a new category of disorders is added, there is a need for professional training meetings regarding the disorder among practitioners involved in the screening (obstetric care providers, screeners, general practitioners, clinical geneticists, laboratory staff).

Information and communication

Expanding the programme to include SCID would have consequences for information and communication. Because this would involve a new category of disorders that can be cured, it would be necessary to adapt the general information leaflet and to include general information on the website for the public and professionals.

Data management

An important part of preparing the pilot for SCID screening is a precise specification for information management and monitoring, because the newly developed NHS information system (new Praeventis) and new NHS-LIMS are still not live in early 2018. It is expected that the validation of analyses/tests will begin in the laboratories in the second half of 2017. At the start of 2018, the actual referral of children will begin, due to abnormal results. Adequate registration to support this process must be possible with regard to SCID from 2018 onwards. For SCID, research was conducted into whether Praeventis and NEONAT can still be adapted to support the pilot. This appears to be possible for SCID. Whether NEORAH also needs to be adapted is still under consideration.

Monitoring and evaluation

For SCID, there is a possibility that, following an abnormal first screening test, a follow-up test must be carried out using whole blood. How this process should be organised will be part of the validation study and the pilot. In order to monitor the quality of this process, a number of new indicators will also need to be developed. The secondary findings and the advantages and disadvantages for these children should also be considered in this.

Implementation

For SCID, RIVM has estimated the timing of the introduction on the basis of the GR's advice and the pilot study for SCID developed by the field and to be launched in 2018. If the pilot produces a positive result, introduction is considered feasible by the end of 2021.

The national NVK Working Group on Immune Deficiency (WID) is closely involved in implementation.

4.7

Conclusions

The main conclusions of this section are:

- A good first-tier test for SCID is available; a second-tier test is required.

- A pilot study will be launched for SCID. The lead time for the pilot is expected to be two years.
- The conclusion of the cost-effectiveness analysis is that the costs per QALY gained almost correspond with the limit set for prevention in the Netherlands.

5 Primary process

In the current neonatal heel prick screening, a heel prick is offered for all new-borns within a few days of birth. Since 1 January 2017, the blood samples have been screened for nineteen rare, mainly hereditary disorders. Early detection of these conditions can prevent or limit serious damage to the physical and mental development of the child. The disorders cannot be cured, but they can be treated. Screening for sickle cell disease can also reveal carrier status. Parents can opt not to receive information about carrier status. All activities involved with the process of selecting children, inviting them for the test, providing information, taking the heel prick and screening the blood, communicating the results and following up with referrals, diagnostics and treatment are collectively known as the primary process.

The extension of the neonatal heel prick screening programme will be based on the following principles:

1. The existing organisation of the NHS programme will be used wherever possible.
2. In the Netherlands, implementation is often combined with the Neonatal Hearing Check programme (NGS).
3. Potential future developments in and extensions of the heel prick screening will be taken into account where this is possible.

This section consists of two parts. The first part outlines the current primary process for the neonatal heel prick screening. In the second part, the required changes and steps to be taken in order to extend the screening programme will be discussed.

5.1 **Current primary process in the neonatal heel prick screening programme**

Figure 1 provides a schematic representation of the primary process of the neonatal heel prick screening in the Netherlands.

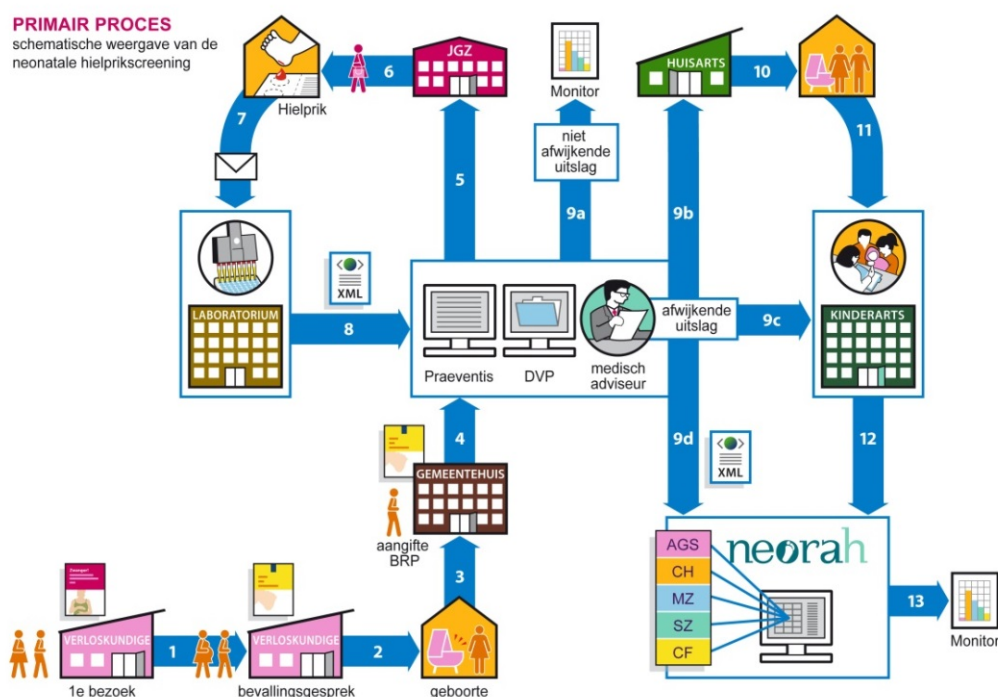


Figure 1: Schematic representation of the primary process of the neonatal heel prick screening in the Netherlands: from first visit (1) to the evaluation of the screening (13).

PRIMAIR PROCES	PRIMARY PROCESS
Hielprik	The heel prick
Monitor	Monitor
Huisarts	GP
Niet afwijkende uitslag	Normal result
Laboratorium	Laboratory
Praeventis	Praeventis
DVP	DVP (Vaccination Provision and Prevention Programme Service)
Medisch adviseur	Medical advisor
Afwijkende uitslag	Abnormal result
Kinderarts	Paediatrician
Aangifte BRP	BRP declaration
Gemeentehuis	Municipality
Verloskundige	Midwife
1 ^e bezoek	First visit
Verloskundige	Midwife
Bevallingsgesprek	Childbirth meeting
Geboorte	Birth
Monitor	Monitor

5.1.1

Selection and invitation Communication

During the first consultation, the obstetric care provider gives the leaflet entitled 'Pregnant!' to the pregnant woman, which contains general

information about the neonatal heel prick screening.¹¹ Obstetric care providers provide information about the neonatal heel prick screening in the third trimester of pregnancy on the basis of a national checklist that obstetricians follow for information meetings. The combined leaflet 'Screening in new-borns. Heel Prick Screening and Hearing Check' is given to the prospective parent(s). The choice of whether or not to be informed about the child's carrier status for sickle cell disease ('informed consent') is discussed specifically.

The official from the municipal Department of Civil Affairs gives them the same leaflet when the birth is registered with the municipality.

Selection

After the parents have registered the birth, the offices of the Vaccination Provision and Prevention Programme Service (DVP) are sent the details of the child from the Basic Personal Registration database (BRP). Meanwhile, within 24 hours of the birth of the child, the DVP also receives a digital statement of the birth through a number of obstetric practices. The aim is for all obstetric practices to be linked to this system.

Invitation

The DVP's regional offices commission the relevant Youth Health Care Services (JGZ) to carry out the heel prick.

If this organisation has the parent's telephone number, it will call to make an appointment with the parents. Otherwise, a home visit is made unannounced.

5.1.2

Screening

The heel prick should be carried out at the earliest opportunity 72 hours after the birth. If the implementing organisation chooses to combine the heel prick screening with the hearing check, it will be carried out at the earliest opportunity 96 hours after the birth. The heel prick must be carried out within 168 hours of the birth. The heel prick is carried out wherever the child is. Most children have their blood taken at home. During the heel prick, a few drops of blood are removed from the child's heel using a heel prick lancet and applied to a heel prick card. The card is then sent to one of the five screening laboratories. The laboratory carries out the tests and reports the results to the regional DVP office digitally.

Where necessary, the initial heel prick test is carried out again. This is done when the blood spots on the heel prick card are not of sufficient quality, the material is unreliable, the heel prick is carried out within 24 hours of a blood transfusion or when the heel prick is carried out within 48 hours after birth. The repeated initial heel prick should always be carried out as soon as possible, preferably as soon as the DVP makes the request to the organisation performing the heel prick.

In the case of a non-conclusive result, a second heel prick is carried out. The second heel prick should also be taken as soon as possible, except in the case of AGS, where the timing depends on the length of pregnancy.

¹¹ Midwives, GPs who provide obstetric care and gynaecologists.

5.1.3 *Communicating the results and referrals*

The parents are not told if the results are normal. In the future, the intention is to inform parents of the results of the heel prick even when the results are normal. To do this, the right information must be developed and appropriate ICT systems must be set up.

If a result is abnormal, the DVP's medical advisor will contact the relevant general practitioner, who will then arrange for a referral to a university medical centre (except in the case of CH; these children may also be referred to a general hospital). A definitive diagnosis will be made at the university medical centre and treatment will be started.

5.1.4 *Diagnostics and treatment*

In principle, all children who have been referred following the screening are treated at a university medical centre (or, for CH, at a general hospital). In cases of sickle cell disease, a child is seen by a paediatric haematologist at a university medical centre before he or she is four weeks old. In cases of carrier status for sickle cell disease, the general practitioner is informed first and the parents are informed afterwards. The general practitioner is responsible for arranging an information meeting and possibly further tests in relation to a subsequent pregnancy if the parents so wish. High-risk couples are referred to a clinical genetic centre. In cases of a metabolic disorder, the child is seen as soon as possible on the same day by a paediatric specialist in metabolic disorders at the university medical centre. In the event of an abnormal result for CF, the general practitioner will refer the child to a paediatric lung specialist from a CF centre within one week.

5.2 **Points for attention in the primary process in relation to the expansion of the heel prick screening programme**

In section 3, the results of preliminary studies and the reflection by the Centre for Population Screening, it was found that the current structure of the primary process is adequate. There are, however, a number of important points for attention. These concern the optimisation of the quality of the blood spots on the heel prick cards, a study of the possibility of an extra heel prick, the adjustments required to the screening laboratories, the use of in-house tests, sex-specific screening and post-analytical tools, turnaround times and the prioritisation of laboratory tests, and the provision of facilities for the pilot studies. Some of these points will also affect quality policy and professional training, communication and information, information management and monitoring and evaluation. In addition, preparing for and implementing the various changes will require personnel capacity from the organisations involved; this capacity is currently generally limited.

5.2.1 *Optimising the quality of the blood spots on the heel prick cards*

The proposed expansion of the neonatal heel prick screening programme will result in more blood being required in order to implement the programme. The current programme requires seven punches for the first-tier tests and up to six pricks for any follow-up tests. The expansion of the programme would involve four extra pricks for the extra first-tier tests and between two and four additional pricks for the follow-up tests. In 2016, research was carried out into the quality of the blood spots on the heel prick cards in anticipation of the expansion of the heel prick

screening programme. It was found that the proposed expansion could lead to an increase in the number of heel prick cards with insufficient material, which would make it necessary to repeat the heel prick; currently this is the case in 1% of tests, but potentially this could rise well into double figures.¹²

This has led to the implementation of improvement measures. It is expected that the current improvement process, which focuses on professional training among screeners, will improve the quality of the blood spots on the heel prick cards to a sufficiently high level to enable the expansion of the programme. If this is not the case, additional measures will be taken, such as increasing the number of circles on the heel prick card where blood needs to be applied, so that more blood is taken. In addition, an investigation is underway into whether the number of duplicate tests in the laboratory can be reduced.

5.2.2 *The possibility of an extra heel prick at a later point in time*

For CPT1, MPS I, MMA, PA and OCTN2, it has been proposed to introduce an additional heel prick at a later point in time in order to optimise the second-tier test in the event of an abnormal test result in the primary test. If it appears from the studies that will be carried out that this would indeed provide added value for one or more of the disorders, it is expected that this could be implemented relatively easily within the (expanded) NHS programme. Even today, extra heel pricks are sometimes required and performed, such as in the case of a non-conclusive result or when the blood spots on the heel prick cards are of insufficient quality. Consideration should be given to how the parents are to be informed about this and which message(s) should be sent.

5.2.3 *Adaptations to the screening laboratory*

The expansion of the heel prick screening programme would result in the use of new tests and the purchase of new equipment or different uses for existing equipment. New requirements would also apply to the design of the laboratory (see section 4 on SCID). Table 9 provides details of the equipment in the screening laboratories that is currently available for the NHS programme.

¹² If the first heel prick card bears too little blood, not all the prescribed tests can be carried out straight away. Where there is insufficient blood, the laboratory protocol IDS-PNB P015 describes the tests to be performed in order of urgency. It will be necessary to adapt this protocol in line with the forthcoming expansion of the heel prick screening programme.

Table 9: Current screening laboratory equipment

Current screening laboratory equipment	Comments
MS/MS device	The laboratories act as a mutual back-up in the case of disruptions or incidents.
Genetic Screening Processor (GSP)	Two per laboratory are required for back-up.
Automatic Immunoassay system	This device has the same function as the GSP. The laboratories therefore use either an AI system or a GSP system.
High-performance liquid chromatography (HPLC) device	
Analysis device that uses Polymerase Chain Reaction (PCR) for 35 CFTR mutations and HPLC	The PCR for the CFTR mutations only takes place in the clinical genetic laboratories in Tilburg, Zwolle and Amsterdam (VUmc).

Expansion of equipment would be necessary for the conditions below.

The test for MPS I requires a different device than the MS/MS device that is currently used. The use of a different device would require an extra run and therefore the purchase of an additional LC-MS/MS device in the five screening laboratories. The new device would also need to be purchased.

Testing for GAMT may also require the purchase of additional LC-MS/MS equipment (see also section 5.2.4).

An important consideration when purchasing equipment is the (possible) need to perform the second-tier test for a number of disorders on an LC-MS/MS device. A study will be needed to establish whether these tests can be carried out on existing or newly purchased LC-MS/MS equipment or whether new equipment must also be purchased for this.

The automated TGAL assay for screening for GALK can be performed on the GSP equipment that is present in the laboratories. Obviously, a study will be needed to establish whether this automated assay can replace the current manual second-tier TGAL assay for screening for galactosemia. This will require a validation study.

5.2.4 Use of in-house testing

No commercial test is currently available for detecting GAMT. However, a test is in use at VUmc that could be developed into an in-house testing method. In-house tests are testing methods that are not commercially available (not usually CE-marked), but have been developed independently by a laboratory. For in-house testing, quality is guaranteed through the accreditation of the laboratory. All five screening laboratories are expected to be ISO15189 certified in the near future.

It is proposed to conduct the GAMT analyses with the available in-house testing method. However, the use of an in-house test will be new to existing screening laboratories and will pose a challenge in terms of upscaling and quality assurance. The involvement of all screening laboratories would also necessitate the purchase of five extra LC-MS/MS devices. One option would be to have a central laboratory perform all GAMT analyses using this testing method. This would save on equipment, but would create a logistical challenge and would require evaluation on feasibility, timeliness and reliability¹³. This could form part of the proposed study into GAMT screening in section 3, part 3.7.

5.2.5 *Sex-specific screening*

A particular challenge for the programme is the screening of only boys for X-ALD. Ideally, girls should not be tested for X-ALD, because the disease is not treatable in females. However, the sex of the child being tested is not currently known when the laboratory tests are carried out, because in the regular programme all children are screened for all conditions. It is also unclear whether it is feasible, in terms of laboratory logistics, to test boys and girls in different ways. More research on this is necessary. Possible scenarios, including the advantages and disadvantages, costs, legal aspects (privacy) and ethical aspects (including the possibility of communicating the detection of an untreatable condition) will need to be examined. The scenarios that need to be investigated are: (1) including an indication of the child's sex on the heel prick card and then testing only boys for X-ALD; and (2) the 'anonymous' testing of all heel prick cards for X-ALD and then only determining the sex of the child in the case of an abnormal result and only reporting the result for boys. In view of the above, the Centre for Population Screening concludes that the introduction date proposed by experts, in 2018-2019, is not feasible.

5.2.6 *Study into the possibilities of using R4S and CLIR*

A number of expert groups and the Programme Committee for the neonatal heel prick screening programme have advised the use of Region 4 Stork (R4S) and Collaborative Laboratory Integrated Reports (CLIR) post-analytical tools. The R4S and CLIR are applications of a unique database of analysis data from healthy new-borns and new-borns with a clinically confirmed disorder included in current heel prick programmes internationally. The database is housed at the Mayo Clinic in the United States. The primary goal of R4S and CLIR is to optimise the predictive value of the individual screening results obtained from MS/MS analysis.

The primary goal of R4S is to assess the cut-off limits based on data on all neonatal screening MS/MS analytes from screening programmes all around the world.

The CLIR software, a second version of R4S, uses advanced statistics based on continuous covariate-adjusted percentiles. The CLIR software makes use of the degree of overlap between markers with a disorder

¹³One point for attention here is the new IVD regulation that also includes in-house testing.

range. What is unique about this software is that it does not use cut-off limits, but provides a risk profile for a certain disorder.

Both applications could potentially be used in the context of the Netherlands' neonatal heel prick screening programme, both to improve the performance of the existing screening and to solve the problems identified by the expert groups in relation to screening for new disorders.

The use of the R4S and CLIR post-analytical tools was discussed by the Research Working Group for the Neonatal Heel Prick Screening Programme (WOHNS). The working group recommended studying the functioning of the database with data that are currently being collected for the Dutch heel prick screening.

In addition to answering questions regarding the possible use (workload for laboratory staff, prompt results, etc.) and effectiveness of the R4S and CLIR post-analytical tools, there are also important questions regarding efficiency, continuity and various legal and ethical aspects, including privacy.

The Centre for Population Screening has now taken steps to ensure that these questions are answered.

5.2.7 *Turnaround times and the prioritisation of laboratory tests*

Because the urgency of treatment can vary depending on the disorder, turnaround times for the various steps in the process (testing, referral for care, etc.) must be specified for each disorder. This also applies to the prioritisation of the various tests in cases where the quality of the blood spots on the heel prick card is not adequate.

5.2.8 *Arrangements for pilot studies*

During the preparatory and implementation phases of the expansion of the neonatal heel prick screening programme, a large number of pilot studies will be initiated. In addition to research based on anonymised data or heel prick cards, non-anonymous research is also required. This type of research requires permission from the parents of the children concerned. Permission for such studies will be granted in accordance with the procedures used in the current programme.

5.3 **Conclusions**

The main conclusions of this section are:

- The current structure of the primary process is generally adequate. However, the preparation and implementation of the various changes would demand significant personnel capacity from the organisations involved; this capacity is currently generally limited.
- The quality of the blood spots on the heel prick cards is expected to improve as a result of various improvement measures, and to be sufficient to enable the extension of the heel prick screening programme.

- In order to detect GAMT, the proposal is to use an in-house test. This will be challenging for the screening laboratories in terms of scaling-up and quality assurance.
- Testing for MPS I and GAMT will require the purchase of two additional LC-MS/MS devices per screening laboratory. Establishing one central laboratory for testing for GAMT would mean that only one LC-MS/MS would be required in each laboratory, plus an additional device at one laboratory (in all, six extra, compared to the current situation); this would also facilitate quality assurance, but would pose logistical challenges within the heel prick screening programme.
- The possibility of having to purchase additional LC-MS/MS equipment to carry out a number of second-tier tests cannot be excluded. This will need to be investigated further.
- Sex-specific screening, as proposed for X-ALD, is not simple to put in place within the current programme and will require extensive study and preparation. Introduction in the period 2018-2019, as proposed in the preliminary studies, is therefore probably not feasible.
- The use of post-analytical tools can reduce the number of false-positive test results. Research will need to be carried out to establish whether the use of these tools can be introduced effectively, efficiently and legally.
- The turnaround times for the various steps in the process steps need to be specified. This also applies to the prioritisation of laboratory tests in cases where the quality of the blood spots on the heel prick card is not adequate.

6 Organisation, tasks and responsibilities

Population screening is fundamentally different from curative care because it is not based on an individual request for help. Partly because of this, the government is committed to achieving outstanding quality through a programmatic approach, uniform implementation and central control of population screening. This ambition has resulted in the National Population Screening Programme (NPB). The features of the NPB are explained in section 6.1.

The Policy Framework for Pre- and Neonatal Screening (<http://www.rivm.nl/bibliotheek/rapporten/2015-0183.pdf>) provides an overview of the legal and policy frameworks for these screenings that are carried out during pregnancy and shortly after birth. This document also describes the collaboration between the parties involved in preparing, leading and implementing the prenatal and neonatal screening programmes.

The organisation, tasks and responsibilities within the neonatal heel prick screening programme are set out in the National Manual for the Neonatal Heel Prick Screening Programme (http://www.rivm.nl/Onderwerpen/H/Hielprik_voor_professionals/Draaiboek_neonatale_hielprikscreening). This section outlines these tasks and responsibilities, and to what extent the expansion of the heel prick screening programme will affect these. Section 6.2 describes the core tasks and responsibilities of the various parties involved in the NHS programme in general terms. Section 6.3 elaborates in greater detail on each link in the chain.

6.1 The National Population Screening Programme (NPB)

The NPB consists of several national population screening tests, funded by central government and overseen by the Centre for Population Screening. The aim of the programme is to identify health risks in order to promote public health.

The NPB consists of the following population surveys and screenings:

- population screening for breast cancer, cervical cancer and colon cancer;
- neonatal heel prick screening and neonatal hearing check;
- prenatal screening for infectious diseases and erythrocyte immunisation (PSIE).

The NPB results in health gains because diseases and disorders are detected at an early stage and they can then be treated.

The Centre for Population Screening directs the implementation of population screenings for citizens on behalf of the Minister, based on the public values of quality, accessibility and affordability. This means that, irrespective of any difference between the national programmes, the same principles are always applied for all programmes.

The public value of **quality**:

- *The programmes are effective*
They are effective in terms of the screening test used (test characteristics), the participation of the target group, and the contribution to health gains and/or the provision of treatment or management options.
- *The programmes are demand-led*
The programmes take account of the needs and wishes of the target group.
- *The programmes are safe, and uniform at the national level.*
The programmes are safe, compliant with public values and uniform at the national level. The benefits of the programme outweigh the possible disadvantages of the screening for the target group. The continuity of the programme is guaranteed.
- *The programmes are innovative*
The parties involved have knowledge and experience, which are used to ensure the continuous and structural improvement of the programmes. Relevant innovations in methodology and screening methods, diagnostics and treatment are communicated in good time. The potential consequences of these innovations for the programmes are discussed with the Ministry of Health, Welfare and Sport, ZonMw, the Health Council and other relevant parties.

The public value of **accessibility**:

- *The programmes are accessible*
The programmes are organised in such a way that barriers to participation are minimised for the target group.
- *The programmes ensure that the required actions are taken in a timely manner.*
The target group is invited to participate in the programme in a timely manner. Turnaround times in the programme are acceptable, including diagnostic testing and treatment.
- *Participation in the programme is voluntary.*
Participation in the programme is a matter of personal choice. In the case of the heel prick, the parents choose on behalf of their child. Information for the general public and the target group is up-to-date, objective and balanced, and helps them make a well-informed choice. Balanced information highlights the pros and cons of the programme.

The public value of **affordability**:

- The costs of the programmes are transparent
The costs of the programme are transparent, enabling the government to balance the public resources required against their possible use for other areas of government activity.
- The programmes are implemented effectively
The programmes are implemented for the lowest possible cost in relation to the quality and accessibility required. The programmes are also cost-effective.

6.2 General allocation of tasks and responsibilities

For the neonatal heel prick screening, tasks and responsibilities are allocated as follows:

1. Commissioning and financing of the neonatal heel prick screening programme: Ministry of Health, Welfare and Sport.
2. National-level management of the national heel prick screening programme: Centre for Population Screening.
3. Advising the Centre for Population Screening on the national heel prick screening programme: the NHS Programme Committee.
4. Representing the interests of citizens and patients: patient and consumer organisations.
5. Regional coordination of implementation and quality assurance for the NHS programme: the DVP (Vaccination Provision and Prevention Programme Service).
6. Implementation of the NHS programme: healthcare professionals. For the NHS programme, this includes youth care staff, hospital staff, general practitioners, obstetric care providers. In the screening laboratories, this includes clinical chemists and analysts.
7. Provision of care in the event of abnormal results: healthcare professionals. For the NHS programme, this mainly includes medical advisors at the DVP, general practitioners, paediatricians and clinical geneticists.
8. National monitoring of the programme: an independent, external party.

Figure 2 shows these actors and the relationships between them in the form of a diagram. The allocation of specific tasks is explained below.

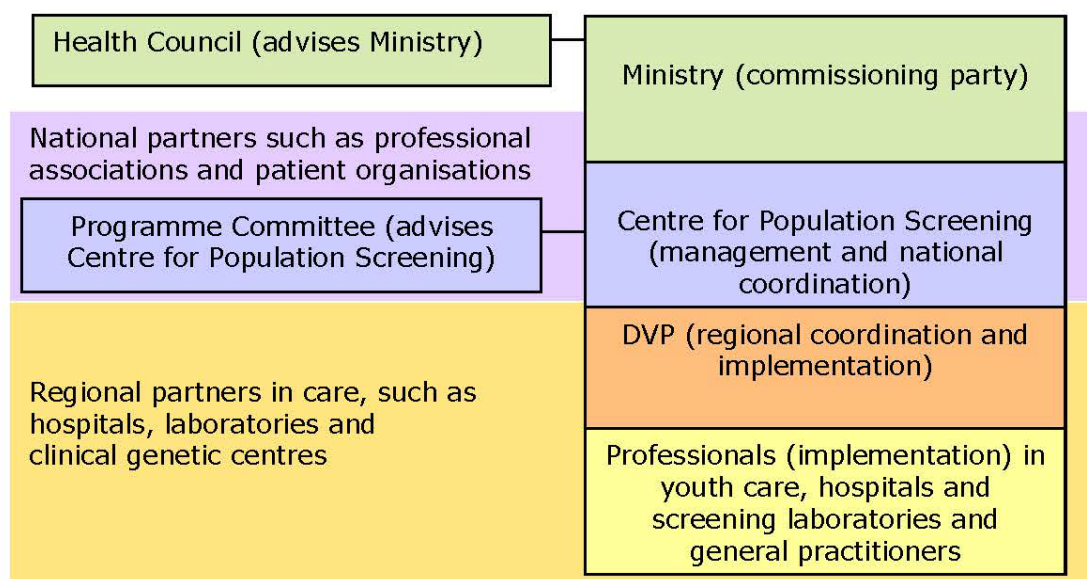


Figure 2: Chart showing relationship between the parties involved in the NHS programme and care provision. The Centre for Population Screening receives advice from the Programme Committee and operates in a network with national partners, such as professional associations and patient organisations. The DVP and professionals operate within a network of regional partners, such as hospitals and laboratories.

Ministry of Health, Welfare and Sport

The Minister of Health, Welfare and Sport (VWS) has political responsibility for the NHS programme and determines policy in relation to the NHS programme. Additionally, the Ministry ensures that the Centre for Population Screening is able to manage the programme at the national level.

Health Council (GR)

The Health Council is an independent scientific advisory body. Pursuant to the Public Health Act, the Council has the task of advising ministers and parliament on public health and research into health and healthcare. Ministers ask the Health Council for advice that they can use to substantiate policy decisions. In addition, the Health Council has a signalling function and can also issue recommendations proactively.

Centre for Population Screening

Since 1 January 2006, the Minister of Health, Welfare and Sport has commissioned RIVM (the National Institute for Public Health and the Environment) with the nationwide management and coordination of prevention programmes. Also in 2006, RIVM established the Centre for Population Screening (CvB) to carry out this task. The Centre for Population Screening provides the link between policy and practice. On the instructions of the Ministry of Health, Welfare and Sport, the Centre for Population Screening directs prenatal and neonatal screening and manages its implementation, so that the legal and policy frameworks, public values and coordination with regular healthcare are assured.

These tasks consist of:

- financing the implementation of the programme;
- quality assurance and professional training;
- national monitoring and evaluation;
- adequately organised infrastructure (including information management);
- the development of national communication materials;
- communicating innovations to the Ministry;
- coordination with IGZ in the event of incidents.

The extension of the NHS programme will also enlarge the scope of the tasks outlined above, because the number of disorders and health conditions screened for will increase.

NHS Programme Committee

A programme committee has been established for the NHS. The NHS Programme Committee advises the Centre for Population Screening on the implementation of the NHS and its coordination with the rest of the healthcare system. Focus areas include, for example, national quality requirements, communication with citizens and professionals, information management, improvements, innovations and the monitoring and evaluation of the programme.

The NHS Programme Committee is chaired by an independent chairperson and is made up of representatives from professional groups, patient organisations and other parties involved. Participation is based purely on expertise. It thus includes a broad spectrum of knowledge and

experience from the relevant fields, which it uses to support the Centre for Population Screening in its management role in relation to the NHS programme.

If the NHS programme is extended to include new disorders, it will be necessary to decide whether additional representatives (from parties who are not currently involved) should be added to the programme committee.

DVP (Vaccination Provision and Prevention Programme Service)

The DVP is responsible for regional coordination and implementation in accordance with the national framework established for this purpose. The DVP is responsible for appropriate proper organisation and efficient implementation. It has three regional offices. These are also responsible for quality, quality assurance and the monitoring and evaluation of primary process activities at the regional level.

The DVP itself carries out a number of activities in the primary process. In addition, the DVP outsources certain activities to other parties, such as youth healthcare services and screening laboratories. The DVP has cooperation agreements/contracts with these parties for the purposes of the NHS programme, and provides them with funding. The DVP sets requirements for these parties regarding quality assurance and data delivery. The DVP also provides professional training for the professionals involved in the population screening.

The DVP ensures good coordination between the NHS programme and healthcare in the region. Partly in order to achieve this, the DVP's regional offices maintain a network with relevant parties, such as hospitals and laboratories in their region.

The medical advisors work for the NHS programme on the instructions of the DVP.

The extension of the NHS programme will also enlarge the scope of the tasks of the DVP and the medical advisors in the NHS programme, because the number of disorders and health conditions screened for will increase.

Reference laboratory

On the instructions of the Centre for Population Screening, RIVM-IDS fulfils a reference function for neonatal heel prick screening. Screening takes place in the five laboratories contracted by RIVM. The purpose of the reference function is to guarantee the uniform quality of screening in these laboratories. The Centre for Population Screening makes annual agreements with IDS regarding the details of this reference function. Activities and products are described annually in a service provision agreement.

The extension of the NHS programme will also enlarge the scope of the tasks of the reference laboratory for the NHS programme with regard to quality assurance of the laboratory techniques used in the NHS programme. The various validation studies and pilot studies that are

required will make significant demands on the capacity and expertise of the reference laboratory.

Screening laboratories

The core tasks of the five current screening laboratories are:

1. Assessing the quality of the heel prick material provided.
2. Carrying out the screening tests according to the nationally agreed protocols.
3. Playing a role in monitoring non-conclusive and abnormal results.

The screening laboratories work according to the quality requirements specified in their contract with RIVM. IDS acts as a reference laboratory to monitor quality and provides national coordination for the screening laboratories.

Patient and consumer organisations

The patient organisations VKS (Association for Adults, Children and Metabolic Disorders) and VSOP (Association of Collaborating Parent and Patient Organisations) represent the interests of their clients with rare genetic disorders. They are both represented in the Programme Committee. The Dutch Cystic Fibrosis Foundation (NCFS) is represented in the advisory committee for the neonatal heel prick screening for Cystic Fibrosis (ANS-CF).

The extension of the heel prick screening will affect the patient organisations involved in the VKS and the VSOP. An assessment will be required regarding to what extent the expansion of the heel prick will require the involvement of new patient organisations to provide knowledge and expertise regarding the disorders added.

Other parties involved in the implementation of the screening programme

Various professionals and organisations are involved in carrying out population screening and associated aspects of healthcare (these include obstetric care specialists, screening laboratories, specialist laboratories, hospitals). They work together on the basis of the manual for the neonatal heel prick screening programme. They are responsible for ensuring that they have sufficient expertise to carry out their work and to do so in a manner that meets quality requirements. The professionals adhere to the relevant guidelines and the nationally specified requirements that have been drawn up within the framework of the NHS programme. Along with the Centre for Population Screening and the implementing organisations, both the professional associations and the professionals themselves are responsible for ensuring coordination and effectiveness.

Monitoring and evaluation

Regional monitoring of the programme is carried out by the DVP in accordance with the minimum data set and the national set of indicators specified in the programme.

National monitoring of the programme is carried out by an independent, external party according to a pre-specified report format.

National evaluation occurs on a more incidental basis, and generally takes place in a cycle of two to five years.

6.3 Responsibilities for each activity in the chain

Every link in the chain of activities, from education to treatment and follow-up, must be properly coordinated. The hand-over between screening and healthcare must occur at some point in any population screening programme. As far as the NHS programme is concerned, additional diagnostic work will take place within the regular healthcare system for those children with an abnormal result (or carrier status). Referrals, including the passing on of data, must be done appropriately and the parties involved have made agreements concerning this within the screening programme and within the healthcare system. These agreements are included in the manual.

Figure 3 shows the activities across the entire chain and also the point at which the transition takes place between the NHS programme and the healthcare system. The party/parties involved with each link in the chain, including tasks and responsibilities, is/are shown. Where tasks and responsibilities will change as a result of the expansion of the programme, this is explained for each link in the chain.

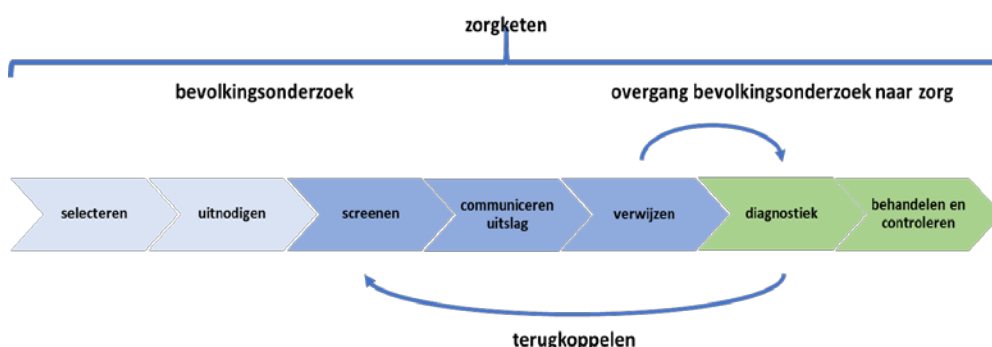


Figure 3: A schematic representation of the activities relating to the NHS programme across the entire chain, including the transition to the general healthcare system.

Zorgketen	Healthcare chain
Bevolkingsonderzoek	Screening programme
Overgang bevolkingsonderzoek naar zorg	Transition from population screening to healthcare
Selecteren	Selection
Uitnodigen	Invitation
Screenen	Screening
Communiceren uitslag	Communicating the test result
Verwijzen	Referral
Diagnostiek	Diagnostic testing
Behandelen en controleren	Treatment and follow-up
Terugkoppelen	Feedback

The expansion of the NHS programme means that it may be necessary to involve new professionals or organisations and to add requirements to the national manual.

Selection and invitation

Obstetric care providers are responsible for providing information and obtaining informed consent in the NHS programme. For further details, see section 8.

The Department of Civil Affairs of the relevant municipality is responsible for giving the information leaflet to parents when the birth is registered.

The parents are responsible for registering the birth of their child within the relevant timeframe. After the parents have registered the birth, the regional DVP's offices receive the details of the child via the Municipal Database (BRP).

The DVP regional offices are then responsible for instructing the relevant Youth Health Care Services (JGZ) to carry out the heel prick. The youth healthcare organisation makes an appointment with the parents by telephone.

The DVP is responsible for selecting, commissioning, coordinating and monitoring the implementation of the neonatal heel prick screening, and ensures that this is implemented in a nationally uniform manner in accordance with the relevant national frameworks. The extension of the heel prick screening will have consequences for the tasks of the DVP with regard to coordinating and monitoring the disorders that will be added.

Screening

The parents are responsible for giving their permission for the heel prick screening and for deciding whether or not they want to receive information regarding carrier status of their child for sickle cell disease ('*informed consent*'). As stated in section 6.1, for the heel prick screening the parents make a decision in the interest of their child. Parents should be informed about this when the heel prick screening is expanded through the addition of further disorders. When participating in a pilot study for a new disorder, parents must be informed about this separately and the informed consent of the parents must also be given for participation in the pilot study.

The screeners working for JGZ organisations are responsible for taking the blood sample for the heel prick. In two provinces (Gelderland and Zuid-Holland) the heel prick is carried out (in part) by midwives, under the responsibility of the JGZ. If a child is hospitalised during the sampling period, the heel prick is performed by an employee of the hospital.

The screeners are responsible for ensuring that their knowledge and expertise are adequate, for providing information and communicating appropriately, for taking blood samples of good quality, for ensuring that all relevant data is provided and for sending the heel prick card to the relevant screening laboratory. The addition of new disorders to the screening will have consequences for the information that screeners give to parents and for informed consent. It may also have consequences for completing the data on the heel prick card, but this remains to be seen

in relation to each specific condition. The start of a pilot study will also have consequences for the work of the screeners in the relevant region in terms of the information provided to parents, informed consent and possibly the recording of data on the heel prick card. For more information see section 8, Communication and Information.

Five screening laboratories are responsible for analysing the heel prick blood. RIVM (IDS) also functions as the reference laboratory.

The analysis, assessment and the associated quality assurance and data registration occur in accordance with the relevant guidelines and national requirements. This is specified in the contracts between the screening laboratories and the implementing organisation.

The laboratories also cooperate actively with the other activities that are carried out in the context of quality and quality assurance. This includes the circulation of material and data, inspections and professional training. The screening laboratories are responsible for the expertise of their personnel.

The laboratories send the results of the heel prick test in digital form to the relevant DVP regional office for further processing by the DVP.

When new conditions are added to the programme, this will have consequences for the work involved in analysing and assessing the blood, for the associated quality assurance, and for the recording and transfer of data. The participation of a screening laboratory in a validation study or pilot study for a new condition will require additional capacity and expertise. Furthermore, the addition of a disorder may affect the set-up of the laboratory function; for example, a new laboratory facility may be needed (for screening for SCID, for example), or an analysis may need to be carried out in a specialist laboratory, rather than in one of the five screening laboratories.

Communicating the results and referrals

The DVP regional offices are responsible for communicating abnormal results or non-conclusive results to the parents, through the medical advisor. They ensure that this is done in a uniform way.

Parents are not informed if the results are normal (negative). In the future, the intention is to inform parents of the results of the heel prick even when the results are normal.

If a result is abnormal, the DVP regional office's medical advisor will contact the general practitioner, who will then arrange for a referral to a university medical centre (except for CH; these children may also be referred to a general hospital).

The DVP regional office is responsible for answering any questions relating to the screening programme, possible results and (general) information about the neonatal heel prick screening programme.

The addition of a new condition to the heel prick screening will have consequences for communicating abnormal results to parents, GPs and paediatricians and for the development of the necessary materials

(results letters, etc.). This also applies to the DVP regional offices that are involved in a pilot study for one of the new disorders.

Diagnostics and treatment

In principle, all children who are referred following the screening are treated at a university medical centre (or, for CH, at a general hospital). A definitive diagnosis is made and treatment is started at the university medical centre. The ANSs from the NVK are responsible for the agreements regarding the diagnosis and treatment of children referred following an abnormal result in the heel prick screening. The (specialist) paediatrician is responsible for providing care for the child and parents within nationally established referral deadlines and for applying the NVK guidelines and protocols that relate to diagnostics and treatment. The (specialist) paediatrician records the results of the diagnostics in NEORAH and DDRMD (for the metabolic disorders). This allows for this information to be fed back to the screening laboratories for quality assurance purposes in relation to the screening.

In cases of carrier status for sickle cell disease, the parents are referred to the relevant GP.

The addition of a new condition will affect the design and implementation of the diagnostic process, care for that particular disorder and the best method of recording data for quality assurance, monitoring and evaluation. Sufficient capacity will be needed in specialist care to be able to provide the necessary expertise for the development of a follow-up protocol, conducting validation research and reflecting on how to evaluate the screening. This also applies in the case of a pilot study for a new condition. Sometimes it will be necessary to involve new experts in the screening programme. This will certainly be necessary for screening for SCID, X-ALD and GAMT.

6.4 Conclusion

The main conclusions of this section are:

For almost all the organisations involved in the heel prick screening programme and their respective tasks, adding a new condition or starting a pilot study for a new condition will have significant consequences. The most significant effect will be on the reference laboratory, screening laboratories, the DVP (implementing organisation), the Centre for Population Screening, and diagnostics and care.

7 Quality policy

Population screening programmes organised by the government must be of high quality, easily accessible and affordable. We can also speak of the public values of population screening (see section 6). Within these public values, various aspects can be distinguished. The public value of quality includes the aspects of effectiveness, demand-orientation, safety, national uniformity and innovation. The public values and aspects apply at the local level (individual contractors and/or healthcare institutions), the regional level and the national or programme level.

A sound quality policy for the population screening is necessary to ensure that these public values are realised. This requires the following:

- that the right tools are used to design the quality policy (section 7.1);
- that the required national quality requirements are established and elaborated in guidelines and working methods (section 7.2);
- that the tasks and responsibilities of the parties involved with regard to quality are specified and allocated (section 6);
- that quality assurance is put in place (section 7.3);
- that professional training takes place (section 7.4);
- that monitoring, evaluation and improvement take place (section 10);
- that appropriate forms of information management (recording information, exchange and availability) are in place (section 9).

7.1 The instruments

For the population screening, various instruments (often formal documents) are available that parties use to record or adjust the relevant requirements, tasks and responsibilities. This section explains the instruments used in relation to each party. In figure 4, this is illustrated in a diagram.

7.1.1 *Legal and regulatory aspects*

Until 2015, the legal basis of the heel prick screening programme was the Exceptional Medical Expenses Act (AWBZ). When the AWBZ was superseded by the Long-term Care Act, Article 4a was inserted into the Public Health Act by means of that act. This replicated the legislation that had previously been included in Article 17 of the AWBZ, Care Claims Decision (Besluit zorgaanspraken AWBZ). Article 17 stipulated that the Minister was responsible for ensuring that new-borns are tested for serious rare diseases, as specified by ministerial regulation. Article 4a is a temporary measure until 1 January 2018, pending a decision on a definitive arrangement. The article specifies that the heel prick screening is to be funded from the National Budget, with effect from 1 January 2015.

The implementation of the NHS programme is regulated in article 3, part a, of the Decision in the RIVM Act. This decision states that RIVM, on behalf of the Minister of Health, Welfare and Sports, is tasked with

directing and overseeing national prevention programmes, including the neonatal heel prick screening programme.

The decision also specifies the tasks of the implementing organisations - the RIVM regional offices of the DVP department.

All the legislation that is applicable to healthcare (such as the WGBO, the WBIG, the WKKGZ and the WBP) is applicable to the neonatal heel prick screening.

The heel prick is implemented in accordance with the requirements of the Individual Healthcare Professionals Act (WBIG); namely, the heel prick is only administered by non-independent practitioners, upon instruction and under specified conditions. The medical advisors act as the commissioning party, giving instructions to carry out the heel prick. Those involved in carrying out the neonatal heel prick screening programme must comply with the Quality, Complaints and Disputes in Care Act (WKKGZ).

Good coordination between the NHS programme and the general healthcare system is very important. The WKKGZ and the Wet BIG apply to the functioning of hospitals and laboratories. When it comes to the criteria for responsible care, the WKKGZ draws strongly on 'field standards', in other words: the protocols, guidelines, and quality requirements that determine professional standards with regard to responsible care. The supervision of the Health Care Inspectorate (IGZ) adopts professional field standards, although in the absence of these, the inspectorate can also determine the frameworks that must be adhered to.

The patient, in the sense of the Medical Treatment Contracts Act (WGBO), is entitled to care that meets the relevant professional standards, i.e. care that meets the 'field standards' mentioned previously. In the case of the heel prick screening, a treatment agreement is concluded between RIVM and the parents of the child. RIVM instructs the heel prick to be carried out; the youth healthcare organisation must then observe the relevant professional standards.

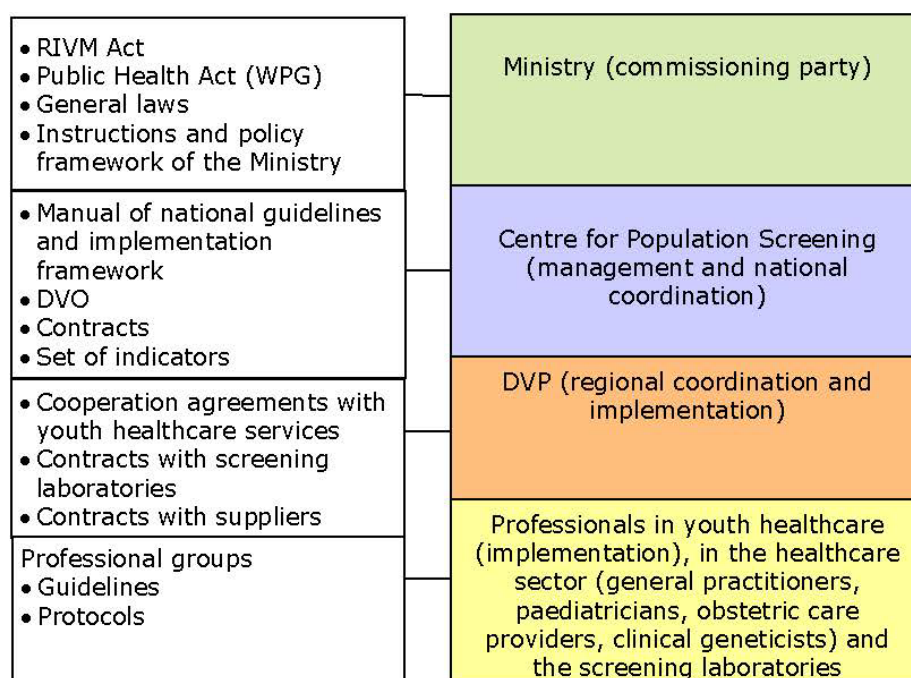


Figure 4: Chart illustrating the various instruments that are available for parties to record and adjust the relevant requirements, tasks or responsibilities.

7.1.2 National frameworks

The Centre for Population Screening directs the neonatal heel prick screening programme provided by the government, and coordinates the relevant parties in relation to policy and the field of implementation. The instructions issued by the Ministry of Health, Welfare and Sport to RIVM every year determine the frameworks and parameters for the management and implementation of the population screening. The population screening must be carried out effectively, efficiently, reliably and uniformly across the whole country, and it must be integrated with the rest of the healthcare system.

The frameworks within which the programme is coordinated and implemented at the regional level have been established between the Centre for Population Screening and the DVP since 1 January 2009. These frameworks relate to the effectiveness, efficiency, quality and national uniformity of the population screening programme and its financial parameters.

The national quality requirements, the set of indicators (described in section 10.4) and the frameworks for the neonatal heel prick screening programme are developed by the Centre for Population Screening and, following advice from the Programme Committee, adopted.

The national quality requirements are included in the neonatal heel prick screening manual and will need to be adapted. The neonatal heel prick screening manual describes what is required for the neonatal heel prick screening to be conducted effectively and within the relevant quality frameworks. It sets national standards for all the parties involved in the implementation of the neonatal hearing check programme. The manual is binding on all professionals involved in the neonatal heel prick

screening programme. The programme involves a chain of activities undertaken by partners who work together, and it is vital that everyone is aware of their role in the screening workflow. The tasks and responsibilities of the parties involved are described in the manual. The national-level manual and the set of indicators are drafted and updated in close consultation and coordination with the relevant actors.

7.1.3 *Contracts and cooperation agreements*

The DVP has a contract with the five screening laboratories that carry out the analyses. The contract sets out tasks and responsibilities, quality requirements and guidelines with regard to the analysis of the blood samples.

As an implementing organisation, the DVP has cooperation agreements with the youth healthcare organisations that are responsible for carrying out the heel prick screening. This cooperation agreement defines the quality requirements that the implementation of the neonatal heel prick screening must meet. This also applies to the desired quality assurance measures, expertise, data recording and data exchange. The DVP finances the implementation of the heel prick screening by the youth healthcare organisations. The Centre for Population Screening agrees an annual service provision agreement with the DVP in which agreements are made about the performance to be delivered in that year.

7.1.4 *Guidelines*

The NVK, NVOG, VKGN, NVKC, VKGL, KNOV and the NHG develop and maintain guidelines that define the relevant professional standards and responsible care. Some of these guidelines apply to care for new-borns or the neonatal heel prick screening programme.

7.2 **Quality requirements**

National quality requirements apply to the various areas of the national population screening programme.

The set of indicators defined in relation to the heel prick programme is part of the national quality requirements for the programme.

The way in which the heel prick screening should be carried out is described in the neonatal heel prick screening manual.

The existing quality requirements apply to the primary process; these are important to the implementation of the heel prick screening. All these requirements have been included in the neonatal heel prick screening manual.

The quality requirements relate to selection and invitation, the educational background of and continuing training for screeners, the implementation of the heel prick, the screening laboratories, the communication of the results and referral, and diagnostics and treatment.

Quality requirements regarding the neonatal heel prick screening also apply to the youth healthcare organisations and to the DVP.

7.3 **Quality assurance**

Population screening requires adequate and appropriate quality assurance, so that the responsible and sustainable implementation of

the population screening can be guaranteed. This section discusses the principles that are applied to quality assurance.

The principles for quality assurance are:

- responsibility for quality and quality assurance resides at various levels;
- monitoring quality is important for the entire process, from invitation to treatment.

Responsibility for quality and quality assurance resides at various levels.

a. The care provider / those carrying out the screening

The care provider is responsible for the proper execution of the population screening and/or for providing the associated care, and he or she must adhere to the established guidelines and quality requirements. The care provider or the organisation where the care provider is employed must establish and maintain an internal system of quality assurance. The care provider is responsible for his/her own professional training and for registration.

b. Quality assurance by means of the reference function

The quality assurance of laboratory tests carried out by the five screening laboratories is assured by the reference laboratory IDS, in accordance with the manual.

c. Quality assurance at the screening laboratories

The screening laboratories are responsible for ensuring a reliable analysis of the blood samples, in accordance with the manual.

d. National-level quality assurance

Quality assurance for the entire programme at the national programme level is the responsibility of the Centre for Population Screening, in light of the advice provided by the Programme Committee. The Centre for Population Screening develops national protocols with the parties involved in order to optimise the quality of the programme. National monitoring and evaluation provide an insight into which aspects of quality policy may require adjustment, and which measures must be taken to enhance the effectiveness of the programme. The IGZ also plays a general supervisory role.

Quality assurance applies to the entire screening process. This means that quality requirements and risks must be described in relation to all parts of the process, so that an appropriate system of external quality control, monitoring and evaluation can be established. Quality assurance must be actioned and recorded in relation to each component.

e. Regional coordination of quality assurance

The responsibility for the regional coordination of quality assurance in the heel prick screening resides with the DVP. Regional quality assurance by DVP extends to the following tasks:

- the dispatch of heel prick sets and informational materials;
- the registration of new-borns;
- the registration of the screening data and results;

- the referral of children in the event of an abnormal heel prick result.

The expansion of the heel prick screening programme will mainly affect quality assurance at the screening laboratories and the reference function, the required specialist diagnostics and care and the implementing organisations. The regional quality assurance of the DVP will also be affected because of the increase in the number of referrals. If new laboratories are used for certain specific steps in the analysis, contracts detailing quality assurance agreements will need to be signed.

7.4 Professional training

By professional training, we refer to the whole range of activities that are aimed at maintaining and increasing the competences of the staff involved in the screening and providing subsequent care.

In consultation with the relevant professional associations, employers, implementing organisations and training institutes, the Centre for Population Screening has deliberately committed itself to providing an appropriate range of professional training activities that focus on the screening, the national manual and the policy framework. The Centre for Population Screening applies the following principles in this regard:

- In principle, the Centre for Population Screening delegates the responsibility for professional training for an ongoing, regular programme to professional groups, professional associations, employers and implementing organisations. However, when innovations occur and when setting up a new programme, the Centre for Population Screening assumes greater responsibility as the national director (see below for the last four principles).
- The Centre for Population Screening provides information on the screening perspective and takes care of the provision of national programme-specific manuals and policy frameworks.
- The Centre for Population Screening informs the relevant professional groups, professional associations, employers, implementing organisations and training institutes about the implementation of a new population screening and about innovations within existing programmes.
- The Centre for Population Screening promotes and upholds the national uniformity, correctness and completeness of professional training when implementing a new programme or innovations within existing programmes.
- The Centre for Population Screening monitors whether the content of professional training meets the national programme-specific manuals and policy frameworks when implementing a new programme or innovations within existing programmes.
- The Centre for Population Screening ensures that professional training activities are as relevant as possible to current systems of continuing training and additional training relating to the accreditation of the various professional groups involved.
- The Centre for Population Screening consults with the Professional Training Working Group (WVDNHS) and the Programme Committee of the relevant programme in relation to the content and organisation of professional training.

The expansion of the heel prick screening programme to include the proposed disorders will require a programme of professional training designed for all the professionals involved in implementation. To this end, a plan must be drafted and implemented in collaboration with the WVDNHS and the relevant organisations and professional groups. An important point to consider is when to provide which information in relation to the phasing in of testing for the additional disorders and the start of the pilot studies, so that all those involved in implementation are aware of the (upcoming) changes in the programme.

In terms of content, professional training must include:

- disorder-specific information regarding the disorders to be added, the process of referral, the respective turn-around times and information about diagnosis and treatment, including the urgency of treatment for each condition. Special attention will be given to screening for X-ALD due to the complexity of this disorder;
- the phasing in of the implementation and the consequences for implementation;
- the pilot studies, such as those for SCID and X-ALD;
- the relationship to the regular screening programme, including a number of optimisation projects;
- the consequences of the expansion for the primary process and the consequences of a possible extra heel prick;
- the consequences of the expansion for the tasks and responsibilities of professionals involved in implementation;
- new guidelines and quality requirements and changes to quality assurance processes;
- the changes to information management that will affect the working method of those involved in implementation.

The screeners who carry out the heel prick at home, in particular, must be properly prepared for all developments in order to be able to respond adequately when communicating with parents.

It will be necessary to organise (regional) professional training meetings, at least for screeners, obstetric care providers, paediatric nurses, general practitioners, paediatricians, laboratory staff, medical advisors and clinical geneticists, in order to prepare them properly for the changes in the programme and to give them the opportunity to ask questions. Wherever possible, the existing system of ongoing training, such as the accredited e-learning module for screeners, which will be updated, will be used as a basis for this. This also applies to the manual, the instruction film for screeners and the reference booklet. The information on the heel prick card may also need to be adjusted. Accreditation will be requested for these meetings.

7.5

Conclusion

The main conclusions of this section are:

- The expansion of the heel prick screening programme will mainly affect quality assurance at the screening laboratories and the reference laboratory, the implementing organisations, and the required specialist diagnostics and care.

- Organising professional training meetings will be necessary, focusing on the professionals involved in the screening programme, prior to the start of a pilot study and prior to the phasing in of the different disorders to be added.

8 Communication and information

Parents and parents-to-be are provided with information at various points in the cycle of the NHS population screening programme and during possible follow-up healthcare. Communication with the professionals involved in the programme is also important. They need to know what is expected of them with respect to the NHS population screening and how they can answer questions from parents and parents-to-be (where applicable).

Paragraph 8.1 briefly describes the target groups and the basic principles of communication in relation to the population screening. The extension of the heel prick screening programme will affect information and communication in relation to both the primary target group (8.2) and the professionals involved (8.3). At the end of this section, the adaptations required in the various materials are summarised in a table.

8.1 Target groups and principles of communication

Target groups

The neonatal heel prick screening has the following three main target groups for communication:

- Parents and parents-to-be of the babies eligible for the heel prick screening.
- Professionals and organisations who have direct contact with parents and parents-to-be: for example, screeners at local Youth Health organisations and obstetric care providers.
- Other professionals and organisations involved in the implementation of the population screening, such as the Department for Vaccine Supply and Prevention Programmes (DVP) and the screening laboratories.

Principles

Due to the wide range of actors that play a role in communication and information with parents and parents-to-be, it is important that they all receive the same clear and unambiguous information wherever possible. The following principles apply here:

- Communication and information is an important part of the entire cycle of the heel prick screening and associated follow-up healthcare. Actors share responsibility for providing clear and unambiguous information to parents and parents-to-be.
- For all communication and information, it is important to use a mix of resources, so that as many parents and parents-to-be as possible receive the information in a form that is appropriate for them.
- The Centre for Population Screening develops educational materials for the target group in collaboration with the other parties involved. The most important principles for this are that the communication is:
 - comprehensible and accessible (tailored to the target group);
 - balanced (advantages and disadvantages are mentioned);
 - up-to-date and relevant (information on the right topics);

- honest and free of moral pressure;
- uniform across the country and unambiguous.
- Communication is designed to be uniform wherever possible.
- Information is offered to the public at various levels; the most important information is provided in leaflets; more in-depth information can be found on the website.
- The Centre for Population Screening is responsible for the content of national communication materials for the public and professionals.
- The DVP is responsible for the distribution of national communication tools and for communication and information about these.
- Checks are performed on the national communication materials at least once a year to ensure that they are up-to-date.
- When developing, updating and evaluating national communication materials, parents and parents-to-be, implementing organisations, professional groups and other relevant field parties are involved.

The general principles described above also apply to communication and information regarding the expansion of the heel prick screening programme.

The expansion of the heel prick screening will require a particular focus on:

- Comprehensible and accessible information.
- Balanced information.
- Up-to-date and relevant information.
- The provision of information at various levels of detail.

This focus is needed because the programme involves very rare (and complex) disorders, which will be added to the current screening package in phases.

8.2 Information and communication resources for the primary target group

8.2.1 *Information and informed consent*

The expansion of the heel prick screening programme will not affect the current procedure with regard to information. The three points at which information is provided will remain:

1. At the first prenatal care appointment during pregnancy (in written form).
2. At the childbirth appointment (orally and in written form).
3. When the parents register the birth (in written form only).

The process for informed consent will in all cases continue to be a matter of asking the parents, on behalf of and in the interest of their new born baby, whether they consent to:

- having their heel prick performed on their child and receiving the results of the blood test;
- receiving information about carrier status for sickle cell disease;
- having the blood sample stored for anonymous scientific research.

Further research in preparation for implementation will be required in order to determine whether additional informed consent from the parents is required in order to participate in the pilot studies and screening for certain disorders (such as X-ALD). Informed consent will be required in all cases where non-anonymised research takes place during the pilot period.

The informed consent is currently recorded on the heel prick card. Research will need to be conducted into whether this will also be the method used for extending informed consent and, if so, for which component.

The general information material for parents and parents-to-be will be amended to include information about the 'new' disorders (also see Table 10). This does not apply to the leaflet entitled 'Zwanger!' because this only provides an outline of the heel prick screening.

In the existing materials, the following points will require attention:

- the occurrence of false-negative test results, in particular in relation to BKT and OCTN2;
- a new category of disorders, namely a disease of the immune system: SCID (also see section 4).
- health benefit only for boys when screening for X-ALD;
- possible secondary findings;
- performing an additional heel prick for CPT1, MPS I, MMA, PA and OCTN2 (where applicable);
- extension of informed consent (where applicable).

8.2.2 *Communicating the results of the screening*

Currently, if no abnormal results are found, the parents are not notified. This situation is going to change. In the future, the plan is to inform parents of the results of the heel prick even when the results are normal. It is expected that this project will get underway in 2018. Where there is an abnormal result, parents will be called by their GP, and receive a letter from the medical adviser. The GP for the child in question will receive a similar results letter.

This means that new results letters must be drafted for the new disorders to be added, both for parents and for general practitioners.

Parents and professionals will also receive background information about the disorder that the abnormal result relates to. This information will be included in the disorder-specific information sheets. The current set will be expanded to include information sheets about the conditions to be added to the programme.

The leaflet entitled 'Extra tests following an abnormal result', which provides information for parents about referral to a hospital, will also be adapted.

8.3 Information and communication resources for professionals

Various resources are used in order to communicate with the professionals and organisations involved with the programme (see Table 10). The extension of the screening will mean that all these resources will need to be amended. No new products are expected to be needed.

Important points for attention for obstetric care providers and screeners in relation to communication are:

- Pilot studies on various disorders.
- The screening for X-ALD and its implications for implementation.
- Performing a possible additional heel prick for CPT1, MPS I, MMA, PA and OCTN2.

And of course the other points mentioned above when providing information to the primary target group (see 8.2).

Table 10: Overview of adaptations required in the information and communication material

	Target group	Action:
<i>Information and communication materials for parents / public</i>		
'Zwanger!' leaflet	Parents	No changes
'Screening in new-borns' leaflet	Parents	Change
The heel prick cartoon story	Parents	Change
Website	Public	Change
Information film	Parents	Change and convert to animation
<i>Communicating the results of the screening</i>		
Letters for abnormal result	Parents/professionals	New
Results letter following second heel prick	Parents/professionals	Change
Results letter for additional heel prick	Parents/professionals	New if required
'Extra tests after the heel prick' leaflet	Parents	Change
Information sheets, disorder-specific	Parents/professionals	New
<i>Information and communication resources for professionals</i>		
Checklist for information meeting	Obstetric care providers	Change
Checklist for implementation	Screeners	Change
Checklist for abnormal result	GPs	Change
Website	Professionals	Change

8.4 Conclusion

Almost all information and communication resources will need to be adapted. Additionally, new material will need to be developed to include disorder-specific information about the conditions to be added to the programme.

9 Data management

9.1 Introduction

The expansion of the heel prick screening programme will have (major) consequences for almost all those involved. Data management forms the infrastructural basis for the ability to carry out the primary process of the programme in an appropriate manner, as well as quality assurance and monitoring, and evaluating the screening and the associated follow-up care. To this end, structured data relating to the babies screened (gender, age at screening, etc.), the results of the screening and other relevant data (where, when and under what conditions the test took place) must be recorded, exchanged and analysed. The expansion of the heel prick programme will have implications for data management. This section elaborates on the impact of the expansion on data management and which adaptations will be necessary.

9.2 The goals of data management

In order to assure quality and oversee the implementation of the heel prick screening, appropriate data management is indispensable. Accurate, timely and complete data registration, the exchange of screening data and subsequent diagnostics and treatment data (short-term follow-up in care after referrals) are crucial for the successful operation of the screening programme.

The use of uniform and structured data recording involves various different levels, each with its own area of application:

- The primary process level: Uniform and structured data capture is important for the accurate and complete implementation of the screening, quality assurance, diagnostics and possible follow-up care (in case of positive results and subsequent referral).
- Monitoring and evaluation (regional/national): The (uniform and structured) data recorded at the primary process level is used to optimise the primary screening process and to ensure that its implementation meets the relevant standards by means of quality monitoring and national evaluations (carried out by external parties).
- Additional studies: In order to support scientific research and/or validation studies with the aim of further improving the screening programme (for example, developing better testing methods, improving cut-off limits, adding new disorders).

9.3 Principles for data management

The Centre for Population Screening applies the public values of quality, accessibility and affordability; these are the principles that guide its population screenings. In terms of data provision, this translates to the following:

- Electronic data transfer, preferably using the latest standards.
- One-off data capture in the source system.
- One-off confirmation and multiple use.
- Uniform definitions and data confirmation (consistent language) on the part of all implementers and caregivers, preferably structured (protocol) and (internationally) coded.
- Relationship with existing data flows where possible.
- Legal aspects (such as privacy and access to data) must be properly regulated, and be compliant with current legislation.
- Security aspects must be assured in accordance with current legislation.

In the context of the feasibility study, the following additional principle has also been specified:

- Coordination between the process of expanding the programme and developments in the regular programme is essential. In the area of data provision, the replacement of the laboratory data system and the renewal of the Praeventis data system are important developments that must be taken into account. In this respect, within the relevant government frameworks for data management, the government must be provided with a detailed description of the required ICT functionality for the expansion of the heel prick screening programme.

9.4 Current implementation of heel prick screening

Under the current situation, the heel prick screening is supported by various data systems. Namely:

- Laboratories are supported by NEONAT, the laboratory data system.
- DVP is supported by Praeventis, the national registration system for the implementation of the primary process.
- The Centre for Population Screening and NVK are supported by NEORAH incl. LTFU in order to register short-term and long-term follow-up care (necessary for quality assurance and evaluation).

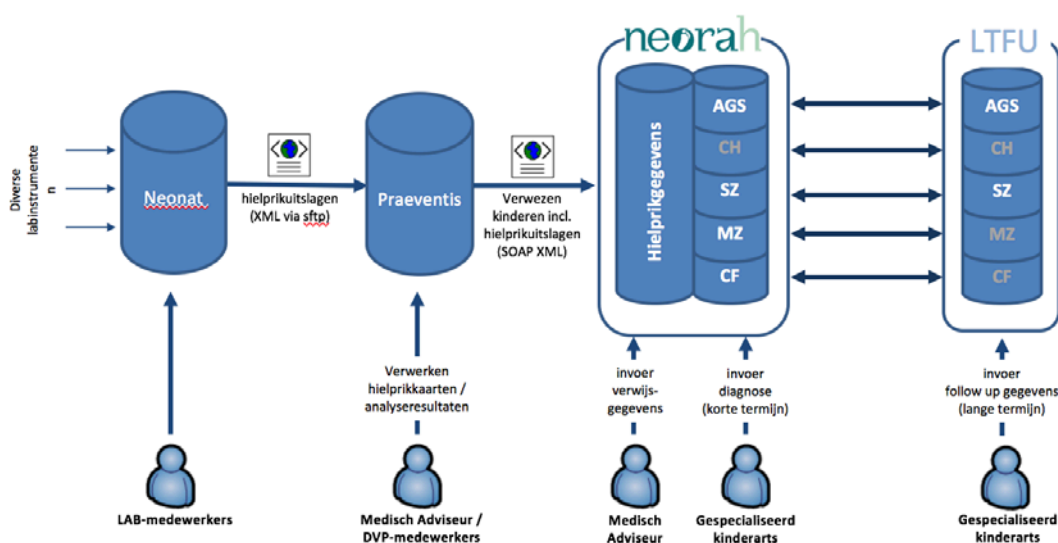


Figure 5: Support systems in the heel prick screening programme

Diverse labinstrumenten	Various lab instruments
Neonat	Neonat
Hieprikuitslagen (XML via sftp)	Heel prick test results (XML via sftp)
Praeventis	Praeventis
Verwezen kinderen incl. hieprikuitslagen (SOAP XML)	Referred children incl. heel prick test results (SOAP XML)
Hieprikggegevens	Heel prick data
Verwerken hieprikkarten/analyseresultaten	Processing of heel prick cards / analysis of results
Invoer verwijzgegevens	Input of referral data
Invoer diagnose (korte termijn)	Input of diagnosis (short term)
Invoer follow up gegevens (lange termijn)	Input of follow-up data (long term)
LAB-medewerkers	LAB employees
Medisch Adviseur/DVP-medewerkers	Medical Adviser/DVP staff
Medisch Adviseur	Medical Adviser
Gespecialiseerd kinderarts	Specialist paediatrician
Gespecialiseerd kinderarts	Specialist paediatrician

In addition to the systems for national registration and operational support for the heel prick screening, a data warehouse (Praemis) has been set up for quality monitoring and evaluation purposes. All these systems together support the implementation of the screening programme in the manner described in summary below.

Selection and invitation

Parents report the birth of their child to the Department of Civil Affairs at the town hall of their municipality. The municipality adds the statement of birth to the Basic Register of Persons (BRP) and it is then forwarded to the DVP. The DVP registers the statement of birth in the registration system Praeventis. In addition to the notification via the BRP, statements of birth can also be received from the administrative birth announcement (AGB), PROBAS (protocol base administration), COA (Central Agency for the Reception of Asylum Seekers) and, in future, from PIVA-V (Personal Information Service for the Netherlands Antilles and Aruba).

The receipt of a statement of birth triggers an instruction to be issued to local youth Health organisations to carry out the heel prick, by the medical adviser. If the screener becomes aware of the birth via a different channel (for example, the screener is the midwife), the heel prick will be taken without prior instructions from the DVP.

Screening

The local Youth Health organisation receives instructions from the DVP to carry out the heel prick. The screener who performs the heel prick applies blood to the heel prick card, adding the relevant personal details and screening data. The card is then sent to one of the five screening laboratories for analysis. The screening laboratory logs the set number and date of arrival of the heel prick card in NEONAT and starts the analysis. In the event of an abnormal result, the relevant personal and

screening data are also registered in NEONAT. The data logged in NEONAT is prepared for processing in Praeventis along with the laboratory test results. In parallel to this process, all heel prick cards are scanned in the laboratory and made digitally available to the DVP. The cards are also sent physically to the DVP and the data is processed in Praeventis. The DVP monitors the screening process with Praeventis. Where necessary, the DVP notifies the local Youth Health organisation if a child has not been tested (no results received) or has been tested too late, or the laboratory if incomplete results have been received.

Communicating the results and referrals

Based on the results of the heel prick, referrals are made via a medical adviser in the event of an abnormal result. The medical adviser will contact the specialist paediatrician associated with that disorder in relation to all abnormal results (with the exception of CH and HbP). The medical adviser will inform the general practitioner by telephone and by letter; the GP contacts the parents. The parents also receive a letter from the DVP stating that an abnormal result has been found in the heel prick screening.

Diagnostics and treatment

If a child has been referred to a paediatrician, the paediatrician will record the date of the first contact, the results of the diagnosis and any treatment provided in NEORAH.

Possible false negatives from the heel prick screening are logged by the Dutch Signalling Centre for Paediatrics (NSCK) at the NVK. The NSCK's report is added to NEORAH for heel prick disorders in order to provide an overall picture of the effectiveness of the screening.

Data systems for the registration of follow-up care and missed children

Currently, two systems are in use for the registration of follow-up care in relation to the heel prick: NEORAH and a CH-database at TNO. In addition, there are three more registers from which data is submitted to NEORAH (DDRMD and NSCK signalling) or which are used to perform checks on completeness (NCFR). The aim is to make data registration in NEORAH as thorough and accurate as possible. See below for a brief description:

Table 11: Registration for follow-up heel prick screening

System/ Application	Description
NEORAH (Centre for Population Screening and NVK)	Neonatal Register for Abnormal Heel Prick Screening Results. National database in which diagnostic data is logged regarding children with an abnormal heel prick result who have been referred for diagnosis and treatment, currently with the exception of congenital hypothyroidism (CH). The aim is to add CH to NEORAH with effect from 1 September 2017.
CH database (TNO)	National database in which diagnostic data is logged regarding children with an abnormal heel prick result for congenital hypothyroidism (CH), who have been referred for diagnosis and treatment.
NSCK	Dutch Signalling Centre for Paediatrics. The NSCK's signalling system aims to provide better insight into the prevalence of rare or new disorders in children aged 0 to 18 and to promote scientific research aimed at the backgrounds, diagnosis, treatment, prognosis and prevention of these disorders. If a child is missed in the screening and/or shows characteristics of a rare disorder at a later age, they are registered in this database by means of a notification from the paediatrician. Feedback is provided to RIVM, after which the child's data is also added to NEORAH.
DDRMD (ANS-MZ)	The Dutch Diagnosis Registration Metabolic Diseases (DDRMD) is a web-based database for the registration of patients with inherited metabolic disorders. Feedback on the children relevant to the heel prick programme is provided to RIVM, after which the child's data is also added to NEORAH.
NCFR	A register of care and treatment outcomes relating to patients with CF, set up by the Dutch Cystic Fibrosis Foundation. The use of annual cross-checks between NEORAH and the NCFR enriches both the NCFR and NEORAH.

The data collected and recorded in these systems is crucial to evaluating the effectiveness of the heel prick programme. The introduction of new disorders also means that the registration of follow-up care in these systems must be accommodated. It is necessary to determine which additions are necessary in close consultation with the paediatricians (responsible for follow-up after referrals) and the NVK. This must be considered in relation to each validation study, pilot or new condition to be introduced.

Quality assurance, monitoring and evaluation

One requirement for quality assurance, monitoring and evaluation is an adequate data management system and a good indicator set and minimum data set. The set of indicators has been established for the current population screening, as well as the minimum data set.

On the instructions of the Centre for Population Screening, an independent party (currently TNO) receives an anonymised file containing data from Praeventis and NEORAH for the purposes of their annual monitor of the neonatal heel prick screening.

9.5 Impact of expansion on current data management systems

For the purposes of the expansion, several steps can be identified in the process of screening and referral that will require adequate support in the form of ICT functionality.

If the heel prick card needs to be adapted, this will result in changes to ICT in order to be able to log all data. For each disorder, ICT will have to be set up in relation to each testing method chosen on the basis of the different steps in the analysis (first tier, second tier and possibly even third tier). A results letter for parents, general practitioners and paediatricians, to be sent in the event of an abnormal result, will need to be composed for each condition. If there is an extra heel prick, an extra letter will also have to be sent for this. For monitoring purposes, it is important to be able to set up a short-cycle monitor, focusing on the turnaround times of screening for each disorder, the number of children referred and the final diagnosis data for follow-up care. It will also be necessary to register any new indicators.

One preference within the current programme is the digitisation of the heel prick card and improvement to the results letter sent to parents. Likewise, there is a desire to integrate the data on the diagnosis of children referred following the heel prick from NEORAH into the Praeventis data system for quality assurance purposes.

A relevant development in the regular programme is that it has become clear that the current laboratory data system (NEONAT) and the registration system (Praeventis) are out of date and in need of renewal. Both systems are, for various reasons, unable to facilitate the anticipated expansion. In anticipation of the feasibility study, renewal processes have already been initiated. This is, on the one hand, to guarantee the continuity of the existing heel prick programme, and also to prepare for the expansion and to facilitate a flexible, state-of-the-art and future-proof system of data management.

NHS: Gegevensuitwisseling Lab – DVP

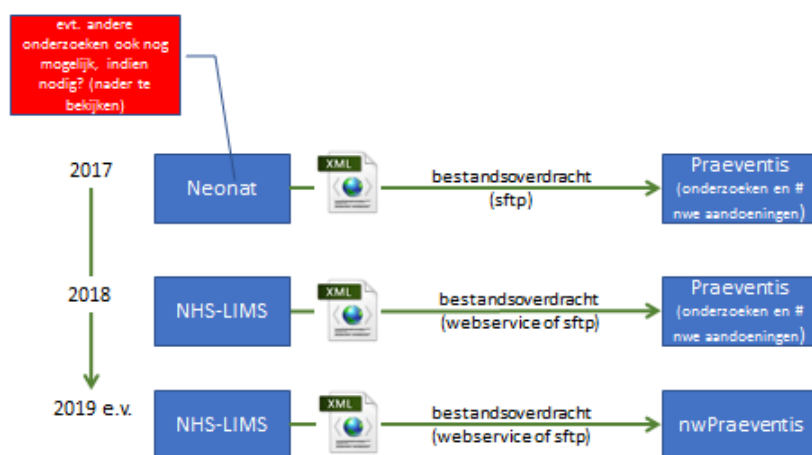


Figure 6: Development path for NHS-LIMS and new NHS data system (nwPraeventis)

NHS: Gegevensuitwisseling Lab - DVP	NHS: Data exchange Lab - DVP
Evt. andere onderzoeken ook nog mogelijk, indien nodig? (nader te bekijken)	Possibly additional studies, if necessary? (to be decided)
Neonat	Neonat
2019 e.v.	2019 e.v.
NHS-LIMS	NHS-LIMS
NHS-LIMS	NHS-LIMS
Bestandsoverdracht (sftp)	File transfer (sftp)
Bestandsoverdracht (webservice of sftp)	File transfer (web service or sftp)
Bestandsoverdracht (webservice of sftp)	File transfer (web service or sftp)
Praeventis (onderzoeken en # nwe aandoeningen)	Praeventis (studies and # nwe disorders)
Praeventis (onderzoeken en # nwe aandoeningen)	Praeventis (studies and # nwe disorders)
nwPraeventis	nwPraeventis

The NHS-LIMS (Laboratory Information Management System) and the new NHS data system (nwPraeventis) are expected to become available in accordance with the table above.

New insights from implementation and introduction, which relate to new, different functionality for data management, will need to be identified and coordinated with the programme for the renewal of Praeventis (PvP) and the NHS-LIMS replacement project in a timely manner.

A specific requirement regarding data management that arises from (preparations for) the expansion of the heel prick programme relates to support for validation studies and (prospective) pilots. For each disorder/validation study/pilot, it will be necessary to consider how this

can be facilitated in every respect. The timing of the start of the study and the specific preferences regarding data registration and process support will be key when opting for particular solutions.

9.5.1 *Support for validation studies / (prospective) pilots*

One aspect of the feasibility study will involve carrying out validation studies and pilots prior to actual implementation, such as for X-ALD. Some of these studies will involve prospective pilots, starting with SCID. The expected start date for the SCID pilot is in early 2018. This pilot can be accommodated using the current version of Praeventis. Whether NEORAH will need to be adapted is still under consideration.

Subsequent prospective pilots or validation studies can be supported within the current version of Praeventis until mid-2019, provided that the studies do not require any software modifications in the current version of Praeventis. This will be kept constantly under review for each study. If it is not possible to support the study using the current version of Praeventis, alternatives will have to be identified. Validation studies or prospective pilots after introduction of the new data system in mid-2019 will be introduced using the new system.

9.5.2 *Expansion of the number of disorders*

The main goal of the feasibility study is to ascertain whether the new disorders can be implemented and which requirements are relevant to this. This expansion cannot be accommodated within the new NHS data system (nwPraeventis), which is still to be developed, immediately, or within the new NHS-LIMS, because these systems will not be live on 1 January 2018.

As is the case for the validation studies and (prospective) pilots, depending on the start date, it will be necessary to ascertain whether Praeventis and NEONAT can be used to support the new condition. If not, it will be necessary to identify alternatives with regard to data management.

Once the timetable for the introduction of screening for the new disorders and the associated testing methods becomes clearer in more detail, it will be necessary to consider whether the new NHS data system (nwPraeventis) and NHS-LIMS are available, whether to adapt Praeventis and/or NEONAT for each condition, or whether to search for other alternatives.

9.5.3 *Legal frameworks*

The laws, regulatory frameworks and principles for the new system of data management have been outlined in a document (Project Start Architecture, PSA) drawn up within the Praeventis Renewal Programme (PvP). The intention is always to use this document as the starting point when it comes to making choices about data management, in such a way that all developments continue to be consistent with this. Additionally, an ICT NHS framework has been adopted by the Centre for Population Screening and the Ministry of Health, Welfare and Sport (VWS) for the purposes of the Praeventis Renewal Programme (PvP). Future developments should also be evaluated against this framework.

The frameworks specified should be respected, but the principle of 'comply or explain' applies at all times.

9.6 Conclusions

The main conclusions of this section are:

- To overhaul the provision of data for the neonatal heel prick screening, a programme and project have already been launched in anticipation of the expansion of the programme: the Praeventis Renewal Programme (PvP) and the Laboratory Data System Replacement Project (NHS-LIMS).
- Once the timetable for the introduction of screening for the new disorders and the associated testing methods becomes clearer in more detail, as well as the details of possible validation studies and prospective pilot studies, it will be necessary to consider whether the new NHS data system (nwPraeventis) and NHS-LIMS are available, whether to adapt Praeventis and/or NEONAT for each condition, or whether to search for other alternatives.
- The quality of the blood spots on the heel prick cards is expected to improve as a result of various improvement measures, and to be sufficient to enable the extension of the heel prick screening programme.
- This will require a great deal of flexibility from the ICT functionality, which must be available to prepare for the introduction of a new condition in good time.

10 Monitoring and evaluation

10.1 Introduction

Monitoring and evaluation are an important aspect of the quality policy in relation to population screening programmes. Both these elements contribute to the continuous process of assuring and improving the quality of such programmes.

Monitoring is a periodic activity which focuses on assuring and improving the implementation processes within the programme, and the link with subsequent care. The Centre for Population Screening is responsible for national monitoring and usually has this carried out on an annual basis. The monitors track the progress of these programmes and identify possible bottlenecks (in the chain). In this way, timely adjustments can be made, and accountability is also ensured with regard to Ministry, the inspectorate, the public and other partners.

National evaluation occurs on a more incidental basis, and generally takes place in a cycle of two to five years. The spectrum of subjects for evaluation includes both standard (such as evaluations of test characteristics) and specific components (such as the evaluation of informed choice).

The basis for proper monitoring and evaluation is made up of indicators and the data collected and/or registered in relation to these (basic dataset). It is therefore important that data collected as part of the heel prick screening programme is also available for studies into the quality of the programme. Indicators are drawn up in close cooperation with the parties involved and in a uniform way in relation to the public values of quality, accessibility and affordability.

10.2 Focus points for the expansion of the heel prick screening programme

Short-cycle monitoring

In addition to the annual monitoring of the neonatal heel prick screening programme, a system of short-cycle monitoring will need to be established.

When optimising or updating a programme, it is important to keep a close eye on developments within that programme (or particular parts of it). Short-cycle monitoring is often used to monitor particular indicators more frequently than usual during the implementation phase. This is done in order to be able to respond quickly to any issues or unintended consequences. New indicators, including target values or signal values, will have to be developed for any changes picked up in the primary process.

The focus points for the monitoring the expansion of the heel prick screening are discussed below.

Low prevalence

Due to the low prevalence of the disorders to be added to the programme, between 20 and 40 children with one of these disorders are expected to be identified annually, in total. For a number of these disorders (CACT, CPT1, BKT), it may take several years for a child to be diagnosed. Any issues or unintended consequences (such as too many false positive referrals or delays in diagnosis) will take longer to be detected due to the low prevalence of these disorders.

Referrals and false positives

The number of referrals is an initial indication of the performance of the screening programme and the tests used. If there are more referrals than the prevalence of the disorder and the predictive value of a test would suggest there should be, an alternative test, a second-tier test or a different cut-off value may be considered. This is also the case if there is an excessive number of false positive results. The percentage of false positive referrals from the current NHS is about two-thirds (the positive predictive value of the NHS was 32% in 2014).

Subsequent care

In relation to the link between the NHS and care services, it will be important to monitor indicators relating to timeliness. In particular, the timeliness of diagnostics is key for metabolic disorders.

Changes in the primary process

For almost all the disorders, using the first-tier test alone would lead to a significant number of false positive referrals. To limit this number, follow-up screening may take place using second and possibly third-tier tests or post-analytical tools. The added value of follow-up screening and post-analytical tools will need to be monitored on the basis of a number of new indicators. These indicators will need to be developed in consultation with the WIKNHS.

For GALK, MPS I and SCID, there is a possibility that following an abnormal first screening test result, a follow-up test will need to be carried out using whole blood. This will probably require a visit to a hospital or GP surgery with experience of taking blood from children. For MPS I, MMA and PA, a selective extra heel prick for the second-tier tests may be required (MPS I may also be possible using whole blood). In order to monitor the quality of this process, a number of new indicators will need to be developed.

Depending on the scenario that is chosen, the X-ALD disorder will need to distinguish between male and female children. This distinction has not previously been made in the programme and will have implications for the entire process, from completing the heel prick card and identifying the disease through to archiving the cards.

Optimising the quality of the blood spots on the heel prick cards

The expansion of the programme means that the number of repeated first heel pricks is likely to increase due to blood spots of insufficient quality on the heel prick card. The quality of the blood stains on the heel prick card will become more important as more punches are needed

(nineteen in total, six more than at present) in order to analyse the blood.

Completing the heel prick cards properly will be an essential step in this process and will therefore be subject to short-cycle monitoring.

For new indicators, a distinction will also be made between a selective extra heel prick and second heel pricks as a result of non-conclusive results. The number of repeated first heel pricks and the number of second heel pricks will therefore be subject to short-cycle monitoring.

Target values

For most indicators, target or signal values will need to be set in order to be able to flag abnormal results. These target or signal values will have to be developed with the relevant ANSs and within the Working Group on Data Management and Quality (WIKNHS), and submitted to the PNHS.

10.3 National evaluation of the expansion of the heel prick screening programme

A national evaluation can be initiated on the basis of abnormal results from monitoring. Often, these are evaluations require data that is relatively difficult to obtain (e.g. through questionnaires or patient file research). National evaluations are usually carried out by an independent party.

It is also important to evaluate the information products among the target group at pre-specified times. For example, the advantages and disadvantages of the programme could be nuanced better in the pilot studies. This will give participants in the programme the opportunity to make a better informed choice.

10.4 Indicators

Indicators are measurable aspects and are used to monitor and evaluate the population screening at the individual, regional and national levels. The indicators are distributed throughout the chain, including the transition from population screening to care, in order to identify potential bottlenecks. The description of the indicators is based on the system of 'European Community Health Indicators' (ECHI), which includes definition, rationale, calculation method, relevant dimension or subgroup, data source and the availability of the indicator. Parties that play a role in monitoring (individual, regional or national) and evaluation are always involved in drawing up these ECHI sheets.

During the preparation phase, the current set of indicators will be adapted where necessary. The Centre for Population Screening expects to adapt the current set so that it is possible to distinguish between first, second and third-tier tests, selective second heel pricks using whole blood and post-analytical tools. A distinction may also be made between male and female babies (X-ALD). Indicators and signal values will need to be developed for indicators relating to test characteristics (e.g. referral rates, number of false positives, predictive values) and timeliness (timeliness of diagnostics, timeliness of results, timeliness of treatment).

10.5 Conclusions

The main conclusions of this section are:

- Because of the low prevalence for these conditions, monitoring will be needed for several years.
- The number of referrals and the number of repeated first heel pricks will be subject to short-cycle monitoring.
- The outcomes of diagnostics and the timeliness of diagnostics will also have to be closely monitored.
- The quality of the blood spots on the heel prick card will need to be monitored closely in order to respond to any issues in this regard.
- The development of new indicators in order to monitor the primary process properly will be necessary.
- New target and signal values will need to be developed for the new conditions.

11 The Caribbean Netherlands

Since 2015, the heel prick screening programme has also been carried out on the islands of Bonaire, Sint Eustatius and Saba, which together form the Caribbean Netherlands (henceforth: the CN). Agreements have been made with Sint Maarten regarding the referral of children from Sint Eustatius and Saba with an abnormal heel prick test result. The current situation is that many children from Sint Eustatius and Saba are born in the hospital in Sint Maarten, but only receive the heel prick when they are back on their home island. Ideally, the heel prick for these children would be carried out in the hospital in Sint Maarten in order to save time. This would be possible if the heel prick can also be introduced for all babies born in Sint Maarten. The Minister of Health, Welfare and Sport has yet to make a decision regarding this because of the wish to use the infrastructure for the Dutch screening programme.

The neonatal heel prick screening programme was introduced in the CN on the basis of the 'Neonatal heel prick screening in the Dutch Caribbean' feasibility study of 2013, which was carried out by the Centre for Population Screening on behalf of the Ministry of Health, Welfare and Sport.

The feasibility study identified the principles that the same heel prick package should be used in the CN as in the European Netherlands and that use should be made of the infrastructure of the European Netherlands for neonatal heel prick screening. This means that the blood collected is sent to the Netherlands and examined by RIVM.

This section describes the focus points for the CN in the event of the expansion of the heel prick screening programme. For each domain, this section describes where changes will need to occur with regard to the implementation of the expansion of the heel prick screening programme in the CN. A description of the current situation of the heel prick screening programme in the CN can be found in the feasibility study entitled [Feasibility Study for Neonatal Heel Prick Screening in the Dutch Caribbean 2013', RIVM](#).

11.1 Support

Conference calls take place on a quarterly basis between the RIVM Heel Prick Screening in the CN Working Group and the contact persons for the CN and Sint Maarten. The contact persons are the representatives of the regional coordinator on the relevant island with regard to the implementation of the heel prick screening programme - namely GGD Bonaire, GGD Sint Eustatius, GGD Saba and CPS Youth Healthcare Section Sint Maarten. During these conference calls, the contact persons in the CN are informed about all current developments in the NHS programme, including the advice of the GR on the expansion of the heel prick programme, the position of the minister on this advice and the instructions provided to the Centre for Population Screening regarding conducting a feasibility study.

The contact persons receive all relevant information regarding the heel prick expansion from the quarterly meetings of the PNHS, the ANSs and the NVK and other relevant meetings such as the stakeholder session on the expansion of the heel prick screening programme of 13 February 2017. On the basis of this information, the contact persons then inform the professionals who implement the heel prick screening programme on the island about all relevant developments.

Support among professionals is evident from the commitment to and discussions during these regular conference calls as well as interim contacts. Public support for the extension has not been evaluated. However, practical experience tells us that the population generally accepts what is proposed by professionals. The expansion of the programme is not expected to have any negative consequences for participation in the screening in the CN.

11.2 Primary process

The expansion of the neonatal heel prick screening would not, in principle, affect the primary process of the heel prick screening programme in the CN.

11.3 Organisation, tasks and responsibilities

The national management and supervision of the neonatal heel prick screening in the CN are carried out by the Centre for Population Screening.

The scope of the Centre for Population Screening's duties regarding the CN will widen as a result of the expansion of the heel prick programme.

The regional coordination of the neonatal heel prick screening programme in the CN is partly carried out by the DVP.

The scope of the DVP's duties regarding the CN will widen as a result of the extension of the heel prick programme. This will mainly have consequences for the registration of screening data and results, the monitoring of the process and the sending of reminders and information letters regarding results. It will also have implications for the number of referrals made by the medical advisers from the DVP.

The regional coordinator for the CN has a role in providing regional coordination on the relevant island. The regional coordinator in the CN is responsible for reporting on the implementation of the heel prick, identifying bottlenecks, promoting cooperation on the island in question and providing information and advice to the implementing organisations. The scope of the duties of the regional coordinator in the CN will widen as a result of the future expansion of the NHS.

11.4 Legal considerations

The Public Health Act (WPG) is expected to provide a definitive legal basis for the neonatal heel prick screening programme with effect from 1 January 2018. Until that time, the NHS is covered by the temporary article 4a of the WPG.

Under the terms of the temporary article, the NHS does not apply to the public bodies Bonaire, Sint Eustatius and Saba. Despite this, the heel prick screening programme is now being carried out on these islands due to the inclusion of a title in Article 16, paragraph 1, sub g of the BES Healthcare Insurance Decree, since 1 January 2015. Since 1 January 2017, screening for alpha and beta thalassaemia has also been added.

Once the WPG enters into force, entitlement under the Healthcare Insurance Decree can be annulled because the proposed article 12a of the new legislative proposal for the WPG will also apply to public bodies and the NHS will be part of the care provided pursuant to that article.

If further disorders are added to the NHS before the WPG comes into force, the BES Health Insurance Decree will need to be amended accordingly. Any such a change should be announced to the administrations of the islands six months in advance, as was the case with the addition of the alpha and beta thalassaemia.

11.5 Quality policy and professional training

11.5.1 Quality policy

In the original instructions, it was agreed that the Centre for Population Screening would publish an 'NHS-CN Manual' and develop the associated protocols for the implementation of the neonatal heel prick screening programme in the CN, where those arrangements differ from the agreements that apply in the European Netherlands.¹⁴ These differences concern the neonatal heel prick screening process, quality requirements and the responsibilities of the chain partners in the CN. Other than that, the national manual for the neonatal heel prick screening will also apply to the CN.

The NHS-CN Manual will need to be adapted where the heel prick expansion will result in a change in the tasks and responsibilities with regard to the CN.

11.5.2 Pilot shipments

For the expansion of the heel prick programme, it will be important to verify whether it is necessary to set up a pilot shipment during the implementation phase using already completed heel prick cards in order to test whether the high temperatures and air humidity in the CN affect the reliability of the analyses carried out in the screening laboratory in relation to the disorders to be added.

11.5.3 Subsequent care

Good quality across the entire chain, with a particular focus on coordination with care, is important. When adding a new condition to the heel prick screening programme, it is important that a follow-up protocol is developed for the diagnosis route and the treatment of children in the CN with an abnormal heel prick test result. This protocol will be established in partnership with doctors in the CN and the relevant ANS-NVK in the European Netherlands. One point that will need to be clarified is whether diagnostics and treatment can take place (in part) on the island itself, or where this should be carried out if it cannot be done

¹⁴ This may take the form of a CN checklist.

locally or regionally. It is important that this follow-up protocol, as a prescribed care path, is approved in writing and confirmed by the BES Healthcare Office and by the Ministry of Health, Welfare and Sport before screening actually begins. This will require close consultation and coordination between the various parties involved.

11.5.4 *Contracts and cooperation agreements*

RIVM will sign a cooperation agreement with the regional coordinator in the CN and the implementer. This agreement will include all the terms agreed between the three parties regarding the neonatal heel prick screening programme in the CN in terms of tasks and responsibilities, quality requirements, expertise regarding the implementation of the heel prick, data logging and data exchange. It will be important to verify whether any parts of the cooperation agreement still need to be adapted as a result of the expansion of the heel prick.

11.5.5 *Professional training*

Obstetric care providers and screeners on the islands will need to be updated in good time about the expansion of the programme.

When SCID is added, this will mean that a new group of disorders is included within the heel prick screening: immune deficiencies. This group will be covered separately in informational material.

For X-ALD, too, separate attention will probably be needed in relation to professional training. Professional training in the CN will be coordinated and matched as closely as possible to that in the European Netherlands. For further information, see section 7 on Quality Policy, and paragraph 7.4 on Professional Training.

11.6 **Communication and information**

Information for primary target group

The expansion of the heel prick screening programme will affect information and communication for parents and parents-to-be in the CN. This will follow the changes required in the European-Dutch programme.

When adding new disorders, adaptations will be needed to the leaflet entitled 'Screening for New-Borns' for the CN, as well as the product for those with low-literacy.

The outbound letters sent to parents in the event of an abnormal result for the new disorders will need to be drafted with an additional overlay sheet for the CN.

Information and communication resources for professionals

Minimal adaptations will be required to the materials for the CN, in line with those for the European Netherlands, or in the specific materials for the CN.

In addition to the specific materials for the CN, the professionals will often use the same information as the professionals in the European Netherlands, such as the websites and the national manual. For adaptations to these materials, see section 8 on Communication and Information.

11.7 Data management

The expansion of the heel prick screening programme will not have significant implications for data management in the CN. The system of electronic birth registration will not require adaptation. If a child with an abnormal result is first seen by a paediatrician, the medical adviser at RIVM will register this information in NEORAH, the digital data system under the responsibility of the NVK and the Centre for Population Screening. All diagnostic data from children who are referred following an abnormal result will be logged by the relevant paediatrician in this system.

False negatives will be logged by the Dutch Signalling Centre for Paediatrics (NSCK) at the NVK. For the CN, this will be done by the relevant paediatricians in the European Netherlands.

Extending the heel prick programme will thus mean an expansion of the duties of the medical adviser regarding the registration of abnormal results in NEORAH for children from the CN who are referred.

11.8 Monitoring and evaluation

For the expansion of the heel prick screening, it may be necessary to monitor components with a higher frequency, so that it is possible to respond swiftly to any problems or unintended effects, and so that coordination between the population screening and the care system can be improved. In addition, the two implementation phases of the extension must be taken into account. This also applies to the CN.

Extra care will continue to be needed with regard to the completeness of the sets from the CN and the number of initial heel pricks repeated in the CN. The amount of blood taken will become more important as more disorders are added. More disorders will need to be detected with the same number of blood spots; this means that more punches will have to be taken from the blood spots in the laboratory than is currently the case. If the blood collected on a heel prick card is not of sufficient quality, the first heel prick will be repeated, which will be reflected in an increase in the number of initial heel pricks that need to be repeated.

Annual monitoring and evaluation of the heel prick screening programme in the CN

In 2017, the first public and professional monitor of the heel prick screening programme in the CN will be published covering the period 2014-2016. When it comes to expanding the heel prick screening programme, information about screening for the new disorders will be included in the CN monitor for the year in which the heel prick was expanded.

11.9 Conclusion

The main focus points for the CN are the question of whether it is necessary to send test shipments to discover whether particular disorders can be reliably analysed for new-borns from the CN.

Furthermore, the development of specific follow-up protocols for diagnostics and care for children with abnormal results merits extra attention.

12 Implementation

This section describes how the expansion of the programme can best be implemented. The preparations required will also be outlined. Before preparations begin, an action plan will be drawn up outlining the activities, tasks and responsibilities. This section also describes who will carry out the activities mentioned.

The requirements formulated in previous sections have been taken as the starting point. After a short paragraph on the decision to proceed with the extension (paragraph 12.1), the section continues with a description of the timeline as the Centre for Population Screening currently sees it (12.2). After a paragraph explaining the various phases that will be required to achieve full implementation (paragraph 12.3), the activities relevant to the various phases are discussed in paragraphs 12.4, 12.5 and 12.6. Potential risks that may impede proper preparation or the introduction will also be outlined.

12.1 Decision to proceed

The Minister for Health, Welfare and Sport will decide on the extension of the neonatal heel prick screening programme based on the results of this feasibility study. The timeline shown in Figure 7 is based on a positive decision by the ministry in the autumn of 2017, and a decision to proceed with the next steps of implementation. Any postponement of a decision will result in a delay in the timeline shown.

12.2 Timeline

Section 3 describes which studies are required for each of the disorders that will be added to the heel prick screening in the years to come. When drafting the proposed timeline, the experts did not explicitly take into account the staffing capacity required in the screening laboratories to carry out multiple pilot studies simultaneously. Neither was the available capacity of specialist diagnostics and care, nor that of the implementing organisations taken into account.

From the studies, in combination with the ability to meet the requirements, the following timeline has been derived for the period up to and including 2022. The relevant parameters include the availability of personnel in, for example, the laboratories and for the other activities of the various parties specified in this feasibility study.

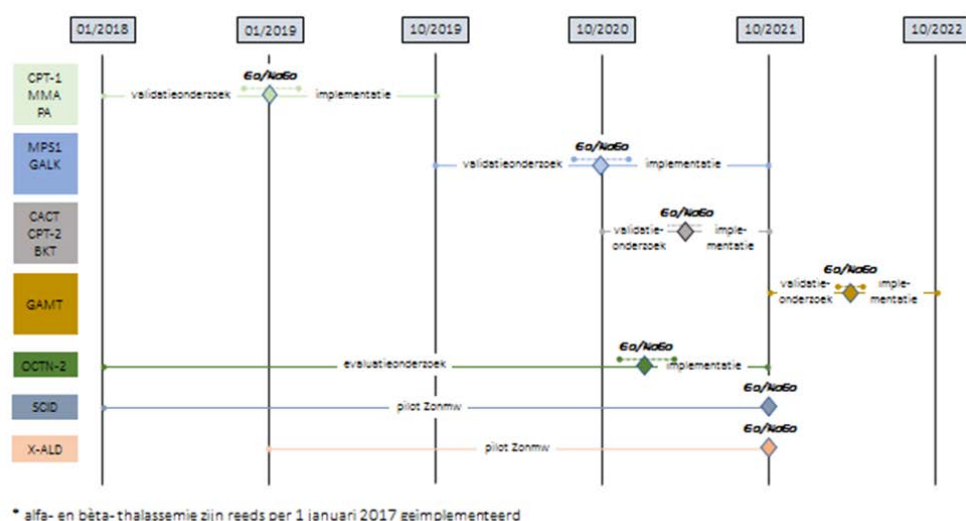


Figure 7: Timeline for studies and implementation of new disorders

Validatieonderzoek	Validation study
implementatie	implementation
Evaluatieonderzoek	Evaluation study
Pilot Zonmw	Pilot Zonmw
Alfa- en bèta-thalassemie zijn reeds per 1 januari 2017 geïmplementeerd	Alpha and beta thalassaemia already implemented on 1 January 2017.

For most disorders, at a minimum validation studies are required, either using the current method or a new method to be purchased, whether first or second tier. This will involve validation of the test(s) for the relevant condition. This includes research regarding the normal values and cut-off points for the test parameters to be used; sometimes research will be required in relation to the optimum test parameters. Close involvement will be required from the screening laboratories. After each of the validation studies, there will be a 'go/no-go' decision. At these points, a decision will need to be made on whether the relevant condition is ready to proceed further in the implementation phase, whether further research is required, or whether the condition is not ready to be added (at that time) to the heel prick screening programme.

For OCTN2, an evaluation study will be required (also see section 3), and after that research there will be a go/no-go decision. For SCID (also see section 4), a pilot study will take place in the next few years. After that, there will be a go/no-go decision as well. And an extensive pilot study will also take place for X-ALD, followed by a go/no-go decision.

Implementation at the end of 2019 now seems feasible for CPT1, MMA and PA. MPS I and GALK will follow at the end of 2020. And by the end of 2021 the introduction of CACT, CPT2 and BKT is planned, as well as OCTN2, SCID and X-ALD. Finally, this will be followed at the end of 2022 by GAMT.

The turnaround times and above timeline have been significantly influenced by factors relating to the implementation of the current programme and external factors, and will most likely continue to be subject to change (faster or slower for different disorders) in the coming years.

The criteria for the go/no-go decision will be described in the plan of action for the expansion of the programme (see 12.3).

The aforementioned timeline is relevant to both the European Netherlands and the Caribbean Netherlands.

The validation phase will be followed by the implementation phase. During this phase, all the processes required to add the new conditions will be established, including providing all the necessary materials, professional training, etc. It will also be important to test the entire chain.

Following the introduction, the additional disorders and the associated processes will be closely monitored, including any disruptions to the existing programme. Adaptations will be made where necessary.

12.3 The various phases

Based on a positive decision to expand neonatal heel prick screening, four phases for each disorder or cluster of disorders will follow.

Plan of action for the expansion

The expansion of the heel prick screening programme to include the proposed disorders will be a far-reaching and complex process. The first step will therefore be to draw up a plan of action including a description of all the relevant activities, tasks and responsibilities in general terms, and to set up the organisation required for implementation. During implementation, further insights will come to light that may influence the subsequent process and the order in which activities need to take place. Establishing a communication plan and a plan of action for professional training will form part of this general plan.

The plan of action will be a 'living document', which will be constantly updated by the Centre for Population Screening, in consultation with chain partners.

The preparatory phase for each disorder or cluster of disorders

The preparatory phase will involve developing and setting up all the processes, quality requirements and products that are required to execute the expansion of the population screening properly (see paragraph 12.4).

The validation studies, pilot studies and evaluation studies will also be carried out during this phase.

Phased introduction for each disorder or cluster of disorders

The various disorders that are part of the expansion of the population screening will be added in phases (see 12.2 for the timeline that is currently expected).

Complete introduction of extension of neonatal heel prick screening programme

In this phase, the expansion of neonatal heel prick screening to cover all disorders or clusters of disorders will have been fully implemented.

12.4 Preparing for the expansion

In broad terms, the following matters will need to be addressed during the preparatory phase:

- prepare for/set up primary process
- redesign organisation and implementation;
- redesign quality policy;
- redesign communication and information;
- redesign data management;
- redesign monitoring and evaluation;
- review implementation costs and financing programme;
- complete tenders.

12.4.1 *Prepare for/set up primary process*

Section 5 describes which adaptations are necessary to the primary process and the relevant steps to be taken. During the preparatory phase, further detail will be added by the various parties and working groups regarding:

- Setting up a validation study for each condition. This will involve conducting research into the normal values and cut-off limits for the test parameters to be used. Sometimes research will be required regarding the best test parameters and, in addition, specific questions will need to be answered for certain disorders.
- Setting up screening laboratories and logistics: drawing up a plan of action for each of the disorders to be added in relation to the adaptations required to equipment, the purchase of new equipment, the use of that equipment, and the use of any new testing methods. This may also have implications for the regular programme, such as the introduction of an automated TGAL assay for the current screening for galactosaemia.
- The use of an in-house testing method: based on the results of research into the use of an in-house test method, draw up a plan of action regarding the logistical arrangements for screening for GAMT.
- Sex-specific screening: conduct research into scenarios in which only boys are tested on the basis of the sex reported on the heel prick card versus anonymous testing or only determining the sex and identity of the child after a positive result for X-ALD.
- Investigate options for using R4S and CLIR: carry out research into the use of the CLIR post-analytical tools database in order to improve the performance of the existing programme and improve the predictive value of the individual screening results obtained using MS/MS analysis for a number of new disorders, with a view to fewer false positive referrals.
- Investigate options for selective extra heel prick: further research into the pros and cons of a (selective) extra heel prick for MPS I, MMA and PA.
- Optimise the quality of the blood spots on the heel prick cards: establish plan of action for evaluating this in 2018. Take

additional steps if necessary, based on the results of this evaluation. The usefulness of the current duplicate analyses in the regular programme will also be examined by the reference laboratory.

- Ensure coordination with healthcare: make agreements with the parties involved regarding good coordination with care with regard to the capacity and expertise required.

12.4.2 *Redesign organisation and implementation*

Section 6 describes the proposed organisational structure. In the preparatory phase, a number of issues will be developed in greater detail and/or carried out by various parties and working groups. This includes a further elaboration of the consequences of the expansion of the heel prick for the tasks and capacity of:

- the national-level management of the national heel prick screening programme (Centre for Population Screening);
- regional implementation and coordination (DVP);
- the RIVM reference laboratory;
- the national Programme Committee and its working groups;
- the implementing organisations (including screening laboratories and screeners);
- patient organisations;
- parties in healthcare.

12.4.3 *Redesign quality policy*

Section 7 describes the quality policy required for the introduction of the proposed population screening. During the preparatory phase, further detail will be added by various parties (such as professional groups) and working groups. This will relate to:

1. Required changes to the temporary article of the WPG if this is not yet effective when adding the new disorders to the heel prick programme.
2. Adaptations to the national (policy) frameworks where necessary.
3. Adaptations to contracts with screening laboratories and cooperation agreements with local Youth Health organisations if necessary.
4. Drafting plans to update guidelines and care paths for the professional groups involved, and then adapting the guidelines and care paths in consultation with them.
5. Drafting national quality requirements and working methods.
6. Reorganising national quality assurance by the national reference laboratory.
7. Announcing the applicability of guidelines and methods for the population screening.
8. Adapting the national manual and e-learning programmes for screeners.
9. Drafting and implementing plan of action for professional training.

12.4.4 *Redesign communication and information*

A communication plan will be drawn up with regard to communication and information for parents and parents-to-be, professionals and relevant organisations. Here, there will be an explicit focus on planning the revision of existing products and developing new products, in

accordance with the phasing of the disorders to be added. Communication regarding this to parents, professionals and stakeholders will also be considered. It will also need to be verified whether the current method of providing informed consent is adequate.

12.4.5 *Redesign data management*

During the preparatory phase of implementation, the following areas will need to be considered, in cooperation with the WIKNHS among others:

- Replacing Praeventis and the LIMS laboratory data system in order to be able to complete the expansion and make the desired adaptations for the new disorders.
- Plan of action for specifications in relation to data management and the monitoring of preparatory pilot studies, in particular regarding SCID in relation to the start of the pilot in 2018.
- Changes to data systems for the registration of follow-up care and children who have been missed: NEORAH, DDRMD and NSCK.

12.4.6 *Redesign monitoring and evaluation*

During the preparatory phase of implementation, the following areas will need to be considered, in cooperation with the WIKNHS among others:

- Adapting and developing the current national set of indicators. This relates to indicators for quality assurance, national (short-cycle) monitoring and evaluation.
- Development of the data set as the basis for the set of indicators.
- Setting up short-cycle monitoring.

12.4.7 *Review implementation costs and financing programme*

Section 13 describes the expected structural implementation costs and the proposed financing. The following activities will be carried out during the preparatory phase in order to adapt the financing of the programme:

1. Preparing and deciding on remuneration for implementing organisations and implementing parties, based on the tariffs.
2. Adapting the macro financial framework for the funding of the neonatal heel prick screening programme.
3. Monitor and if necessary follow up on parameters for good coordination with healthcare (in relation to the capacity and expertise required, among other things).

12.4.8 *Completion of tenders*

During the preparatory phase, tenders will be conducted for new testing methods, the heel prick lancet and possibly equipment. Furthermore, the part of Praeventis required for the NHS is expected to be held for tender in 2017. In 2018, preparations for the tendering process will be made for the screening laboratories.

The tendering procedure will consist of the following steps:

- Establish project organisation and set up plan of action
- Determine tender strategy and define provisional requirements.
- Prepare tender, including possible exploration of the market.
- Conduct the tender.

The choice of a contractor, for each individual tender, will be based on the chosen procurement strategy and the various responsibilities of the parties involved. In a phase of innovation and preparation for implementation, the contracting organisation will usually be the Centre for Population Screening, where this concerns tenders for new testing methods and contracting screening laboratories, based on its leading role within the programme. These tenders will be prepared and carried out in close coordination with the other parties involved (such as the DVP, IDS and Procurement Implementation Centre (IUC) of RIVM). The tender for renewal of Praeventis will be carried out by the DVP, in close coordination with the Centre for Population Screening.

12.4.9 *Risks during the preparatory phase*

The introduction of the phased expansion of the heel prick programme will be an extensive undertaking. This is the expansion of an existing programme through the addition of a large number of complex, rare disorders.

During the preparatory phase, the following risks will be relevant in relation to realisation and the start of implementation:

- Insufficient availability and capacity among the parties involved
A large number of parties will be involved in the preparatory phase. These parties are often made up of the same people who are also closely involved in the regular programme due to their expertise and experience. Sometimes, they are small groups of highly committed professionals who play an important role in the diagnosis and treatment of children and are therefore closely involved with the national programme. Collaboration between all parties will be paramount in order to complete preparations for the introduction in a timely manner. In addition, there is a high number of disorders to be added to the programme and there are still complex processes that need to be worked on in parallel, often by the same parties and professionals.
- Discontinuity within the regular programme
The current programme must be able to continue operating at the same level of quality, even though the extension of the heel prick screening programme will demand a great deal of attention from many of the parties involved in it, such as the screening laboratories, reference laboratory, ANS-MZ, national and regional coordination.
- Inadequate coordination with care
The ANS-MZ has asked for particular focus (see appendix 13) on the need for agreements regarding adequate capacity and expertise in care services for the relevant metabolic disorders, so that it is possible to develop guidelines, protocols and follow-up evaluation research into metabolic disorders. This is covered separately in 12.4.10.
- Insufficient (or late) funding for pilot studies, validation studies, evaluation studies.
- (European) tenders
A number of activities will need to be put out to tender, such as testing methods, IT systems, equipment and the laboratory function. Unforeseen complications (often relating to legal matters) may arise regarding tenders, which may cause delays.

- Data management and data exchange
Currently, Praeventis is being replaced across RIVM. This is the data system that supports NHS processes as well as the National Immunisation Program (RVP) and the PSIE programme. The new data system needs to be designed, put out to tender, specified and implemented. This will require a lengthy lead time. Unforeseen complications may arise, which may cause delays. The creation of links between Praeventis and other source systems (LIMS and NEORAH) in order to ensure that the right data is available for monitoring and evaluation may also require a lengthy lead time. Currently, the new ICT system for the NHS is scheduled to be ready for production in mid-2019. For those disorders that can be added before mid-2019 and those pilot studies that will require support using Praeventis, an analysis will need to be carried out to verify whether they can be introduced using the existing Praeventis system.

12.4.10 *Expertise and treatment capacity for the relevant metabolic disorders*
Since 1 January 2017, the neonatal heel prick screening programme has involved screening for nineteen disorders. Thirteen of these are metabolic disorders. Eleven of the twelve disorders that will be added in the expansion are also metabolic disorders.

All these disorders are rare and serious. They cannot be cured, but they can be treated. Most of the disorders also have several variants. In the Netherlands, 15.2 paediatricians (FTE) are available to diagnose and treat children with metabolic disorders. This is done in close cooperation with laboratory specialists and analysts and specialist dietitians. Because specific specialist expertise is involved, the paediatricians in particular are frequently required to take action in relation to: wrongly referred children (false positive results) and reassurance of their parents, meetings with the parents of correctly referred children, the development of guidelines and follow-up programmes for new variants of (new) disorders, (inter-)national meetings with other specialists, working groups, researching long-term outcomes, supplying data for the DDRMD (Dutch Diagnosis Registration Metabolic Diseases) which is required for the proper evaluation of the process from screening through to diagnosis, and providing information about the programme. All this work demands a high degree of specific expertise and this may not undermine regular care for children with a metabolic disorder.

Currently, the metabolic paediatricians, laboratory specialists working at the metabolic disorder laboratories and dietitians for metabolic disorders are already experiencing serious capacity constraints with regard to the thirteen metabolic disorders that are already screened for. The expansion of the heel prick screening programme to include eleven more metabolic disorders will demand more capacity.

Expansion in 2007

In 2007, the neonatal heel prick screening was expanded through the addition of thirteen metabolic disorders, among others. A TDC is used to calculate the cost of diagnosis and treatment for each child referred. However, the additional tasks mentioned above, which metabolic paediatricians are often required to carry out, are not funded in this

way. In addition, the metabolic paediatricians have asked for structural training for five fellows for metabolic disorders.

Similar capacity problems among metabolic paediatricians were also reported and addressed in 2007. In response to these indications, the Ministry of Health, Welfare and Sport has allowed an annual amount of €2.7 million in extra financing for inpatient care for 2007 and later years, so that the outcome of local negotiations could lead to an increase in the budgets of the UMCs concerned (about €335,000 for each of the eight). Although this is the normal situation when treatments are added to the insurance package, it has been found in practice that the 'production agreements' between health insurers and hospitals have not led to the planned expansion of the necessary formation of metabolic paediatricians, laboratory staff and the like. The amount of financing provided in relation to the (limited) number of UMCs that provide this care and the scale of the overall financial agreements between insurers and hospitals and internally within the UMCs, has meant that these resources have 'evaporated' within the field as a whole. As a result, no capacity has been added for the additional workload that is generated alongside diagnostics and treatment.

This notwithstanding the letter that the Centre for Population Screening wrote to the Boards of Directors of the UMCs in 2006 to point out the agreements that had been made for the heel prick programme. Only direct patient care-related activities can be financed through 'production agreements', and not the preparatory activities (development of protocols and guidelines) or the design of the underlying organisation of care as part of the expansion of the heel prick screening programme. These activities will require a different type of financing.

Future expansion

Over the next five years, a further eleven metabolic disorders will be added to the neonatal heel prick screening programme. Paediatricians expect a multitude of children will be referred with false positive results during the first two years, who will need to undergo an extensive diagnostic process. The expansion involves disorders that have not yet been included in the heel prick screening programmes of other countries - even more so than in 2007. This means that the learning curve regarding these disorders will largely take place within the Netherlands, and this will obviously require extra time. The metabolic paediatricians believe that in addition to the annual amount of €2.7 million dating from 2007 (which has so far 'evaporated') an annual earmarked amount of €1 million will be required for this further expansion of the programme.

Possible solutions

At the beginning of March 2017, representatives of metabolic paediatricians, the Capacity Unit, the patient organisation VKS, the National Plan for Rare Diseases, NFU, NVK, ZonMw, the Ministry of Health Welfare and Sport and the academic hospitals discussed the bottlenecks they experienced and anticipate, as well as ideas on how to address these bottlenecks.

Various possible solutions were raised at this meeting. These are also outlined in the letter from the ANS-MZ (Appendix 13). The details of these solutions will need to be developed.

12.4.11 *Cost of the preparatory phase*

Before the (phased) introduction can begin, the activities described above will need to be prepared, set up and carried out. In addition to the project structure, good organisation, implementation and the financing of the programme within the parameters set by the Ministry of Health, Welfare and Sport (VWS), the new parties that may have a role to play will also need to be brought into the process. In addition, there will be costs for pilot studies, validation studies and evaluation studies, implementation costs in the laboratories for each new condition that is added, and implementation costs for the new Praeventis system and the new LIMS.

Investment will also be required for adaptations to the existing data systems to enable implementation, monitoring and evaluation to take place. An estimated cost overview is provided in Table 12. The costs described will be incurred by the Centre for Population Screening and the other parties that the Centre for Population Screening commissions to carry out additional work in relation to the expansion.

The one-off costs during the preparatory phase and during the phased introduction are summarised in Table 12.

Preparations for a number of disorders will occur in parallel with the phased introduction of other disorders (also see Figure 7 in paragraph 12.2). Table 12 therefore includes preparation for the entire first year, and combined preparation and phased introduction during the subsequent years.

Table 12: One-off costs during the preparatory phase and during the phased introduction are summarised in Table (in thousands of euro).

Working activities	Notes	Preparation	Preparation/ phased introduction	Preparation/ phased introduction
<i>Setting up</i>		<i>First year</i>	<i>Second - third years</i>	<i>Fourth - fifth years</i>
Project structure	Programme coordination, consultation, working groups etc.	200	400	400
Organisation and implementation	Oversight of phased introduction, costs of implementing organisation	586	1,543	973
Financing	Review of rates, advice and supervision of procurement	38	76	76
Communication and information	Adaptation, development and testing of products, customisation of websites	133	266	266
Quality policy	Quality requirements for each disorder, adjustments to the manual	156	312	312
Primary process	Implementation costs for laboratories, pilots and validation studies	290	3,243	1,603
Professional education and training	Plan of action and implementation of professional training, <i>e-learning</i>	116	262	232
Data management	Preparations for renewal of Praeventis and LIMS, changes to ICT systems ¹⁵	1,883	184	74
Monitoring and evaluation	Adaptation of indicators and dataset	21	42	42
Knowledge and innovation	Working visits, procedure for adding new disorders	25	50	50
Total implementation budget		3,448	6,378	4,228

¹⁵ This does not relate to investment in the renewal of Praeventis, but the costs incurred in relation to preparing for this investment.

12.4.12 *Caribbean Netherlands*

Section 11 describes the focus points for the CN in relation to the expansion of the heel prick screening programme. During the preparatory phase, a plan of action will be drawn up (see 12.3) and, where necessary, the required specific activities per domain will be included with regard to the CN. Particular attention must also be paid to coordination with care services.

12.5 **Phased introduction**

12.5.1 *Focus points during phased introduction*

Focus points during this phase are:

- professional education and professional training;
- Quality assurance, including more intensive monitoring of a number of indicators in order to be able to respond swiftly where necessary.

12.5.2 *Risks during the phased introduction*

After the start of the expansion of the population screening, the same risks may occur as during the preparatory phase (see 12.4.9).

12.6 **Knowledge and innovation**

It is important that the infrastructure of the heel prick programme can respond flexibly to future innovations. A number of parameters for future innovations must be put in place. The Centre for Population Screening will recommend the development of proposals on adding new candidate disorders to the heel prick screening programme, so that a timely decision can be made.

13 Costs

13.1 Introduction

This section focuses on the cost of implementing the expanded heel prick population screening programme. This will involve an increase in structural implementation costs. The costs associated with the implementation of the expansion itself are one-off costs, and are described in section 12 (Implementation).

The implementation costs presented are an estimate, and are based on a set of assumptions. The estimation of the costs is often based on an estimation of the required capacity and the expansion of that capacity in relation to existing capacity.

This section does not specify pricing. An independent consultancy firm has carried out research regarding the pricing structure for the implementation of the heel prick and the pricing structure for analysis in the screening laboratories, under the supervision of the temporary working group on finances. However, these fees will depend partly on the results of tenders, such as those for equipment. The actual costs will in part only be known after the completion of these tenders, and will also depend on the pace at which the population screening is expanded to include the additional disorders.

The implementation of the heel prick screening programme will be funded by central government. This is clarified further in paragraph 13.2. That paragraph also covers the existing pricing.

13.2 Financing and existing pricing for heel prick screening

The implementation of the heel prick screening programme has been funded by central government since 1 January 2015. Before that time, the programme was financed under the Exceptional Medical Expenses Act (AWBZ).

The programme currently has three prices: for the heel prick set, the implementation of the heel prick, and for laboratory analysis. The price of a heel prick set in 2017 was €3.62. For the implementation of the heel prick, the implementing party received a fee of €20.30 in 2017. The fee for the analysis of the heel prick blood in the laboratory was €50.62 in 2017.

Funding is provided using the method known as $p \times q$. A price set in advance by the Ministry of Health, Welfare and Sport for the transactions for each participating new-born ('p' for price) is multiplied by the number of new-borns ('q' for quantity).

The cost of logging data, distributing informational materials and regional coordination are part of the DVP's own organisational costs. At present, around €19.1 million is spent annually on the neonatal heel prick screening programme.

Referrals for diagnostics and treatment are funded as part of regular care through the Healthcare Insurance Act.

13.3 Principles relating to the cost of expanding the programme

The following points and principles are relevant to the expansion of the programme and the setting of new prices:

- It is based on the primary process and organisation described in sections 5 and 6.
- The number of new-borns is based on the numbers from Statistics Netherlands for December 2016.
- The participation percentage is based on the participation rate in the 2015 monitor (99.3%).
- The expansion will be phased in. The phasing indicated in chapter 12 has been used to calculate the costs for the various years.
- The activities and the capacity of the laboratories after each phase of the expansion are based on a calculation made by the laboratories for the benefit of the working group on finances, as well as the assumptions regarding the quantity of equipment required from section 3.
- Tenders will be announced for equipment (LC-MS/MS and other equipment). The actual costs of the tests can only be estimated after these tenders have taken place.
- The costs associated with the reference laboratory have also been included.

13.4 Forecast of annual costs

The following chart shows the total cost of implementing the heel prick screening, including the current costs of the programme.

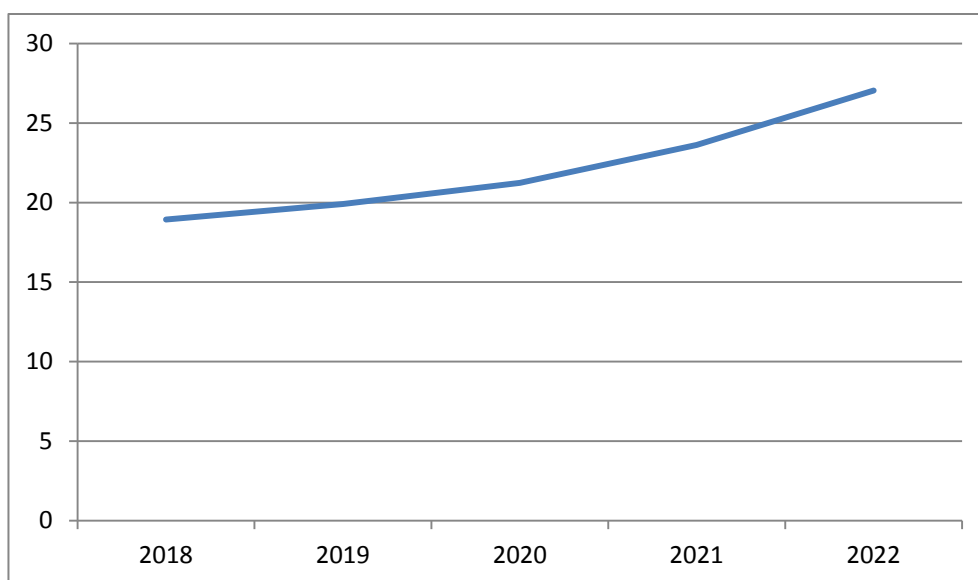


Figure 8: Forecast of annual costs for the implementation of neonatal heel prick screening (in millions of euro)

The structural annual costs will increase from approximately €19.1 million in 2017 to €19.9 million in 2019 and €27.0 million in 2022. The cost per heel prick will also rise from approximately €105.20 in 2017 to €144.10 in the year 2022.

The above estimates are based on the phased introduction of the various disorders, as described in section 12.

The addition of MPS I means an additional LC-MS/MS device will need to be purchased (also see 3.3).

The increase in structural costs resulting from the new LIMS and nwPraeventis is also included in the above forecast.

13.5 Conclusion

The main conclusions of this section are:

- The structural annual costs will increase from approximately €19.1 million in 2017 to €19.9 million in 2019 and €27.0 million in 2022.

14 Key points and advice

14.1 Introduction

In the Netherlands, almost all new-born babies (approximately 175,000 per year) are currently screened using the heel prick for cystic fibrosis, sickle cell disease, adrenogenital syndrome, congenital hypothyroidism and thirteen metabolic disorders. These disorders cannot be cured, but they can be treated. Around 200 sick children are identified every year from among those tested; around 800 children are referred due to abnormalities revealed by the heel prick test. In addition, each year some 800 children are identified as carriers of sickle cell disease.

On 8 April 2015, the Health Council of the Netherlands (HC) recommended adding fourteen further disorders to the screening programme in its 'Neonatal screening: new recommendations' advisory report.

The Centre for Population Screening has set up this feasibility study at the request of the Ministry of Health, Welfare and Sport. The feasibility study involves research into the feasibility of implementing the screening for fourteen new disorders in the neonatal heel prick screening, and the parameters within which this expansion could take place.

Based on the results of the feasibility study, the Minister for Health, Welfare and Sport will make a decision regarding the expansion of the neonatal heel prick screening programme.

In order to carry out the feasibility study, the minister asked for priority to be given to the addition of, among other things, the disorders of alpha and beta thalassaemia, which were reported as an incidental finding in 2015. Screening for alpha and beta thalassaemia has already been implemented, on 1 January 2017.

14.2 Preliminary research into feasibility and timeframe for introduction

The Centre for Population Screening has had a number of preliminary studies carried out. The purpose of these preliminary studies was to gather additional information regarding feasibility and the parameters for including the new disorders in the neonatal heel prick screening programme.

A preliminary study into feasibility and the timeframe for introduction was necessary to acquire further insight into the availability, quality (clinical validity), reliability and practical applicability of the testing method as well as the implications for follow-up healthcare.

An evaluation framework was developed and, subsequently, groups of external experts were set up for each disorder or group of disorders. Based on the evaluation framework and the (international) literature reviewed, the expert groups advised the Centre for Population Screening whether and when each disorder could be added to the heel prick screening programme. The expert groups also indicated which actions

would need to be carried out, such as which research (validation, pilot, evaluation) is still required.

14.3 Conclusions of preliminary studies

The preliminary studies produced the following conclusions:

- The conditions to be added are rare or very rare. Between 20 and 40 children with one of these disorders are expected to be identified annually, in total.
- A primary or first-tier screening test is available for all conditions. For almost all the disorders, the implementation of the first-tier test alone would lead to a significant number of false positive referrals.
- For most of the disorders, a second-tier test would be necessary, and possibly even a third-tier test, to reduce the number of false positive referrals. For CACT and CPT2 there is no second-tier test, however, and for MMA and PA, problems concerning the second and third-tier tests have yet to be resolved. Neither can all of the tests be applied in a screening setting (GALK and MPS I require whole blood).
- In addition to the issue of false positive results, false negative test results are another issue for a number of the disorders to be added to heel prick screening. This concerns BKT and OCTN2.
- A number of expert groups (CACT/CPT2, BKT, MPS I, MMA/PA and OCTN2) as well as the programme committee for the neonatal heel prick screening programme have advised using Region 4 Stork (R4S) and Collaborative Laboratory Integrated Reports (CLIR) post-analytical tools, in order to minimise the number of false positive results. Before these post-analytical tools can be used for the neonatal heel prick screening, however, a number of important questions will need to be answered regarding effectiveness, efficiency, continuity and privacy and so on.
- Some of the first-tier tests may require adjustments to logistical and laboratory organisation, which still require further study (in-house test GAMT, sex-specific screening X-ALD). For a number of disorders, there will also be consequences for the purchase of equipment and the layout of the laboratories (extra LC-MS / MS equipment for GAMT and MPS I). It is expected that most second and third-tier tests can be carried out using the existing infrastructure of the screening laboratories. For GAMT, BKT and X-ALD this has yet to be determined definitively, however.
- In relation to all disorders, further research is required before the introduction of screening can proceed. The expert groups have formulated research questions that relate to validation studies and/or supplementary studies and the implications for laboratory logistics. The validation studies concern research regarding the normal values and cut-off points for the test parameters to be used; sometimes research will be required in relation to the optimum test parameters. Close involvement is required from the screening laboratories. The supplementary research concerns more scientific questions, such as effectivity. The involvement of ZonMw is preferable in order to carry out four of the research studies.

- A number of expert groups also drew attention to the importance of conducting a structural evaluation study on the new screenings (and those already introduced) to assess whether the effectiveness of the screening is adequate.
- In all cases involving non-treatable secondary findings, the HC has prioritised the health benefit of screening for the condition for the child concerned over the disadvantages for the child (and the parents), in the event of a secondary finding. This prioritisation was not questioned by the expert groups, with the exception of OCTN2.
- In order to realise the potential health benefits of screening, good integration with care and adequate capacity for diagnostics and good-quality treatment will be required. Before screening for a certain condition can be introduced, there must be clarity on the period within which referral and admission to a hospital should occur. Policy must also be developed regarding diagnosis and treatment, preferably in the form of guidelines and protocols proposed by the relevant professional group. An important development in relation to quality of care is the development of centres of expertise for rare diseases.
- Based on these questions that have yet to be answered and the research that will be required to do this, the various expert meetings estimated a minimum timeframe in order to ensure a responsible introduction of screening for the various additional disorders. Introduction in the period 2018-2019 for the screening of CPT1, GALK, MPS I, MMA, PA and X-ALD is currently considered feasible by the experts. For the other disorders, more time will be needed for responsible implementation. The introduction of the screening for these disorders (CACT, CPT2, GAMT, BKT, OCTN2, SCID) is considered feasible for the period 2019-2021.

The main conclusions for SCID are:

- A good first-tier test for SCID is available; a second-tier test is required.
- A pilot study will be launched for SCID. The lead time for the pilot is expected to be two years.
- The conclusion of the cost-effectiveness analysis is that the costs per QALY gained almost correspond with the limit set for prevention in the Netherlands.

14.4 Timeframe for introduction

The advice of the expert groups on phasing differs in some respects from the HC's advice and the letter to parliament of the Minister. The reason for this is the change of insights in the light of the results of additional studies and developments occurring since the publication of the HC's advice in 2015.

RIVM wishes to make a number of comments regarding implementation according to the proposed timeframe.

When drafting the proposed timeframe, the experts took no account of the personnel capacity required in the screening laboratories to carry

out multiple pilot studies simultaneously, nor of the available capacity among metabolic paediatricians. The experts also assumed that there would be no financial limitations with regard to the implementation of the pilots and the supplementary research required.

It is therefore necessary to accurately estimate the turnaround times for the various simultaneous studies. In addition, the costs of the research and the financial resources available must also be estimated as quickly as possible. The same applies to the personnel capacity required and available in screening laboratories.

Furthermore, the proposed timeframe is, of course, dependent on the results of the various research projects. If the results of a study are inadequate, this may lead to the postponement or even the abandonment of screening for the relevant condition.

14.5 Complexity of introduction

Based on the preliminary study and its own knowledge and experience, the Centre for Population Screening is of the opinion that the intended expansion of the heel prick screening is a complex undertaking, due to the number of disorders, logistics and organisation in the laboratories, testing methods, validation studies and supplementary research that all need to be completed, and the required integration with the care system.

The expansion of the heel prick screening is also taking place in the context of the optimisation of the current screening. This includes, for example, improving the quality of the blood spots, tightening referral periods and preparing various tenders such as for the screening equipment, the laboratory data management system and the laboratories themselves. The existing data management system, Praeventis from the DVP, which handles (among other things) the implementation of the heel prick screening, must also be replaced. These changes to the heel prick screening programme are, to a large extent, conditional on the proper implementation of the expansion of the programme and may affect the proposed timeframe in a positive or negative way.

Finally, the expansion will have consequences for information and communication, professional training, data management, monitoring and evaluation in the current screening programme. The small changes required in relation to these and other aspects may prove complex and time-consuming.

14.6 The establishment of screening

The Centre for Population Screening has reached the following conclusions with regard to the various domains of the screening structure:

Primary process

- The current structure of the primary process is generally adequate. However, the preparation and implementation of the various changes would demand significant personnel capacity

from the organisations involved; this capacity is currently generally limited.

- The quality of the blood spots on the heel prick cards is expected to improve as a result of various improvement measures, and to be sufficient to enable the extension of the heel prick screening programme.
- In order to detect GAMT, the proposal is to use an in-house test. This will be challenging for the screening laboratories in terms of scaling-up and quality assurance.
- Testing for MPS I and GAMT will require the purchase of two additional LC-MS/MS devices per screening laboratory. Establishing one central laboratory for testing for GAMT would mean that only one LC-MS/MS would be required in each laboratory, plus an additional device at one laboratory (in all, six extra, compared to the current situation); this would also facilitate quality assurance, but would pose logistical challenges within the heel prick screening programme.
- The possibility of having to purchase additional LC-MS/MS equipment to carry out a number of second-tier tests cannot be excluded. This will need to be investigated further.
- Sex-specific screening, as proposed for X-ALD, is not easy to put in place within the current programme and will require extensive study and preparation. Introduction in the period 2018-2019, as proposed in the preliminary studies, is therefore probably not feasible.
- The use of post-analytical tools may reduce the number of false-positive test results. Research will need to be carried out to establish whether the use of these tools can be implemented effectively, efficiently and legally.
- The turnaround times for the various steps in the process need to be specified. This also applies to the prioritisation of laboratory tests in cases where the quality of the blood spots on the heel prick card is not adequate.

Organisation, tasks and responsibilities

For almost all the organisations involved in the heel prick screening programme and their respective tasks, adding a new condition or starting a pilot study for a new condition will have significant consequences. The most significant effect will be on the reference laboratory, screening laboratories, the DVP (implementing organisation), the Centre for Population Screening, and diagnostics and care.

Quality policy

- The expansion of the heel prick screening programme will mainly affect quality assurance at the screening laboratories and the reference laboratory, the implementing organisations, and the required specialist diagnostics and care.
- Organising professional training meetings will be necessary, focusing on the professionals involved in the screening programme, prior to the start of a pilot study and prior to the phasing in of the different disorders to be added.

Communication and information

Almost all information and communication resources will need to be adapted. Additionally, new material will need to be developed to include disorder-specific information about the conditions to be added to the programme.

Data management

- To overhaul the provision of data for the neonatal heel prick screening, a programme and project have already been launched in anticipation of the expansion of the programme: the Praeventis Renewal Programme (PvP) and the Laboratory Data System Replacement Project (NHS-LIMS).
- Once the timetable for the introduction of screening for the new disorders and the associated testing methods becomes clearer in more detail, as well as the details of possible validation studies and prospective pilot studies, it will be necessary to consider whether the new NHS data system (nwPraeventis) and NHS-LIMS are available, whether to adapt Praeventis and/or NEONAT for each condition, or whether to search for other alternatives.
- The quality of the blood spots on the heel prick cards is expected to improve as a result of various improvement measures, and to be sufficient to enable the extension of the heel prick screening programme.
- This will require a great deal of flexibility from the ICT functionality, which must be available to prepare for the introduction of a new condition in good time.

Monitoring and evaluation

- Due to the low prevalence of these conditions, short-cycle monitoring will be needed for several years.
- The number of referrals and the number of repeated first heel pricks will be subject to short-cycle monitoring.
- The outcomes of diagnostics and the timeliness of diagnostics will also have to be closely monitored.
- The quality of the blood spots on the heel prick card will need to be monitored closely in order to respond to any issues in this regard.
- The development of new indicators in order to monitor the primary process properly will be necessary.
- New target and signal values will need to be developed for the new conditions.

The Caribbean Netherlands

- The main focus points for the CN are the question of whether it is necessary to send test shipments to discover whether particular disorders can be reliably analysed for new-borns from the CN.
- Furthermore, the development of specific follow-up protocols for diagnostics and care for children with abnormal results merits extra attention.

Costs

The structural annual costs will increase from approximately €19.1 million in 2017 to €19.9 million in 2019 and €27.0 million in 2022.

14.7 Implementation

Assuming a positive decision on expanding the neonatal heel prick screening programme and that RIVM is commissioned for the subsequent development of this expansion, four phases for each disorder or cluster of disorders will follow: drawing up a plan of action; a preparatory phase; and the phased introduction and full implementation of the expansion of the neonatal heel prick screening programme.

During implementation, further insights will come to light that may influence the subsequent process and the order in which activities need to take place.

One important focus point during implementation will be the validation studies, pilot studies and evaluation studies (see 12.2). Following each component, a decision will need to be made on whether the relevant condition is ready to proceed further in the implementation phase, whether further research is required, or whether the condition is not ready to be added (at that time) to the heel prick screening programme.

The following risks will be relevant during the preparatory phase and during phased introduction:

- Insufficient availability and capacity among the parties involved;
- Insufficient (or late) funding for studies;
- Inadequate coordination with care services;
- Discontinuity in the regular programme;
- Tenders;
- Data management and data exchange.

The costs of the implementation will be €14.05 million over a period of five years. These costs are made up as follows: €3.45 million in the first year, €6.38 million in the second and third years combined, and €4.22 million in the fourth and fifth years combined.

14.8 Advice

The feasibility study shows that the phased expansion of neonatal heel prick screening programme to include fourteen additional disorders, as advised by the HC, is possible. In 2017, alpha and beta thalassaemia were already added to the programme.

There is sufficient support among the parties involved for further expansion. The broad public acceptance of the neonatal heel prick screening must not be undermined by (preparations for) the expansion of the programme. This will necessitate careful implementation.

A primary or first-tier screening test is available for all the conditions. For most of the disorders, a second-tier test would be necessary, and possibly even a third-tier test, to reduce the number of false positive referrals.

The expert groups noted that further research is necessary in relation to all disorders before the introduction of screening can take place.

The various disorders that are part of the expansion of the population screening programme will be added in phases to the programme.

Implementation at the end of 2019 now seems feasible for CPT1, MMA and PA. MPS I and GALK will follow at the end of 2020. And by the end of 2021 the introduction of CACT, CPT2 and BKT is planned, as well as OCTN2, SCID and X-ALD. Finally, this will be followed at the end of 2022 by GAMT.

The turnaround times and the above timeline have been significantly influenced by factors relating to the implementation of the current programme and external factors (see parameters, in the following section), and will most likely continue to be subject to change (faster or slower for different disorders) in the coming years.

The Centre for Population Screening emphasises once more that the intended expansion of the heel prick screening is a complex undertaking, due to the number of disorders, logistics and organisation in the laboratories, testing methods, validation studies and supplementary research that all need to be completed, and the required integration with the care system.

The disorders that will be added are rare and have not yet been included in the screening package by many other countries. This means that limited knowledge is available at the international level. The addition of these disorders to the Dutch programme will therefore be complex.

Proper preparation of the phased expansion of the programme will be necessary to design and implement the required adjustments. From the start of the phased expansion, monitoring of the quality and continuity of the screening programme and of subsequent care will be important.

The following parameters will be essential to the expansion:

- The activities referred to in this report in preparation for the expansion of neonatal heel prick screening programme must all be completed before the phased expansion can begin.
- For each condition that is added, the required research (validation, pilot or evaluation studies) must first be completed, and a minimum preparatory period of one year applies in all cases.
- The proposed timeframe is therefore subject to sufficient personnel capacity and funding availability for the validation, pilot and evaluation studies.
- Achieving the structural addition of the conditions will depend on sufficient personnel capacity and funding availability for all the organisations involved.
- The availability of flexible ICT functionality that can be implemented according to the specifications for each condition is also essential.
- Preparations for introducing the additional disorders will need to be made in accordance with the applicable laws and regulations with regard to, for example, procurement law.
- The quality of the regular neonatal heel prick screening must not be undermined by the expansion of the programme.

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On behalf of the authors,
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Glossary

Additional heel prick	An additional heel prick carried out at a later moment; different from a repeated initial heel prick and a second heel prick
False negative	A child who does have a disorder but is not referred for care following the results of the screening
False positive	A child who does not have a disorder but is referred for care following the results of the screening
Repeated initial heel prick	If the 'quality of the blood spots is insufficient', the heel prick must be repeated. To avoid confusion with the term 'second heel prick', we speak of a repeated initial heel prick
Quality of blood spots	The quality of the blood spots is good if sufficient blood of reliable quality is collected on the filter paper
Screeener	The person who performs the heel prick
Screening laboratory	Laboratory that performs the screening test
Second heel prick	In the case of a non-conclusive result, a second heel prick is carried out.
Obstetric care provider	Midwives, GPs who provide obstetric care and gynaecologists.
First-tier test	Primary test
Second- and third-tier test	Additional tests that are necessary to reduce the number of false positive test results

Abbreviations

List of general abbreviations

CN	The Caribbean Netherlands
DVO	Service provision agreement
HC	Health Council of the Netherlands
JGZ	Youth healthcare services
KNOV	Royal Netherlands Organisation of Midwives
LC-MS/MS	Liquid Chromatography tandem Mass Spectrometry
LIMS	Laboratory Data Management System
NHG	Netherlands College of General Practitioners
NHS	Neonatal heel prick screening programme
NPB	National Population Screening Programme
NVK	Netherlands Association of Paediatricians
NVKC	Netherlands Association of Clinical Chemistry and Laboratory Medicine
NVOG	Netherlands Association of Obstetricians and Gynaecologists
PNHS	Programme Committee for the neonatal heel prick screening programme
RIVM	National Institute for Public Health and the Environment
RIVM-CvB	Centre for Population Screening (part of RIVM)
RIVM-DVP	Vaccine Provision and Prevention Programmes (part of RIVM)
RIVM-GZB	Centre for Health Protection (part of RIVM)
RIVM-IDS	Laboratory for Infectious Diseases, Diagnosis and Screening (part of RIVM)
RIVM-IUC	The Purchasing Implementation Centre (part of RIVM)
VKGL	Association of Clinical Genetic Laboratory Diagnostics
VKGN	Netherlands Association of Clinical Genetics
VKS	Adults, Children and Metabolic Disorders
VKZ	Obstetric care provider
VSOP	Association of Collaborating Parent and Patient Organisations
VWS	Ministry of Health, Welfare and Sport
WIKNHS	Working Group for Data Management and Quality, Neonatal Heel Prick Screening Programme
WONHS	Working Group for Research, Neonatal Heel Prick Screening Programme
WVDNHS	Working Group for Information and Professional Training Promotion Neonatal Heel Prick Screening Programme
ZonMw	Netherlands Organisation for Health Research and Development

List of abbreviations of disorders

BKT	Beta-ketothiolase deficiency
CACT	Carnitine acylcarnitine translocase deficiency
CPT1	Carnitine palmitoyltransferase deficiency type 1
CPT2	Carnitine palmitoyltransferase deficiency type 2
GALK	Galactokinase deficiency
GAMT	Guanidinoacetate methyltransferase deficiency

MMA	Methylmalonic acidemia
MPS I	Mucopolysaccharidosis type 1
OCTN2	Organic cation transporter 2 deficiency
PA	Propion acidemia
SCID	Severe combined immune deficiency
TM	Beta thalassaemia major
X-ALD	X-linked adrenoleukodystrophy

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All appendices can be found on

www.rivm.nl/uitvoeringstoets_uitbreiding_neonatale_hielprikscreening

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