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Projectgegevens / Project information

Samenvatting / Summary

Nederlands
Severe combined immunodeficiency (SCID) is een ernstige erfelijke aandoening van het immuunsysteem, die in Nederland voorkomt bij 1 op de 40.000 pasgeborenen. Afhankelijk van het genetisch defect verloopt de overerving X-linked of autosomaal recessief. De eerste symptomen zijn ernstige (virale) infecties, slecht gedijen en diarree; de symptomen presenteren zich gedurende de eerste levensmaanden. Zonder behandeling (i.e. beenmergtransplantatie of gentherapie) overlijden deze patiënten in het eerste levensjaar. Het stellen van een vroege diagnose in de presymptomatische fase is essentieel omdat dit de kans op overleving aanzienlijk vergroot en zorgt voor minder morbiditeit.
De minister van Volksgezondheid heeft in 2015 ingestemd met de toevoeging van SCID aan de neonatale hielprikscreening, zoals voorgesteld in het rapport van de Gezondheidsraad ‘Neonatale screening - nieuwe aanbevelingen’. Daarvoor zou een zogeheten TREC analyse moeten worden toegevoegd aan het screeningsprogramma. SCID patiënten kunnen bij de screening

dan geïdentificeerd worden omdat zij weinig of geen TRECs hebben. Een diagnostisch vervolgtraject is nodig om de diagnose 'SCID' te bevestigen. Op deze manier wordt SCID kort na de geboorte gediagnosticeerd en kan behandeling snel worden ingezet. SCID screening is inmiddels in een groot aantal landen ingevoerd (o.a. in de meeste staten van de Verenigde Staten, Israël en Japan). In diverse andere landen (o.a. Zweden, Frankrijk, Spanje en Engeland) zijn uitgebreide pilot studies uitgevoerd.
Het doel van deze prospectieve pilot-studie is om een optimale implementatie van SCID screening mogelijk te maken door de testkarakteristieke en de praktische implicaties van de TREC screening te onderzoeken. Dit betreft logistieke implicaties (zowel ICT als analytisch), informatievoorziening, zorgtraject en nevenbevindingen, psychosociale aspecten en een beknopte analyse van zorgkosten.
Deze pilot screening zal worden uitgevoerd binnen de infrastructuur van het huidige screeningsprogramma, waarbij twee screeningslaboratoria en twee RIVM-DVP regiokantoren betrokken zijn. Er zullen 70.000 kinderen worden geïncludeerd, wat overeenkomt met een jaarlijkse workload van twee laboratoria.

Engels
Severe combined immunodeficiency (SCID) is one of the most severe inherited disorders of the immune system, with an estimated incidence in the Netherlands of 1:40.000 newborns. Depending on the genetic defect SCID has an X-linked or autosomal recessive mode of inheritance, both forms are characterized by absence of functional T-cells. The first symptoms are severe (viral) infections, failure to thrive, diarrhea, which present during the first months of life. Without curative treatment (i.e. a hematopoietic stem cell transplantation or gene therapy) these children die within the first year of life. Early diagnosis in the pre-symptomatic phase is crucial, because this increases the chance of survival greatly and results in a reduction of comorbidity.
The Dutch Ministry of Health in 2015 adopted the advice of the Dutch Health Council ('Neonatal screening: new recommendations') to add SCID screening to the neonatal screening panel. To that end a so-called "TREC assay" needs to be added to the panel of screening assays, as applied by the Dutch screening laboratories. (Semi-) quantitative measurement of TRECs (T-cell recombination Excision Circles) is used as a marker for the presence of T-cells. As SCID patients present with absence of T-cells, the TREC assay allows for the identification of these patients directly after birth. In case of absent or strongly reduced TRECs after screening, a diagnostic phase will be initiated to make the SCID diagnosis, followed by a treatment phase. The TREC assay has already been successfully implemented in several countries including most states of the United States, Israel and Japan (Barbaro et al., 2017). In several other countries (e.g. Sweden ,France, United Kingdom and Spain) extensive pilot studies have been performed successfully.
The main aim of this prospective pilot study in the Netherlands is to enable a flawless implementation of newborn SCID screening by studying test qualities with special reference to the Dutch screening population. These include including logistic implications, both ICT-wise as well as analytical, concise cost-effectiveness, and practical implications covering diagnostic and clinical follow-up issues, including unintended findings, and estimation of the true incidence/prevalence of SCID,
This pilot screening is set up as a screening performed using the infrastructure of the screening program, with the involvement of two screening laboratories and two RIVM-DVP regional offices. We will include 70.000 children in this pilot study which approximates the yearly workload of two laboratories.

Trefwoorden / Keywords
Severe combined immunodeficiency (SCID), newborn screening, neonatal screening, heel prick, TREC

Samenwerking / Collaboration

Samenwerking tussen onderzoek en praktijk / Cooperation between research and practice:
Ja / Yes

Inhoud / Content

Probleemstelling / Problem definition
SCID
Severe combined immunodeficiency (SCID) is one of the most life-threatening inherited disorders of the immune system. SCID patients present during the first months of life with severe (viral) infections, chronic diarrhea and failure to thrive. In addition, they suffer from dysregulation of the immune system (autoimmunity) and allergy-like symptoms. Three subtypes of SCID can be defined: typical SCID, leaky SCID and Omenn syndrome, hereafter collectively referred to as SCID (1). SCID is often diagnosed too late, usually with fatal outcome. The cause of SCID is a genetic defect, which results in absence of (functional) T-cells. T-cells are crucial in the immune defense against viral infections. Until now, 21 genes have been identified in which mutations can cause SCID.

SCID IN THE NETHERLANDS
Recently, the Dutch national Working Party on Immunodeficiencies (WID) evaluated all known SCID patients over a period of 15 years in the Netherlands (2). In this cohort we analyzed the presenting symptoms, morbidity, delay in diagnosis and treatment and mortality. In total, 43 SCID patients were identified, 11 of whom were atypical SCID (with a presentation beyond the first year). On a total population of approximately 180.000 newborns/year, the incidence in this period was around 1:63,000. The cohort was retrospectively collected and may show underrepresentation as only known diagnosed patients could obviously be included. In total, 32 patients were treated with hematopoietic stem cell transplantation and two with gene correction

therapy. Nine patients died after they received curative treatment due to infectious and allo-reactive complications. Moreover, nine patients died due to severe infectious complications before curative treatment could be initiated.

NEONATAL SCREENING WITH THE TREC ASSAY
Early diagnosis is essential for effective treatment. Early treatment strongly improves survival of SCID patients (from 40% to 90%) (3). The probability of survival depends on the age of transplantation and the infection status (i.e. type and amount of infections in a patient) (4). The probability of survival was highest in case the transplantation was performed before the age of 3.5 months. In patients older than 3.5 months, best results were obtained when there was no infection or when the infection was resolved.
Neonatal screening for SCID is based on quantification of T-cell receptor Excision Circles (TRECs), which are generated during T-cell development (5). Using quantitative PCR TRECs can be quantified in neonatal screening cards (6,8). Absence of TRECs is indicative for absence of T-cells, however, follow-up diagnostics are necessary to make the final SCID diagnosis.
It is known from literature that low TREC levels can also be identified in children with T-cell lymphopenia not related to SCID. These findings are considered secondary findings of the neonatal screening (1).

Follow-up diagnostics can be divided in 1. flow-cytometric immunophenotyping to confirm absence or strong reduction of T-cells in peripheral blood and 2. genetic analysis to identify the genetic defect in one of the SCID candidate genes (7). It is important to note that absence of T-cells can also be related to e.g. premature birth, congenital malformations or infections. After the SCID diagnosis the treatment phase will be initiated, which consists of hematopoietic stem cell transplantation or (if available) gene therapy. An efficient diagnostic and treatment plan as follow-up of the TREC assay is an essential part for neonatal SCID screening.
In a study of the US in which 3 million children were screened, 52 SCID patients were identified. In addition, 411 patients with non-SCID T-cell lymphopenia were identified with TREC screening (1).

TREC SCREENING AND FOLLOW-UP DIAGNOSTICS AND TREATMENT IN THE NETHERLANDS
In June 2015, the Dutch Ministry of Health decided – based on the advice of the Dutch Health Council – to implement neonatal screening for SCID (based on the TREC assay) in the national neonatal screening program, allowing for the identification of SCID directly after birth, during the pre-symptomatic phase.
While TREC-based screening for SCID will be implemented in the next coming years, the organizational lay-out is already in place. The responsibility for the implementation of SCID screening after a final decision by the Ministry of Health is allocated to the RIVM-Center for Population Screening. The expertise on the logistic, analytical and ICT aspects of the screening test are laid down at the RIVM-reference laboratory for neonatal screening. The information for parents and healthcare providers will be developed in a multi-disciplinary working group and distributed by the regional organizations (RIVM-DVP). The medical academic immunodeficiency centers (represented by the Dutch national Working Party on Immunodeficiencies or WID) in this project have taken up the responsibility to shape the diagnostic and treatment follow-up.

Relevantie / Relevance

June 2015, the Dutch Ministry of Health decided to expand the neonatal screening program with 14 disorders, including SCID. Without curative treatment children with SCID usually die within the first year of life. With a hematopoietic stem cell transplantation, these children can be cured, implying SCID would be the first disorder in the national neonatal screening program which can be completely cured. However, the chance of survival is dependent on the clinical condition at the time of diagnosis. If SCID is diagnosed in the pre-symptomatic phase, the survival is above 90% whereas the survival drops to 40% in case of late diagnosis (i.e. diagnosis at the time of life-threatening infections). In all observations, early treatment clearly demonstrates a significantly better outcome. SCID patients accumulate infectious agents, (including respiratory and systemic viruses, bacteria and fungi), all leading to increased treatment related complications and poorer outcome. SCID patients without active infections have a significantly better overall survival. The presence of severe infections will greatly increase morbidity and costs and will decrease effectiveness of the subsequent transplant procedure.

Implementation of neonatal screening for SCID is complex due to expensive screening-methods and radical treatment options. Moreover, there is a number of uncertainties (ranging from the expected number of referrals, analytical difficulties and unanticipated logistic challenges to unexpected screening outcomes and identification of cases other than SCID) that may seriously hamper the introduction of SCID screening in the routine program, if not first identified and tackled in an extensive pilot screening. Therefore, a pilot project, similar to pilot projects previously supported by ZonMW, (e.g. for genetic screening for Cystic Fibrosis) is needed to study neonatal screening for SCID in the real-life situation. This project aims to gather knowledge about the practical implication of neonatal screening for SCID, test qualities, costs and the perspective of users (i.e. health care providers and parents). Thus, the relevance of this project is that it is essential to research the possibilities of implementing SCID screening as part of the national neonatal screening program, as advised by the Health Council and requested by the Secretary of Health, that will yearly save the lives of affected neonates.
The Health Council reviewed the ethical, legal, and societal implications (ELSIs) of screening for all disorders in the expanded screening program, including SCID. Since SCID is a case example of the disorders in the expanded program with high impact secondary findings, and potential false positive rates, the ELSIs of SCID screening will also be studied in this research project. The ELSIs will be operationalized through studying the perspectives of parents and their health care providers.

Kennisoverdracht, implementatie, bestendiging / Knowledge transfer, Implementation Consolidation

We shaped the project team towards a ‘mini-consortium’, enveloping all relevant parties within the Dutch neonatal screening, to maximize expertise and support within the neonatal screening program. Moreover, as all representatives of the screening are involved, communication lines are short, enabling swift transfer of results. Additionally, this multidisciplinary team is able to weigh consequences of this project for the screening program, analytically as well as logistically, or where patient information, support of patient advocacy groups, diagnosis, clinical consequences and therapy are involved. The project team is very well

positioned to manage this innovational development up to an optimal preparation of SCID implementation in routine screening. All members have been involved in such developments in the past and all parties are deeply involved in the implementation of the expansion of the current screening program. Finally, the team is well positioned and capable of disseminating the results to ZonMW through which the Ministry of Health and the RIVM-Centre for Population screening will be advised in their final decisions concerning the implementation of SCID-screening. Through the intimate entanglement of the project team with the screening setting, the direct use and application of all the lessons learned through this pilot project will pave the way for a swift introduction of neonatal SCID screening.

Doelstelling / Objective

The aim of this pilot study is to obtain knowledge about the practical implications, test qualities, costs and the perspectives of the users of the TREC screening for SCID in real practice to ensure optimal implementation in the national neonatal screening program.

This will be done by answering the following research questions:

1. How could the T-cell receptor excision circles (TREC)- screening method be implemented in the current neonatal screening program?
2. What are the test qualities of TREC screening in “real life” in the Netherlands?
3. What are the costs for introduction of TREC screening in the neonatal screening program?
4. How can adequate information and counseling facilitate an acceptable screening process for parents and their health care providers?

Plan van Aanpak / Strategy

General remark:
The project team will be supported a guidance committee, that will be involved in the project where necessary. The advisory committee is planned to consist of:
• Elske van den Akker-van Marle, health economist, LUMC
• Marielle van Gijn, laboratory specialist clinical genetics, UMCU
• Peter van Hasselt, pediatrician metabolic diseases, UMC-WKZ
• Marleen Jansen, expert on implementation studies, RIVM
• Mandy Jansen, account manager heel prick screening, RIVM-DVP
• Taco Kuijpers, pediatric immunologist, AMC, on behalf of the WID
• Arjan Lock, medical advisor population screening, RIVM-Centre for Population screening
• Joris van Montfrans, pediatric immunologist, UMC-WKZ, on behalf of the WID
• Gijs van Santen, clinical geneticist, LUMC
• Hans van der Voorn, regional manager DVP-West
• Representative of the Dutch patient Organisation Stichting afweerstoornissen (SAS)
• Representative of the Dutch Organization of Obstetricians(KNOV) or individual obstetricians and maternity care workers will be contacted during the pilot study.
• Representative of the Geboortebeweging, Moederraad or Academic Workplace Youth & Health will be contacted during the pilot study.

In this implementation pilot study, many partners are involved. For this reason, two or three partners are allocated as responsible partners per work package (WP). A researcher (PhD student with a MD degree and a Master in Biomedical Sciences) will be appointed to perform the research. The project management team (i.e. the three project leaders) are responsible for the overall project, including monitoring.
The RIVM-Centre for Population screening will offer the project group a monitoring/control-framework in order to monitor and evaluate all deliverables. This close collaboration will not only improve efficiency and quality of the deliverables, it will also ensure the concurrent execution of the pilot study and the routine screening program.

WP1 IMPLEMENTATION OF THE TREC-SCREENING METHOD IN THE CURRENT NEONATAL SCREENING PROGRAM

Objective
The pilot screening is set up as a screening performed using the infrastructure of the national screening program with the involvement of three provinces (Utrecht, Gelderland and Zuid-Holland) and two screening laboratories (IJsselland Hospital in Capelle a/d IJssel and the reference laboratory at RIVM-Bilthoven). The regional DVP-offices involved are DVP West and DVP Noord-Oost. We aim at including 70.000 analyses in this pilot study which approximates the yearly workload of two laboratories. Before starting the pilot, a number of procurements needs to be in place. This work package is divided in six parts all addressing one of the procurements (WP1.1-1.6).

1) Balanced information to the parents on SCID screening should be provided, enabling informed decision making to participate or not.
2) Screeners need to be briefed on how to inform parents on SCID screening.
3) Screening laboratories need to be equipped (both concerning analytical hardware and analysis software, including connection to local LIMS and the reporting software of RIVM-DVP (Praeventis), with special reference to the availability of PCR facilities).
4) The analytical work-up of the samples needs to be determined and laid down in laboratory standard operating procedures, including procedures for re-analysis and repeat sample request. This also includes providing proficiency samples or external QC samples issued by a trusted organization (e.g. Centers for Disease Control, Atlanta).

5) Procedures need to be in place and RIVM-DVP needs to be briefed on how and when to refer neonates with low TREC levels.
6) Procedures need to be in place for diagnostic work-up and treatment in university/academic hospitals with proper archiving of the diagnostic results and the various immune disorders found.

WP1.1 Information to the parents on SCID screening
Relevant information for parents on the background of SCID and the principles of the TREC screening will be collected and summarized in an information leaflet by the researcher. The internationally available information will be used and adapted for the Dutch setting. In addition, a more extended information sheet (one A4) will be written for the website. Standard formats of the RIVM will be used. It should provide balanced information, enabling the parents informed decision to participate.
Responsible partners: researcher, pediatric immunologist (RB), medical advisor DVP*
* NB: The whole project the project team is involved, but per work package a responsible partner is assigned.

WP1.2 Information for screeners
In addition to the information brochure for parents an extensive brochure (2 A4) will be developed for the screeners. This will include information on the disease and disease course, the set-up of the study, how to obtain informed consent, practical aspects of sampling and routing, information for family doctors and midwives. When the leaflet is ready, an information meeting will be organized for screeners.
Responsible partners: researcher, pediatric immunologist (RB), medical advisor DVP (GW)

WP1.3 Set up of screening laboratories
Prior to the project a comparable analysis will be performed (Sept-Oct 2017) to select the best TREC assay for the pilot study at the RIVM reference laboratory under supervision of Peter Schielen. Based on the results of this comparative analysis the participating laboratories will be equipped with the PCR analysis instruments. Analysis software will be designed and connected to the local LIMS (Neonat) and the monitoring software of RIVM-DVP (Praeventis) by the ICT department.
Responsible partners: heads of the screening laboratories (PS and EK)

WP1.4 Technical aspects of TREC analysis
The analytical work-up of the samples will be described and laid down in laboratory standard operating procedures, including procedures for re-analysis and repeat sample request. This also includes providing proficiency samples or external QC samples issued by a trusted organization (e.g. Centers for Disease Control, Atlanta) and validation assays. The procedure for re-sampling will be included in the documents. Cut-off values will be defined and the screening policy will be described. Technicians will be trained to perform the assays. Finally, during a short period (3 weeks) the assay will be run on anonymized samples, without referrals to test the entire technical system.
Responsible partners: researcher, heads of the screening laboratories (PS and EK)

WP1.5 Procedure for referral of neonates
The exact procedure of referral of neonates will be written in a work instruction document for RIVM-DVP. It should contain an official referral to the family doctor and a pediatric immunologist in an academic hospital. The two RIVM-DVP regional offices will be briefed on how and when the neonates will be referred in case of low TREC levels. An ICT link from Neonat to Praeventis will be made. Moreover, SCID will be added to the software of Praeventis in order to monitor the screenings process, progress and follow-up. Standardized letters will be developed to inform family doctors, pediatricians and parents about an aberrant test result.
Responsible partners: researcher, medical advisor DVP, account manager heel prick screening DVP, head of the screening laboratories (PS en EK), pediatric immunologist (RB)

WP1.6 Follow-up diagnostics work-up and therapeutic intervention
Procedures will be documented for the diagnostic work-up and treatment in academic hospitals. Concerning diagnostic work-up and therapeutic intervention, some specifics are already in place, and elaborated by the WID. In case of absent of reduced TREC levels, the backbone of the diagnostic procedures will comprise the referral to a pediatric immunologist in one of the academic hospitals, as soon as possible but not later than one week after the screening result is available. Immunological evaluation including flow-cytometric immunophenotyping will be performed to determine the presence and phenotype of T-cells and other lymphocyte subpopulations. National consensus guidelines for lymphocyte phenotyping will be followed. Based on the results of flow-cytometric immunophenotyping, genetic testing will be performed using an NGS based SCID panel containing all defined SCID genes. The results need to be available within 2-4 weeks after flow-cytometric results. If no genetic diagnosis is obtained, a broader genetic screen such as (CITO) whole exome sequencing with primary immunodeficiency (PID) panel gene analysis should be considered. This goes beyond the current neonatal SCID screening project and is to be discussed with a clinical geneticist following clinical guidelines. In cases where a reduced TREC count is measured but SCID is not diagnosed (T cell lymphopenia other than SCID), nationwide clinical guidelines for counselling, treatment and follow up will be followed. It will be part of this subproject to completely and reliably implement this part of the follow-up of screening, also reporting on the follow-up of non-SCID primary immune disorders.
Concerning therapeutic intervention, the main aim of early diagnosis of T cell lymphopenia is to start anti-microbiologic prophylaxis and treatment to prevent infections and immune dysregulation and the occurrence of complications. Therefore, already at time of referral to the immunologist, parents and health care providers need to be alarmed that there is a possible ‘medical emergency’, and that urgent action is needed. Besides, and in parallel of the confirmation of the T cell deficiency, various prophylactic measures will be initiated immediately. Options for definitive treatment need to be explored and a search for a suitable donor for transplantation needs to be initiated. It will be part of this subproject to completely and reliably implement this part of the follow-up of screening, also reporting on the therapeutic possibilities for non-SCID primary immune disorders. A database will be developed for collection and monitoring of all follow-up data.
Responsible partners: WID, researcher, pediatric immunologist (RB)

WP1.7 Preparing a complete roadmap document to execute WP2
For optimal management and workflow needed to execute WP2, a complete and comprehensive roadmap will be written summing up all actions and responsibilities to execute. This roadmap could include references to the roadmap of the routine neonatal screening or 'Draaiboek Neonatale hielprikscreening of the RIVM'.
Responsible partners: researcher, project leaders (MB,RB, PS)

Deliverables
D1.1 Parent information brochure on SCID screening
D1.2 Information leaflet for screeners how to inform parents distributed during information meeting
D1.3 Equipment for screening laboratories (analytical hardware and reporting software)
D1.4 Laboratory standard operating procedures for TREC screening
D1.5 Written procedures for RIVM-DVP about how and when to refer neonates with low TREC levels
D1.6 Written procedure for follow-up diagnostics and treatment plan for SCID and non-SCID
D1.7 A complete and comprehensive roadmap, summing up all actions and responsibilities to execute WP2.

WP2 TEST QUALITIES OF "REAL-LIFE"TREC SCREENING IN THE NETHERLANDS

Objective: To determine the test qualities of "real-life" TREC screening

WP2.1 Phase 1 of "real-life" TREC screening
The pilot will officially start as planned and described in WP1. All data regarding TREC testing, resampling, referral and follow-up diagnostics will be collected in the database. After three months of screening (approximately 15-20.000 analyses), a provisional evaluation will be performed, to enable fine-tuning of cut-off levels for decisions on repeat analysis, repeat sampling or referral. An interim report will be produced and discussed with the entire project group and support group and the procedures might be adopted based on the interim report.
Responsible partners: heads of the screening laboratories (PS and EK), pediatric immunologist (RB), medical advisor DVP, researcher

WP2.2 Phase 2 of "real-life" TREC screening
In the next part (up to one year) the rest/remainder of the pilot-project will be executed, until the number of 70.000 inclusions is reached.
Responsible partners: heads of the screening laboratories (PS and EK), pediatric immunologist (RB), researcher

WP2.3 Data analysis and report
All the available data of the project will be analyzed and an overview of the number of re-analyses, requests for second samples and referrals will be produced. Based on the results together a final report will be produced, including the final advice on how to implement SCID screening in routine neonatal screening in the Netherlands. This advice will be made available to ZonMW to further inform the Ministry of Health.
This report will describe the most profitable way to introduce SCID screening in routine screening, also providing the main areas of risk as well as opportunities to optimize the screening. Issues covered include but are not limited to:
• analytical hardware and software
• LIMS software and connection to Praeventis
• laboratory personnel capacity demand/and personnel RIVM-DVP
• appropriate cut-off values
• procedures for re-sampling and referral
• ease of access to diagnostic procedures to confirm SCID
• the ICT-database demands to record diagnosed immune disorders, traceable to the original heel prick sample.
• ease of access to therapeutic intervention

While it is not an aim of this pilot study to give an exact estimate, stratified in specificity and positive and negative predictive value, of the performance of SCID screening in routine Dutch newborn screening, the results of WP1 can be used, when combined with experience of international SCID screening initiatives, to approximate the expected performance. These data will also be included in the final report. This final report will also include recommendations for future research and TREC screening.
Responsible partners: researcher, heads of screenings laboratories (PS and EK), pediatric immunologist (RB)

D2.1 An interim report will be produced.
D2.2 Final report of results of TREC screening
D2.3 Report and advice to ZonMW
D2.4 Peer reviewed scientific publication of the results on implementation of TREC screening

WP3 COSTS FOR INTRODUCTION OF TREC SCREENING IN THE NEONATAL SCREENING PROGRAM

Objective: To update the estimated cost-effectiveness of screening for SCID by TREC screening in the Dutch neonatal screening program, by using real-life data from the pilot study.

Prior to the project an explorative cost- effectiveness analysis (CEA) for SCID screening was performed by TNO/LUMC from a healthcare perspective, as requested by the RIVM-Centre for Population screening in 2016.9 The data from WP1 and WP2 will provide real-life input for screening and diagnostic cost parameters of the earlier developed cost-effectiveness model, specific for the Dutch screening program. Also more precise data on treatment costs based on a retrospective review of patient records

will be obtained, as the TNO/LUMC cost-effectiveness analysis has shown that these costs have a large impact on the cost-effectiveness of SCID screening. Furthermore, as data on quality of life of SCID patients are lacking, a brief assessment of quality of life will take place by means of a quality of life questionnaire (EQ-5D) to (adult) SCID patients. In this way, the estimate of cost-effectiveness for SCID screening in the Netherlands can be improved. Currently at best general assumptions can be made about the screening policy and model, and rough estimates of cut-off values to be applied. WP1 and WP2 will give valuable information on the model parameters of the model that is intended to be implemented in routine screening. In this way the best estimate of cost and effect for SCID screening in the Netherlands can be provided.
Responsible partners: health economist, epidemiologist, researcher

D3.1 Update of the cost-effectiveness analysis as part of the final report
D3.2 Scientific publication of cost- effectiveness analysis for introduction of TREC screening in the Netherlands

WP4 EXPERIENCE OF THE INTRODUCTION OF TREC SCREENING BY PARENTS AND HEALTH CARE PROVIDERS

Objective: To investigate the experiences of the introduction of TREC screening by parents and health care providers.

Societal acceptance of screening for a specific disorder is a major criterion for the introduction of screening. While the clinical benefit of screening for SCID seems evident, the societal acceptance should not be taken for granted. It is important to recognize that the introduction of a disorder into the screening program could influence the willingness of parents to participate. One of the hallmarks of the Dutch national screening program is its almost complete, voluntary participation of the neonatal population, and this will remain one of the most pertinent aims in the future. Thus, introduction of SCID in the screening process should be done prudently, ensuring the informed participation of parents and their newborn(s).
Throughout the screening process – from informing the parents during pregnancy up to the actual heel prick - many factors influence the willingness to participate to neonatal screening. Informing parents adequately is highly relevant to enable them to make an informed decision about participation. Parents may opt in or out for various reasons, such as the perceived acceptability of the screening test. Counselling prior to screening, but also after screening is of vital importance. Anxiety may for example arise when a positive screening test result is reported and the implications of this result should be explained clearly to the parents. Factors that contribute to the willingness to participate, such as the acceptability of screening, but also the information that young parents need from their health care providers in different stages of the screening process will be studied.

WP4.1 Development of questionnaires and study design for ELSI of screening
The ethical, legal and social implications (ELSI)-part of the project will focus on the following questions:
• In general, how do parents perceive the expansion of the neonatal screening program and what factors increase or decrease the acceptability of screening for a disorder?
• What is the willingness of parents to participate in the SCID screening, also identifying possible reasons to opt in or out?
• What information do health care providers and parents need to feel adequately informed during counselling about neonatal screening on SCID?
• What feelings of anxiety are associated with the referral of a child for putative SCID (based on a positive screening result), what is the best way to address these and what is the residual anxiety at the end of the screening process and at one year?
These questions will be studied both from the perspective of the parent as well as health care providers (screeners, midwives, GPs, clinical immunologists). To this end multiple qualitative and quantitative techniques will be used including focus group-interviews and questionnaire studies. For the focus groups, interview topics will be developed after a literature review. Consistent with standard qualitative research techniques, these topics will evolve during the focus groups through an iterative process to ensure that the questions will capture all relevant emerging themes. With the focus group data, a quantitative questionnaire will be developed.

WP4.2 ELSI data collection and analysis
During the course of WP2 (real-life TREC screening), data on ELSI will be collected from the parents and health care providers and subsequently analysed. This will result in a report on experience of introduction of TREC screening submitted to ZonMW and the Health Research Council and one or more scientific publications.
Responsible partners: medical ethicist, researcher
Deliverables
D4.1 Report on experience of introduction of TREC screening by parents and health care providers as part of the final report to ZonMW and the Heath Research Council.
D4.2 Scientific publication of results of experience of introduction of TREC screening

MILESTONES
M1 Ready to start pilot TREC screening
M2 70.000 newborns have been screened
M3 Implementation pilot is finished and written advice has been reported to ZonMW and the Health Research Council

Expertise, voorgaande activiteiten en producten / Expertise, prior activities and products

Projectleader/coordinator:
Dr. Mirjam van der Burg, PhD immunologist at the Dept. of Immunology, Erasmus MC.
Since 2002 Head of the Workgroup Primary Immunodeficiency and responsible for immunological and genetic diagnostics of patients PID (esp. SCID and antibody deficiencies) and scientifically active in the field of SCID, V(D)J recombination, B-cell differentiation and DNA repair.

Deputy project leader

Dr. Robbert G.M. Bredius, MD, PhD is pediatrician-immunologist, working as transplant physician at the LUMC. He is a member of the Working Party on Immunodeficiencies and scientifically active in the field of PID and SCID. In addition he is active member of the Working Party Inborn Errors of the European Blood and Marrow Transplantation Group, EBMT. Furthermore, he is actively involved in the Medical School in the LUMC, and coordinator of the Minor - Clinical Immunology of the medical curriculum at the Faculty of Medicine.

Deputy project leader
Dr. Peter (C.J.I.) Schielen, PhD is the Head of the reference laboratory neonatal screening at the RIVM since May, 2012. He has been a senior scientist at the Centre for Infectious diseases research, Diagnostics and Screening of the National Institute for Public Health and the Environment (RIVM) since august 1999.

Description of the WID
The Working Party on Immunodeficiencies (WID) meets four times per year for a scientific meeting, which is public, and a meeting of the “core-group” in which all Dutch academic centers are represented by a pediatrician-immunologist, an internist-immunologist and a laboratory specialist (i.e. a (medical) immunologist). One of the subgroups is the SCID subgroup, which deals with all aspects of SCID, including the neonatal screening, and which communicates directly with the RIVM concerning this topic. The SCID subgroup reports back to the “core-group”.

Publicaties / Publications

Publications of the projectteam on Neonatal SCID screening

1. Blom M, Pico-Knijnenburg I, Sijne-van Veen M, Boelen A, Bredius RGM, van der Burg M, Schielen PCJI. An evaluation of the TREC assay with regard to the integration of SCID screening into the Dutch newborn screening program. Clin Immunol. 2017;180:106-110.

2. de Pagter AP, Bredius RG, Kuijpers TW, Tramper J, van der Burg M, van Montfrans J, Driessen GJ, Dutch Working Party for I. Overview of 15-year severe combined immunodeficiency in the Netherlands: towards newborn blood spot screening. Eur J Pediatr. 2015;174:1183-1188.

3. van der Spek J, Groenwold RH, van der Burg M, van Montfrans JM. TREC Based Newborn Screening for Severe Combined Immunodeficiency Disease: A Systematic Review. J Clin Immunol. 2015;35:416-430.

4. Hannon WH, Abraham RS, Kobrynski L, Vogt RF, Adair O, Aznar C, Baker M, Brower AM, Caggana M, A.M. C, Grossman W, Lee FK, J.M. P, Taylor JL, Turley DM, Van der Burg M, Warman B, Yazdanpanah MS, Ylikoski A. Newborn Blood Spot Screening for Severe Combined Immunodeficiency by measurement of T-cell Receptor Excision Circles; Approved Guideline. ISBN 1-56238-871-1. Vol. 33 No.4: Clinical and Laboratory Standards Institute (CLSI); 2013:1-74.

Referenties / References

1. Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK, Baker M, Ballow M, Bartoshesky LE, Bonilla FA, Brokopp C, Brooks E, Caggana M, Celestin J, Church JA, Comeau AM, Connelly JA, Cowan MJ, Cunningham-Rundles C, Dasu T, Dave N, De La Morena MT, Duffner U, Fong CT, Forbes L, Freedenberg D, Gelfand EW, Hale JE, Hanson IC, Hay BN, Hu D, Infante A, Johnson D, Kapoor N, Kay DM, Kohn DB, Lee R, Lehman H, Lin Z, Lorey F, Abdel-Mageed A, Manning A, McGhee S, Moore TB, Naides SJ, Notarangelo LD, Orange JS, Pai SY, Porteus M, Rodriguez R, Romberg N, Routes J, Ruehle M, Rubenstein A, Saavedra-Matiz CA, Scott G, Scott PM, Secord E, Seroogy C, Shearer WT, Siegel S, Silvers SK, Stiehm ER, Sugerman RW, Sullivan JL, Tanksley S, Tierce MLt, Verbsky J, Vogel B, Walker R, Walkovich K, Walter JE, Wasserman RL, Watson MS, Weinberg GA, Weiner LB, Wood H, Yates AB, Puck JM. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. JAMA. 2014;312:729-738.
2. de Pagter AP, Bredius RG, Kuijpers TW, Tramper J, van der Burg M, van Montfrans J, Driessen GJ, Dutch Working Party for Immunodeficiencies. Overview of 15-year severe combined immunodeficiency in the Netherlands: towards newborn blood spot screening. Eur J Pediatr. 2015;174:1183-1188.
3. Brown L, Xu-Bayford J, Allwood Z, Slatter M, Cant A, Davies EG, Veys P, Gennery AR, Gaspar HB. Neonatal diagnosis of severe combined immunodeficiency leads to significantly improved survival outcome: the case for newborn screening. Blood. 2011;117:3243-3246.
4. Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, Kapoor N, Hanson IC, Filipovich AH, Jyonouchi S, Sullivan KE, Small TN, Burroughs L, Skoda-Smith S, Haight AE, Grizzle A, Pulsipher MA, Chan KW, Fuleihan RL, Haddad E, Loechelt B, Aquino VM, Gillio A, Davis J, Knutsen A, Smith AR, Moore TB, Schroeder ML, Goldman FD, Connelly JA, Porteus MH, Xiang Q, Shearer WT, Fleisher TA, Kohn DB, Puck JM, Notarangelo LD, Cowan MJ, O'Reilly RJ. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. N Engl J Med. 2014;371:434-446.
5. Hazenberg MD, Verschuren MC, Hamann D, Miedema F, van Dongen JJ. T cell receptor excision circles as markers for recent thymic emigrants: basic aspects, technical approach, and guidelines for interpretation. J Mol Med. 2001;79:631-640.
6. Puck JM. Laboratory technology for population-based screening for severe combined immunodeficiency in neonates: the winner is T-cell receptor excision circles. J Allergy Clin Immunol. 2012;129:607-616.
7.van der Burg M, Gennery AR. Educational paper : The expanding clinical and immunological spectrum of severe combined immunodeficiency. Eur J Pediatr. 2011;170:561-571.
8. Blom M, Pico-Knijnenburg I, Sijne-van Veen M, Boelen A, Bredius RGM, van der Burg M, Schielen PCJI. An evaluation of the TREC assay with regard to the integration of SCID screening into the Dutch newborn screening program. Clin Immunol. 2017;180:106-110.
9. van der Ploeg K, van den Akker-van Marle E, Bredius R, Staal F, van den Burg M, Verkerk P. Kosteneffectiviteits- en

kostenbatenanalyse (KEA/KBA) voor het screenen op SCID binnen de Nederlandse hielprikscreening. TNO/LUMC, TNO-rapport R10422, april 2017. (released by RIVM July 2017).

Financiële gegevens / Financial data

ZonMw budget

	Jaar / Year								
Kostenpost	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	**Totaal / Total**
Personeel	83.750	83.750	0	0	0	0	0	0	167.500
Materieel	218.750	218.750	0	0	0	0	0	0	437.500
Implementatie	16.250	16.250	0	0	0	0	0	0	32.500
Apparatuur	0	0	0	0	0	0	0	0	0
Overig	5.000	7.500	0	0	0	0	0	0	12.500
Totaal / Total	**323.750**	**326.250**	**0**	**0**	**0**	**0**	**0**	**0**	**650.000**

Co-financiering / Cofinancing

Naam co-financier / Name of cofinancier	Bedrag / Amount	Status
Ministerie van Volksgezondheid, Welzijn en Sport	313.452	Toegekend

Bijzondere gegevens / Additional information

Vergunningen / Permits

	Verklaring nodig / Statement required?		Status verklaring / Statement status		
	Ja / Yes	Nee / No	Verkregen / Acquired	Aangevraagd / Applied	Nog niet aangevraagd / Not applied yet
METC	X				X
DEC		X			
WBO		X			

Onderschrijvingen / Assents

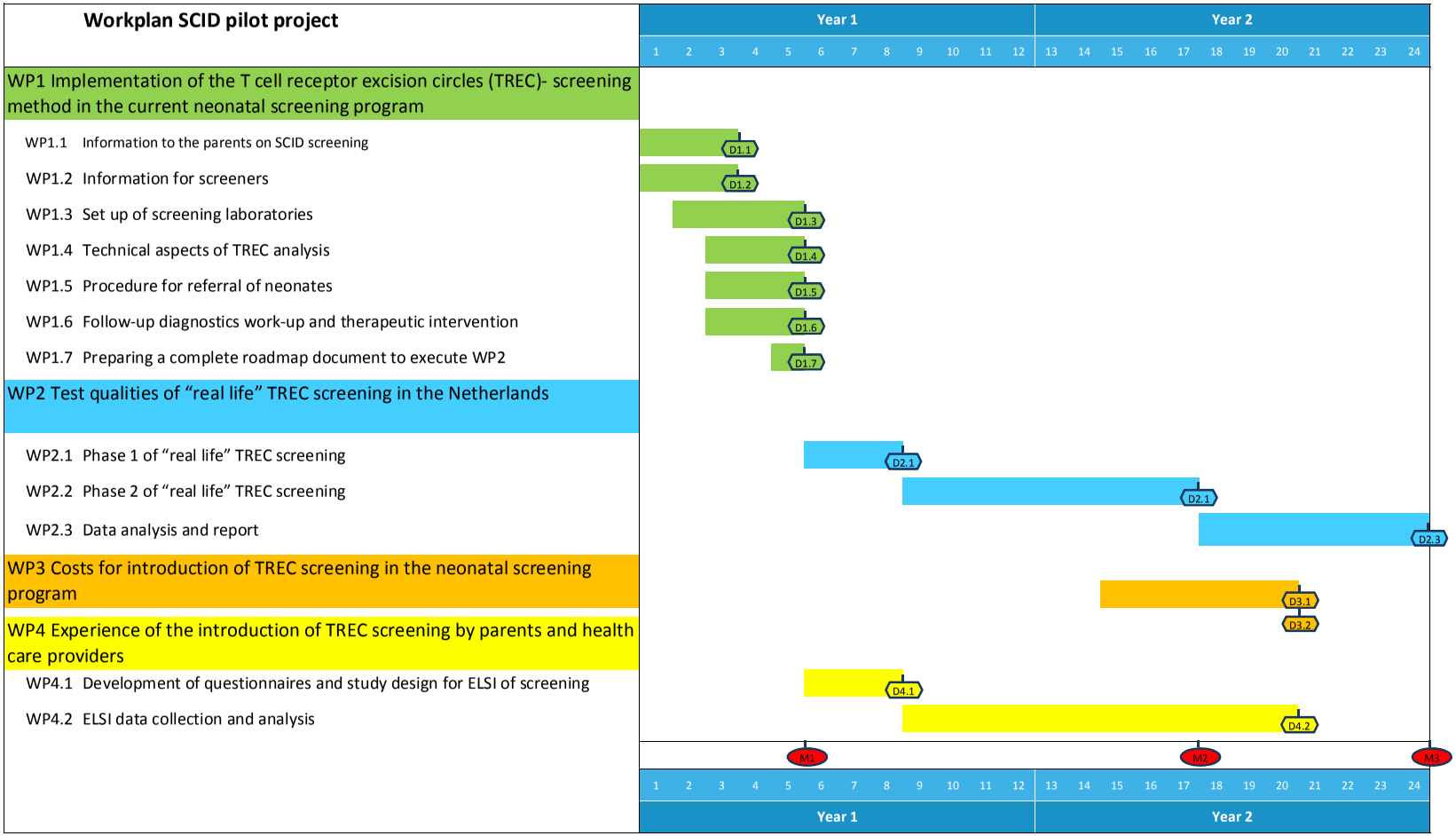
	Ja / Yes	Nee / No	N.v.t. / N.A.
Code biosecurity / Code Biosecurity	X		
Code openheid dierproeven / Code Transparency of Animal Testing			X

Andere vergunningen / Other permits

Approval for this project will be sought through review by a local Ethical Review Board. Approval to perform this pilot screening within the framework of the Dutch neonatal screening program will be sought through review by the Working Group Research-Neonatal heelprick screening, and approval by the Program Committee neonatal heelprick screening.

Historie subsidieaanvraag / History grant application

Deze aanvraag is ook ingediend bij organisatie / This grant application has also been submitted to organization:



Deliverables

D1.1 Parent information brochure on SCID screening
D1.2 Information leaflet for screeners how to inform parents distributed during information meeting
D1.3 Equipment for screening laboratories (analytical hardware and reporting software)
D1.4 Laboratory standard operating procedures for TREC screening
D1.5 Written procedures for RIVM-DVP about how and when to refer neonates with low TREC levels
D1.6 Written procedure for follow-up diagnostics and treatment plan
D1.7 A complete and comprehensive roadmap, summing up all actions and responsibilities to execute WP2
D2.1 An interim report will be produced
D2.2 Final Report of results of TREC screening
D2.3 Report and advice to ZonMW
D2.4 Peer reviewed scientific publication of the results on implementation of TREC screening
D3.1 Update of the cost- and effect analysis
D3.2 Scientific publication of cost-and effect analysis for introduction of TREC screening
D4.1 Report on experience of introduction of TREC screening by parents and health care providers
D4.2 Scientific publication of results of experience of introduction of TREC screening

Milestones

M1 Ready to start TREC screening
M2 70.000 newborns have been screened
M3 Implementation pilot is finished and written advice has been reported to ZonMW and the Health Research Council

Begroting voor subsidie-aanvragen ZonMw

Format voor wetenschappelijke instellingen

Dossiernummer Project:
Titel Project: Pilotonderzoek SCID-screening ten behoeve van opname in de Neonatale Hielprik Screening
Aantal maanden looptijd Project: 24

Alvorens u deze begroting invult, verzoeken wij u kennis te nemen van de Subsidievoorwaarden ZonMw per 1 juli 2013 en bekostigingsbesluit wetenschappelijke instellingen
De geldende tabelbedragen zijn eveneens te vinden op de website van ZonMw: www.zonmw.nl/nl/subsidies/voorwaarden-en-financien/

*Er is een onderscheid tussen VSNU instellingen (o.a. Universiteiten) en NFU instellingen (o.a. UMC's). Voor **VSNU** instellingen gelden de volgende functies: Promovendi, Senior wetenschappelijk medewerker, Niet-wetenschappelijk personeel MBO, Niet-wetenschappelijk personeel HBO en Niet-wetenschappelijk personeel Academisch.*

*Voor **NFU** instellingen gelden de volgende functies: Promovendi, PostDoc, (Arts)onderzoeker, Niet-Wetenschappelijk medewerker MBO, Niet-wetenschappelijk medewerker HBO en Niet-wetenschappelijk medewerker Academisch.*

1. Personeel

Soort aanstelling/functie	**Werkzaamheden (in steekwoorden)**	**Aantal maanden**	**Tabelbedrag** *(bij "afrekening indien aantal maanden")*	**Fte (%)**	**Totaal (€)**
Onderzoeker (AIO)	Onderzoeker SCID pilot project in het kader van een promotie traject	24	€ 129.000,00	100%	€ 129.000,00
Projectleider	Project management en monitoring	24	€ 240.000,00	10%	€ 24.000,00
Administratief medewerker	Ondersteuning in projectadministratie	24	€ 145.000,00	10%	€ 14.500,00
Analist screeningslab 1	Uitvoeren analyses	18	€ 75.000,00	50%	€ 37.500,00
Analist screeningslab 2	Uitvoeren analyses	18	€ 75.000,00	50%	€ 37.500,00
Hoofd screeningslaboratorium	Supervisie analyses en projectbegeleiding	24	€ 400.000,00	5%	€ 20.000,00
Hoofd screeningslaboratorium	Supervisie analyses en projectbegeleiding	24	€ 400.000,00	5%	€ 20.000,00
					€ -
					€ -
Totaal					**€ 282.500,00**

2. Persoonsgebonden benchfee (per aanstelling van wetenschappelijk personeel conform art.2.2 van het bekostigingsbesluit)

Omschrijving	Totaal (€)
Bench Fee onderzoeker	€ 10.000,00
Totaal	**€ 10.000,00**

3. Materieel, Apparatuur, Verbruiksgoederen gespecificeerd (conform art.2.3 van het bekostigingsbesluit

Omschrijving	Totaal (€)
Reagentia analyses & follow-up diagnostiek	€ 427.500,00
Apparatuur per screeningslab	€ 100.000,00
Software (implementatie procesregistratie, evaluatie, licentiekostern	€ 40.000,00
Totaal	**€ 567.500,00**

4. Implementatiekosten (gespecificeerd)

Omschrijving	Totaal (€)
Reiskosten	€ 2.500,00
Communicatie en implementatiekosten	€ 32.500,00
Kosten KEA	€ 10.000,00
Kosten regiokantoren DVP & communicatie deskundigheidsbevordering	€ 58.452,00
Totaal	**€ 103.452,00**

5. Bijdragen van VWS

Omschrijving	Totaal (€)
Apparatuur per screeningslab	€ 100.000,00
Software (implementatie procesregistratie, evaluatie, licentiekostern	€ 40.000,00
Personeel analisten	€ 75.000,00
Hoofd screening laboratoria	€ 40.000,00
Kosten regiokantoren DVP & communicatie deskundigheidsbevordering	€ 58.452,00
Totaal	**€ 313.452,00**

ZonMw budget

Kostenpost	Totaal (€)
1. Personeel	€ 282.500,00
2. Persoonsgebonden benchfee (per aanstelling cf. Subsidievoorwaarden)	€ 10.000,00
3. Materieel, Apparatuur, Verbruiksgoederen (gespecificeerd)	€ 567.500,00
4. Implementatiekosten (gespecificeerd)	€ 103.452,00
Totale lasten	€ 963.452,00
Minus:	
5. Bijdragen van eigen instelling c.q. derden	€ 313.452,00
Aan te vragen subsidie bij ZonMw	**€ 650.000,00**

Hoofdaanvrager:

Naam: dr. Mirjam van der Burg
Functie: Universitair Hoofddocent

Financieel verantwoordelijke ontvangende instelling:

Naam: Dhr. M.M. Gouweleeuw
Functie: Business controller
Tel.nr.: 010-70432885
E-mailadres m.gouweleeuw@erasmusmc.nl

Datum: 30-jun-17