



Review

# A Practical Guide to Implementing Population Newborn Screening (NBS) for Severe Combined Immunodeficiency (SCID)

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**Abstract:** This review should be seen as a practical tool, one which we hope illustrates potential routes to follow when seeking to implement or lobby for severe combined immunodeficiency newborn screening (SCID NBS) at a national or regional level. Experience has shown that there are country- and region-wide variations in terms of awareness of the need for SCID NBS and the processes required to demonstrate and prove the importance of SCID NBS. This guide therefore aims to share experiences and equip readers with evidence while also directing them to key further reading and resources that provide support, data, and existing frameworks that are relevant to making the case for mandatory NBS for SCID.

**Keywords:** SCID; T-cell receptor excision circles (TRECs); newborn screening

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## 1. Introduction

This guide has been put together for all those with an interest in seeking population-based screening for severe combined immunodeficiency (SCID) introduced as a mandatory part of national newborn disease screening practices. It offers top-line practical tips, pointers, and experiences that are valuable to understanding the need for SCID newborn screening (NBS) and to helping those involved in lobbying, campaigning, and seeking to implement or gain agreement for SCID NBS in European settings.

We aim here to provide readers with succinct answers and references to the major issues about SCID and NBS for SCID. The answers here are based both on evidence and on the expertise gained through working closely in recent years with a variety of SCID and NBS stakeholders.

## 2. The Need to Screen for Severe Combined Immunodeficiency (SCID)

Population-based newborn screening (NBS) is recognised as a successful method of diagnosing a number of serious clinical conditions. Severe combined immunodeficiencies (SCIDs) are the most severe form of inherited primary immune deficiency (PID) and SCID, although rare (incidence of 1:58,000 in the USA), is considered a paediatric emergency.

Children with SCID are born without cellular immunity and have severely impaired humoral immunity. Classical SCID is a condition defined by very low numbers of autologous T-cells, absent or non-functional B-cells, and recurrent severe opportunistic infections that impact adversely on mortality. There are also “leaky” or “atypical” forms of SCID where there is development of some autologous T cells but these are abnormal in profile and function and lead to the same severe clinical phenotype.

Without early detection and effective intervention, the condition is associated with almost 100% mortality. Delay in recognising SCID can be fatal. Delay also reduces the chances of a successful outcome following haematopoietic stem cell transplantation (HSCT). We know that early HSCT can be curative and offers long-term disease correction, reducing morbidity and mortality and improving

quality of life of children with SCID. Thus, diagnosis at birth would prevent the onset of early infections and complications and allow earlier curative procedures.

In summary, there are clear clinical arguments in support of diagnosing SCID at birth given the gravity of the diagnosis. The case for NBS for SCID is further strengthened by the fact that this otherwise devastating condition can be cured if detected and treated early.

### 3. SCID and the Criteria for Population-Based Newborn Screening (NBS)

There are established criteria that any condition must meet before it can be considered suitable for newborn screening. These criteria are as follows:

- It is an important health problem;
- There is an accepted treatment for patients with recognised disease;
- Facilities for diagnosis and treatment are available;
- There is a recognisable latent stage;
- There is a suitable test for SCID;
- That test is acceptable (to the population);
- The natural history of the condition is adequately understood;
- There can be agreed policies on whom to treat;
- The cost of case-finding (including diagnosis) and its economic balance in relation to possible expenditure on medical healthcare as a whole can be illustrated;
- Case-finding will be a continuing process (and not a once-and-for-all project).

JMG Wilson and G Jungner; Principles and Practice of Screening for Disease, World Health Organization, 1968.

As outlined in this document and other references, SCID meets these criteria and thus is a strong candidate for newborn screening

Unusually, compared with many diseases screened for today in NBS panels, SCID is potentially curable if recognised and treated early. While it may be possible to be alert to and to identify cases of SCID in siblings of children with known SCID, population screening will capture all cases of SCID.

Screening aims to find infants with low T-cells without delay, with the purpose of avoiding harm from otherwise beneficial health interventions (such as immunisation with live attenuated rotavirus or BCG) and identifying infants with SCID who could benefit from HSCT. Screening endeavours in Europe (largely pilot screening or retrospective screening of dried blood spot samples (DBS)) and elsewhere are helping to define the true incidence of SCID in different populations.

In the US—where screening for SCID was pioneered—NBS for this condition is now a reality in almost all states. Screening has determined that, for example, in the state of California, SCID has an incidence of 1/55,000 [1]. Since introducing NBS in this state, SCID patient overall survival has reached 95%.

### 4. Adding a Disease to the NBS Programme in Europe

In most European countries, the collection of a single Guthrie DBS in the first days of life is common practice and is the means for NBS for serious medical conditions. Every country has its own NBS policy and its own panel of conditions and approaches to sampling, screening, and then treatment. In some member states there may also be autonomous regions or provinces with their own policies (as in Belgium, Germany, Italy, Spain, and the UK). Across Europe there is also great variation in the number of screening laboratories and the number of samples screened per lab. While some countries screen for 20 or more conditions, others currently only screen for one or two diseases. It is most common in Eastern Europe and the former Soviet Union countries to screen for a low number of conditions.

**In summary, the route to getting a rare disease added to a NBS panel will be found at country level.**

## 5. Who Do We Need to Influence, Educate, Talk to and Approach?

The decision-makers and stakeholders involved with NBS are likely to differ from country to country. A first step is to understand the structure and processes in your country and identify the key decision-makers and payers who need to be convinced of the case for mandatory SCID NBS. There are examples from on-going efforts in different European countries that highlight some of the national and governmental agencies that may typically play a role in decision making—agencies and bodies that need to be helped to understand the issues and who may be vital to engage with as part of your lobbying and educational efforts.

### 5.1. The Clinical, Scientific and Patient-Support Communities

Gaining consensus among paediatricians, screeners and laboratory scientists on the need for SCID NBS is an important first step. In our experience and based on the current literature supporting the importance of this topic, it should not be difficult to reach a consensus at a country or even regional level. Support is likely to also be forthcoming from local patient organisations, and lists of relevant country organisations can be found on the IPOPI website at <https://ipopi.org/> (accessed on 10 November 2017). What is more challenging is taking the collective clinical, scientific and community-based evidence and knowledge to the right people, and conveying key messages in a manner that resonates with each decision-maker.

### 5.2. Political Decision Makers

The key decision-makers on NBS policy will vary from country to country. Our country experiences also highlight that talking to healthcare providers, health insurers and payers may be helpful in understanding which committees and agencies are involved in healthcare policy decisions. In Germany for example, it was through discussions with health insurers that NBS clinicians came to understand that decisions are made by the Gemeinsamer Bundesausschuss (GBA)—an agency that defines NBS directives, and by the Institute for Quality and Efficiency in Health Care (IQWiG)—an institute that considers the economic case for health interventions and conducts their own independent evaluation of proposed projects. Notably, the last time a new disease was added to the NBS panel in Germany was in 2005. This is despite an application submitted in 2008 to have cystic fibrosis added to NBS panels. Germany has yet to decide on this matter as a nation and just one state offers cystic fibrosis NBS at present. This national example highlights that decision-making processes regarding NBS can be protracted. In many countries—France, the Netherlands and Switzerland—the Ministries of Health are the bodies involved in decision-making, and they often establish or have Health Councils or Committees that focus on NBS. In the UK, there is a national screening committee which considers cases and conducts independent cost-effectiveness assessments for proposed NBS interventions.

### 5.3. Health Insurers and Payers

The cost and cost effectiveness of SCID NBS often has to be demonstrated to government ministries and payers as part of the argument. In our experiences to date, in many countries, decision-making agencies and payers are likely to want to conduct their own independent cost evaluations. However, the clinical, screening, and patient communities are well-placed to equip such bodies with essential facts, figures, and data. This will ensure computations are well founded, accurate, and take into account all aspects of SCID screening and the burden of unscreened SCID and its management.

## 6. The Essential Facts Needed to Persuade National Agencies of the Importance and Need for SCID NBS

### 1. Incidence of SCID

- In the context of the national birth rate, it is important to estimate annual incidence of SCID;

- In your country or region, data on incidence of SCID may need to be based on estimates from retrospective study or registry data (clinical records or DBS retrospective studies);
  - In some countries, agencies may request pilot screening studies—these may be needed to explore the practicalities and costs of national screening, and can be a useful device to obtain incidence estimates;
  - Having an idea of incidence at national level is a key foundation fact and vital to making realistic estimates regarding the costs and cost benefits of screening for SCID;
  - Local incidence data can then be backed up by data and experiences from other countries.
2. Details of the methods proposed for SCID NBS
    - The screening test to be employed;
    - The number of labs involved and the impact of adding SCID NBS on current NBS lab practices;
    - The practicalities of adding SCID to NBS and the potential impact on screening lab infrastructure.
  3. Clear explanation of the process for managing SCID cases that will be detected by screening
    - Details of the clinical pathways/protocols of care after diagnosis of SCID are confirmed;
    - Reassurance that there is healthcare capacity to manage SCID cases detected by NBS;
    - Details of clinical pathways for management of children with non-SCID T cell lymphopaenia who may also be identified by NBS.
  4. Data and arguments to support the health-economic case for implementing SCID

## 7. Countries Currently Screening for SCID

National SCID NBS has not yet started any European country, but several pilot schemes are underway and many countries are close to gaining agreement on implementing SCID NBS (see the IPOPI map). Screening to identify newborns with low T-cell receptor excision circles (TRECs) was first piloted in the US in 2008 and 2009, leading to the USA Department of Health and Human Service (DHHS) Secretary's Advisory Committee agreeing to add SCID to the uniform panel of screened disorders in 2010. Over 40 states now have SCID NBS (as at the time of writing). In California, where screening has been running for 4 years, no cases of SCID have been missed, robust data has been gathered on SCID incidence, and cost-effectiveness data has been generated supporting the value of this intervention [1,2]. Israel has recently succeeded in having SCID added to the NBS panel. International data sets and a local pilot study were used to make the case.

Literature based on UK, US, and Israeli experiences which may be helpful in your argument building include the following references: A paper highlighting the benefits of neonatal diagnosis and early HSCT on survival [3]. A cost-benefit decision tool showing the cost savings from screening and early intervention [4]. The systematic evidence review of Lipstein et al., 2010 [5]. The findings of a pilot study in Israel [6].

## 8. Screening Tests Being Used for SCID NBS

A number of screening tests may be used in SCID NBS. All screening tests look to identify T-cell lymphopaenia and their primary target is identifying SCID cases. Assay of dried blood spot (DBS) specimens for TRECs offers a surrogate marker of thymic activity and therefore T cell production. The test is based on assay of DNA extracted from a standard 3-mm punch from a standard DBS collected at birth, with TREC levels quantified using quantitative PCR.

In addition to assay of TRECs only, some screening methods may also look at K-deleting recombination excision circles (KRECs) (duplex screening). An internal  $\beta$ -actin PCR is performed to ensure that the quantity of DNA extracted is sufficient. There are a number of commercial (proprietary) screening kits or labs may use their own screens. There is a good literature on screening

methods, including a recent systematic review which will be used to define cut-off for TRECs in the Netherlands [7].

Although there is continued debate on choice of test and cut-off levels for TREC screening, this has not prevented screening implementation in the US or in pilot studies in Europe, and available tests all appear to adequately detect SCID. UK assessments of the performance of a commercial TREC assay suggests that a cut off of 20 copies is acceptable and has shown that TREC-based screening with a duplex kit (TREC and  $\beta$ -Actin) should identify all newborns with SCID using a smaller DBS punch (1.5 mm in size) (this cut-off is particular for this assay and other different TREC assays may have a different cut-off; therefore, each assay will need testing to determine its own specific cut-off) [8]. This smaller punch ensures there is no leftover genomic DNA after an assay run. The UK experience with a duplex test is that it would fit quite well within existing screening programmes in UK labs—requiring only the DNA based kit and a dedicated hood and bench clean area for operation.

The quality assurance of any chosen screening platform can be made through use of US Centers for Disease Control and Prevention (CDC) standard samples. In Switzerland, the Ministry of Health noted that commercial kits offering duplex screening (TRECs and KRECs) had a lower cost than TREC-only screening. SCID screening is currently founded on TRECs, and provided screening kits adequately determine TRECs, and this is the focus of screening, the nature of the tool (TRECs only or duplex/triplex) is less of an issue than the ability to detect and measure TRECs. Cut-off levels and choice of assay should not be viewed as problems but simply as technical issues—each country should be able to decide what is an acceptable level to choose for their population in order to detect cases of SCID.

## 9. The Health Economics Case for SCID NBS

The core of the health economics argument for SCID NBS is to demonstrate that the costs consequences of not screening are greater than those of adding SCID to current NBS practices and panels. There is growing literature on health economics with respect to SCID NBS, however, many countries will require local health economics or a health-technology-assessment (HTA)-style assessment of screening based on local costs, local incidence, and local care pathways. We would advise getting a health economist involved with planning and taking an expert, or their findings, to meetings with decision-makers, payers and policy-makers. As we have described, local data may need to be found to support the local health economic arguments.

The essential data needed for any health-economic case will typically include:

- National birth rate
- Estimates of SCID incidence nationally (remembering to account for sibling cases that could be detected without screening)
- Costs of health care visits for false-positive recalls in the screening programme
- Number of labs and lab costs, costs of retests, and follow-on test costs
- Costs of managing SCID detected after birth

We refer readers to the health economic literature for more detailed analyses [9–11].

**Conflicts of Interest:** The authors declare no conflict of interest.

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