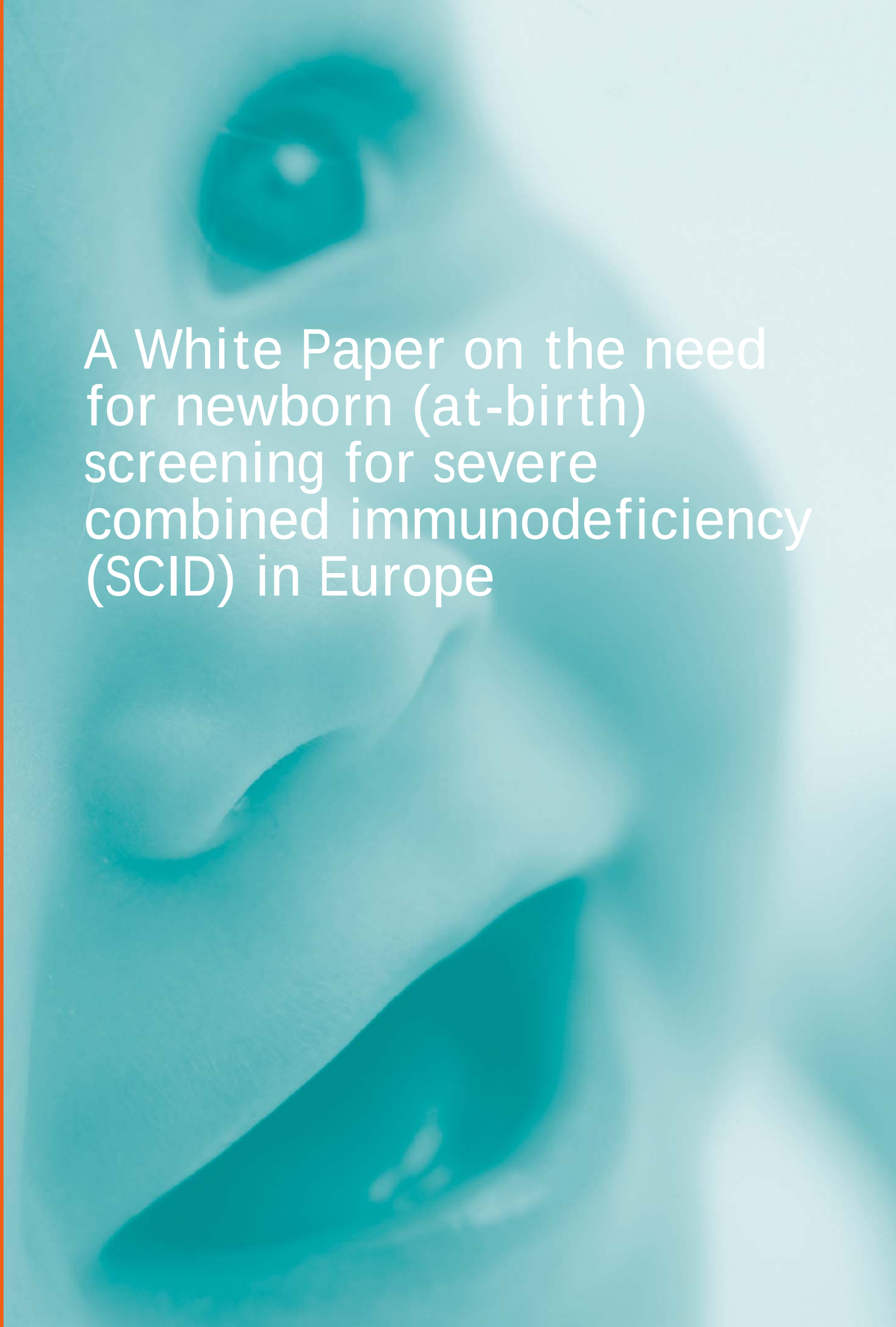

# A White Paper on the need for newborn (at-birth) screening for severe combined immunodeficiency (SCID) in Europe

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# Executive summary

- Newborn (at-birth) screening (NBS) for severe combined immunodeficiency (SCID) should be mandatory in all European countries
- SCID meets the criteria for clinical conditions that should be included in NBS programmes
- SCID is a life-threatening inherited condition for which an effective screening tool exists using standard Guthrie (dried blood spot (DBS)) samples already collected
- Delay in recognising and detecting SCID generally has fatal consequences and reduces the success of the available curative option for SCID: haematopoietic stem cell transplantation (HSCT)
- SCID fulfils the internationally recognised criteria for a clinical condition to be screened for at birth through newborn screening (NBS)
- The condition is an important health problem
  - SCID is a paediatric emergency
  - SCID is frequently undiagnosed or diagnosed too late
  - Babies with SCID have the most severe form of primary immunodeficiency
  - Unless SCID is detected at birth, infants are at risk of severe infection and death
  - Late diagnosis of SCID compromises attempts to provide successful curative treatment
- There is an accepted treatment for patients with recognised SCID
  - Haematopoietic stem cell transplantation (HSCT) is a curative treatment for SCID
  - Early intervention significantly reduces morbidity and mortality and improves quality of life for SCID patients
  - Screening for SCID would prevent children from dying before HSCT can be attempted
  - Screening for SCID would prevent serious infections and therefore improve the outcome following HSCT
- Facilities for diagnosis and treatment are available
  - There is a validated test (the T-cell receptor excision circles (TREC) assay) which can be used to screen for SCID
  - The test is performed on Guthrie/dried blood spot samples already collected at birth for NBS
  - Confirmatory testing using flow cytometry to enumerate T-cells is a routine clinical test
  - Once SCID is diagnosed, there are dedicated, specialist treatment centres where patients can be managed
- There is a recognisable latent stage
  - Children born with SCID are partially protected from infection in the first few weeks to months of life by transfer of maternal antibodies
  - However, this window of opportunity for recognising and managing the condition is short
  - Screening and detection at birth offers the vital chance to intervene before severe infection affects prognosis

- There is a suitable test for SCID which allows the condition to be diagnosed before the onset of life-threatening infection
  - The TREC assay can be performed on current NBS blood samples and has been shown to reliably identify patients with SCID
  - Use of the TREC assay allows earlier and more successful management of SCID
- The test should be acceptable to the population
  - SCID NBS involves no new testing and leads to early detection and better prospects for cure of life-threatening SCID
- The natural history of SCID is well understood
  - Without early (within weeks to months of birth) HSCT to provide cure, patients with SCID will succumb to severe infection that may be fatal and which will compromise attempts at, and the success of, curative treatment
  - The risk of death is high (90–100%)
- The policy for treatment of SCID will not be altered by the introduction of SCID NBS
  - However, the opportunity and success of curative options will be enhanced by earlier diagnosis at birth
  - All SCID cases identified through NBS will be scheduled for HSCT, as is current practice for all SCID diagnoses
- SCID is a paediatric emergency associated with a high burden
  - The burden of SCID includes high healthcare resource use and unquantifiable burden in terms of psychological and emotional impact on children and families
  - Earlier detection and diagnosis of SCID through NBS will improve prospects for curative treatment
  - Preliminary health economic evaluations suggest that the cost-effectiveness of screening for SCID compares favourably with cost-effectiveness of other health interventions
- Case finding will be a continuing process since SCID is an inherited condition
  - SCID NBS will allow detection of the disease at birth, enhancing the opportunities for cure in individual patients
  - The disease per se will not be eradicated by NBS
- The benefits of SCID NBS outweigh the harm

## SCID – A paediatric emergency

SCID is the most severe form of inherited primary immunodeficiency (Lipstein 2010). Affected children are born without cellular and humoral immunity and are therefore highly susceptible to bacterial, viral, fungal and opportunistic infections. SCID is a paediatric emergency and is life-threatening when diagnosed too late (van der Burg 2011).

The condition typically presents in infancy as failure to thrive or with severe infection that either threatens survival or compromises attempts at intervention. The treatment and prevention of such infections may prolong life, but this does not cure SCID. The only curative option is haematopoietic stem cell transplantation (HSCT) but the outcome of this is highly dependent on the clinical state of the child and the age at which transplant is performed. Newborn screening (NBS) that allows SCID to be identified at the time of birth will prevent children dying from infection and significantly improve survival after HSCT.

Haematopoietic stem cell (bone marrow) transplantation (HSCT) is an extremely effective treatment for SCID and offers a curative option, allowing the majority of SCID children to live normal and fully functional lives. However, the success of HSCT is greatly influenced by whether the affected child has already suffered recurrent or opportunistic infections (Antoine 2003) and by the age at SCID diagnosis and presentation (Antoine 2003, Buckley 1999). Transplantation performed before the age of 6 months is more effective than transplantation at later ages (Antoine 2003), and furthermore, there is evidence that when performed within the first 28 days of life, HSCT offers long-term survival benefits for infants with SCID (Myers 2002). HSCT is a lifelong curative option. In this regard, the case for SCID screening at birth can be said to be stronger than that for a number of conditions currently screened for in NBS, including cystic fibrosis and hypothyroidism where no cure can be achieved.

There is strong evidence that in families with multiple cases of SCID the outlook for the first-born child is significantly worse than that for any subsequent children, because the diagnosis of SCID in second and subsequent children may be anticipated, allowing definitive treatment to be instigated before the onset of a first, severe infection (Brown 2011).

Patients, families, healthcare workers and organisations involved in the care and support of patients with SCID recognise that the outlook for SCID patients could be changed for the better if there was earlier detection of SCID. Identifying SCID at birth through newborn screening (NBS) would permit more timely and improved opportunities for curative intervention. A number of professional clinical bodies, including the European Society for Immunodeficiencies (ESID) and the European Group for Bone Marrow Transplantation (EBMT), also actively support screening for SCID at birth.

This White Paper sets out the case for SCID to be included in national and European-wide population-based NBS programmes. The case for SCID NBS is justified by:

1. the burden and gravity of SCID
2. the ability to successfully screen for SCID in newborns
3. the evidence showing that SCID fulfils the internationally recognised criteria for a clinical condition to be included within the standard battery of NBS diseases.

As this paper will describe, the rationale for SCID NBS is further supported by evidence from NBS programmes outside Europe, and pilot studies in a number of European countries, that

lend real-world experience and data that demonstrate the feasibility, utility and benefits of SCID NBS.

## The burden and impact of SCID

The exact frequency of SCID is unknown. Estimates put the incidence at approximately 1:50,000–1:100,000 live births but this may be a significant underestimate as children may die from severe infection without an underlying diagnosis being made. The numbers of reported cases of SCID also vary according to the populations studied and may vary from one country to another.

Undiagnosed or late-diagnosed disease has a major impact upon the child and their family. In many cases, children will die early in childhood from severe infection problems before they are diagnosed or before they can be offered transplant, or will experience a high rate of problems during attempted transplant. These factors contribute to the already high healthcare resource use, social burden and costs associated with SCID.

## The solution: population-based screening at birth – newborn screening (NBS)

Newborn screening (NBS) aims to identify infants who are healthy at birth but suffer from a clinical condition known to be associated with severe morbidity and mortality.

Population-based NBS is standard practice in most countries providing integrated healthcare services and is recognised as a successful means of diagnosing a number of serious clinical conditions, such as congenital hypothyroidism, phenylketonuria, sickle cell anaemia, cystic fibrosis, galactosaemia, congenital adrenal insufficiency and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. Unlike SCID, many of these conditions included within current NBS programmes have no curative option. SCID will be the first condition that can be cured lifelong as a result of screening at birth.

## How and why SCID meets the criteria for NBS

The WHO criteria for screening are widely accepted as the template and standard to guide the selection of conditions that would be suitable for screening based on, among other factors, the capacity to detect the condition at an early stage and the availability of an acceptable treatment (Andermann 2008, Wilson & Jungner 1968). Ten criteria should be met:

1. The condition sought should be an important health problem
2. There should be an accepted treatment for patients with recognised disease
3. Facilities for diagnosis and treatment should be available
4. There should be a recognisable latent or early symptomatic stage
5. There should be a suitable test or examination
6. The test should be acceptable to the population
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood
8. There should be an agreed policy on whom to treat
9. The cost of case finding (including diagnosis) should be economically balanced in relation to possible expenditure on medical healthcare as a whole
10. Case finding should be a continuing process and not a “once and for all” project

Additionally:

11. There should be scientific evidence of screening programme effectiveness and the benefits of screening should be shown to outweigh the harm.

There is both evidence and experience to show that SCID meets each of the WHO criteria and is therefore a condition that should be included within NBS programmes.

# The case for SCID NBS

## 1. The condition sought should be an important health problem

### The supporting evidence

SCID is an extremely important inherited child health condition. Infants and children with SCID are born with no cellular or humoral immunity and are unable to fight infection. As the most severe form of inherited primary immunodeficiency, SCID is a life-threatening paediatric emergency (Lipstein 2010).

SCID is a rare condition and precise estimates of its frequency based on large scale population studies are lacking. Conservative estimates are that SCID incidence may be around 1:50,000–1:100,000 live births (in a country the size of the UK this would mean ~ 14 children born with the condition per year) but the true incidence may be higher. Early data from SCID screening programmes in the US suggest that 1:30,000 children may be born with SCID and data from countries such as Turkey, Saudi Arabia and Kuwait indicate higher rates. Where there is a high rate of consanguinity, the incidence of SCID is higher than for the general population.

Without effective intervention, the condition is associated with almost 100% mortality. A retrospective study in the UK highlights the importance of early diagnosis of SCID to outcome. In families with multiple cases of SCID, the overall survival in infants presenting first in the family is lower at ~ 40% compared with ~ 90% for siblings who were diagnosed, antenatally or at birth, on the basis of family history (Brown 2011). This study also highlighted that there was high mortality (35%) during the period before patients could receive definitive treatment. There are similar reports in the literature of improved survival following early diagnosis and treatment of SCID (Myers 2002).

SCID is a group of inherited conditions all of which are characterised by defects in T-cell development and all of which present early in life.

In the US, a number of states, recognising the important health problem of SCID, have instigated NBS (Comeau 2010, Routes 2009, Verbsky 2011). Emerging data show that the incidence of SCID varies in different states according to the ethnic mix of the population. Data (presented at meetings) suggest that in Wisconsin the incidence of SCID is 1:51,000. In California, which has a greater ethnic diversity, estimated incidence based on SCID NBS is 1:33,000. Within the Hispanic population in California, the figure is 1:22,000.

As a consequence, the US Department of Health and Human Services has recently recommended NBS for SCID across all states (Accetta Pedersen 2011).

Where SCID NBS is not available, currently, other than physician education to alert early diagnosis, there are no other means of further improving outcome for children with SCID. Physicians are only alerted once children present with infection, by which time chances of a successful transplant outcome are already compromised.

**Summary**

- SCID is a paediatric emergency
- SCID is frequently undiagnosed or diagnosed too late

- Babies with SCID have the most severe form of primary immunodeficiency (PID)
- Unless SCID is detected at birth, infants are at risk of severe infection and death
- Late diagnosis of SCID compromises attempts to provide successful curative treatment

*Key reference sources*

*Accetta Pederson 2011, Brown 2011, Comeau 2010, Lipstein 2010, Myers 2002, Routes 2009, Verbsky 2011*

## 2. There should be an accepted treatment for patients with recognised disease

### The supporting evidence

There is an accepted treatment for patients with recognised disease. Haematopoietic stem cell transplantation (HSCT) is an extremely effective treatment for SCID. For some patients, gene therapy is also an option when a suitable HSCT donor is not available. Screening at birth will change the outcome in SCID allowing more babies to have HSCT. Early intervention not only reduces morbidity and mortality and improves quality of life for SCID patients, but is curative (Borghans 2006, Brown 2011, Buckley 1999, Gaspar 2011a,b, Lipstein 2010, Mazzolari 2007, Myers 2002, Neven 2009, Puck 2007, Puck 2011, Titman 2008)

If SCID is not screened for at birth, patients suffer recurrent infection and survival is compromised. Furthermore, transplantation becomes more difficult and less successful.

The survival following transplant is significantly influenced by the type of donor available, by the type of SCID and importantly by the presence of respiratory infection (Antoine 2003). When a matched sibling donor is available, survival following transplant is over 90% but after mismatched transplants, survival is ~ 60% (Antoine 2003, Fischer 1990).

Data are available to show that survival following transplant in SCID patients diagnosed at birth (as a result of previous family history) and transplanted in the first month of life is ~ 92% (Brown 2011, Myers 2002). This outcome is regardless of donor status, the type of conditioning regimen used and the type of SCID (Brown 2011). With initiation of prophylactic antibiotics and immunoglobulin replacement at birth, SCID patients diagnosed at birth can be kept free of infection and have a significantly improved transplant outcome and less pre-transplant morbidity. Data also support the fact that the quality of long-term immune reconstitution is improved following transplant in the first month of life (Myers 2002).

In addition to this, other larger studies show that children transplanted at an earlier age (< 6 months in one study (Antoine 2003); < 3.5 months in another (Buckley 1999)) have a significantly improved survival outcome, and these cohorts included children who were not necessarily diagnosed at birth but who presented earlier.

### Summary

- There is an accepted treatment for patients with recognised SCID
- Transplantation (HSCT) is a curative treatment for SCID
- Early intervention significantly reduces morbidity and mortality and improves quality of life for SCID patients

Screening for SCID would prevent children from dying before the opportunity for HSCT and would improve the outcome following HSCT by allowing transplantation to occur before serious infection

*Key reference sources*

*Antoine 2003, Borghans 2006, Brown 2011, Buckley 1999, Fischer 1990, Gaspar 2011a,b, Lipstein 2010, Mazzolari 2007, Myers 2002, Neven 2009, Puck 2007, Puck 2011, Titman 2008*

## 3. Facilities for diagnosis and treatment should be available

### The supporting evidence

*Diagnosis*

All SCID can be diagnosed by the absence of T-cells. There is a validated test which can be used for NBS for SCID. The T-cell receptor excision circle (TREC) quantification (see below) is being used in the US and this assay is now available in Europe. A standardised commercial TREC assay is in development.

The test is performed on Guthrie (dried blood spot (DBS)) samples which are currently collected in a standardised fashion at birth, in all European countries. Thus, no additional sample collection is required for SCID to be included in NBS batteries and the test requires equipment found in most contemporary laboratories involved in NBS assays. Further confirmatory tests are routinely available in laboratories across Europe.

*Treatment*

Once SCID is diagnosed, there are dedicated, specialist treatment centres where patients are managed. Patients identified through SCID NBS will be treated according to the current protocols for care of SCID. Specialist management involves care provided at expert centres working in collaboration with transplant centre networks and according to established practices for diseases arising from inborn errors and in accord with the EBMT recommendations and guidance (http://www.ebmt.org/Contents/About-EBMT/Who-We-Are/Workingparties/Documents/EBMT_ESID%20GUIDELINES%20FOR%20INBORN%20ERRORS%20FINAL%202011.pdf).

**Summary**

- SCID can be diagnosed by the absence of T-cells
- There is a validated test (the TREC assay) which can be used to screen for SCID
- The test is performed on Guthrie/dried blood spot samples already collected at birth for NBS
- Once SCID is diagnosed, there are dedicated, specialist treatment centres where patients are managed

*Key reference sources*

*(http://www.ebmt.org/Contents/About-EBMT/Who-We-Are/Workingparties/Documents/EBMT_ESID%20GUIDELINES%20FOR%20INBORN%20ERRORS%20FINAL%202011.pdf)*

## 4. There should be a recognisable latent or early symptomatic stage

### The supporting evidence

Having no T-cell development is incompatible with life. Children with SCID are born without T-cells and therefore lack immunity. Immediately following birth, SCID can go undiagnosed as children may be asymptomatic. Since children exhibit no other physical findings, SCID is usually not diagnosed until several months after birth when infections begin. Children born with SCID are initially and partially protected against infections by the passive placental transfer of maternal immunoglobulin (Ig). There is, therefore, a short window when babies with SCID are protected – a window that exactly corresponds with the ideal window for NBS and diagnosis of SCID. However, as maternal Ig wanes in the first few months of life, the lack of endogenous immune development leads to recurrent infections. The medical literature suggests that, without newborn screening, SCID diagnosis used to be made at around 6 months of age (Buckley 1997) but current experiences are that recognition of SCID is taking place earlier. Diagnosis at birth – through NBS – would prevent onset of early infections and complications and allow an earlier curative procedure. In one cohort of SCID infants, it was shown that ~ 35% of patients presenting acutely die at first presentation of their infective problems and before transplant can be undertaken (Brown 2011).

**Summary**

- There is a latent stage during which children may not display signs and symptoms of SCID
- Children born with SCID are partially protected from infection in the first few weeks of life by maternal antibodies
- However, this window of opportunity for recognising and managing the condition is short
- Screening and detection at birth offers the vital chance to intervene before severe infection affects prognosis

*Key reference sources*

*Brown 2011, Buckley 1997*

## 5. There should be a suitable test or examination

### The supporting evidence

There is a validated test which can be used in NBS for SCID.

SCID arises from a number of different genetic defects but in all cases there is an abnormality of T-cell development in the thymus. During normal thymic processing, T-cells have to undergo T-cell receptor (TCR) gene splicing and rearrangement which leads to the accumulation intracellularly of by-products known as T-cell receptor excision circles (TREC). Importantly, TREC do not replicate when cells divide, thus they are only found in naïve T-cells that have left the thymus. In newborns, assay of Guthrie specimens for TREC offers a surrogate marker of T-cell production and activity. The test is based on assay of DNA extracted from a regular punch from a standard dried blood spot (DBS) collected at birth, with TREC levels quantified using quantitative polymerase chain reaction (PCR).

The ability of TREC quantification to distinguish between normal and SCID individuals has now been demonstrated by a number of different studies (Baker 2009, Borte 2011, Chan 2005, Morinishi 2009). In addition, in cases of maternal engraftment of T-cells, there can be a number of T-cells in the blood. These cells will not contain TREC, so the TREC screen is a better marker of naïve T-cells than peripheral blood analysis of T-cell counts.

Mutation detection is not part of the primary screen. Following a positive TREC test, diagnostic confirmatory tests will look to exclude other diseases and immunological phenotyping of peripheral blood lymphocytes will be required to establish the diagnosis of SCID. Following the establishment of a SCID diagnosis, a second tier of tests will be used to establish the SCID phenotype. There are at least 18 different genetic defects that are now known to lead to a SCID phenotype, although mutations in 5–6 genes account for the vast majority.

A number of US states have already adopted SCID NBS based on the TREC assay. The success of these programmes has recently led to the US Department of Health and Human Services recommending NBS for SCID nationwide (Accetta Pedersen 2011).

In Wisconsin, SCID NBS has been in place for several years (Baker 2010, Routes 2009, Verbsky 2011). Screening began in Wisconsin in 2008, and after 3 years of the pilot programme 207,696 babies had been screened. Importantly, the specificity of this test is > 99.98%, meaning that very few babies had to be retested. In comparison to other newborn screening tests, the TREC assay is outstanding, with high specificity and a high positive predictive value (PPV).

In the California NBS programme, screening of 265,544 samples has shown the predictive value of screening to be ~ 40% and the specificity > 99.99%.

Approaches to laboratory tests and procedures are being standardised (Borte 2011).

**Summary**

- There is a suitable test for SCID which allows the condition to be diagnosed before the onset of life-threatening infection
- The test, TREC assay, can be performed on current NBS blood samples and has been shown to reliably identify patients with SCID
- TREC assay allows earlier and more successful management of SCID

*Key reference sources*

*Accetta Pedersen 2011, Baker 2009, Baker 2010, Borte 2011, Chan 2005, Morinishi 2009, Routes 2009, Verbsky 2011*

## 6. The test should be acceptable to the population

**The supporting evidence**

*Blood sample – collection and use*

The test for SCID can be carried out on samples currently collected for NBS (no additional procedures or bloods are required).

The Guthrie/DBS is acceptable and the TREC test follows the same procedures for established methods of newborn disease screening. Screening for SCID is in accord with existing protocols for sampling and screening – samples are not stored or used for research purposes and the screen does not generate any genetic data.

*Communication*

Positive diagnoses will be counselled as is the case for other diseases detected through NBS. Families can be offered evidence that early detection is favourable in terms of opportunities for cure, over delayed diagnosis.

*Current advocates for SCID NBS*

In the US, the drive for newborn screening (NBS) has been enthusiastically supported and, in part, funded by the Jeffrey Modell Foundation which is a patient-led organisation that supports research and education into primary immunodeficiencies. The Immune Deficiency Foundation also supports SCID NBS.

In Europe there is support for newborn screening for SCID from immunodeficiency patient organisations. Notably, IPOPI (the International Patient Organisation for Primary Immunodeficiency) has advocated and presented to the European Parliament a request that NBS for SCID is implemented across Europe. The PiA (UK Primary Immunodeficiency Association) has apprised the UK Parliament of the case for SCID NBS and similar delegations have called for SCID NBS in Sweden.

**Summary**

- The SCID NBS test should be acceptable to the general population
- SCID NBS involves no new testing and leads to early detection and better prospects for cure of life-threatening SCID

## 7. The natural history of the condition, including development from latent to declared disease, should be adequately understood

### The supporting evidence

The rare nature of SCID means that there are no prospective cohort studies of untreated patients. However, it is known that without intervention SCID children will inevitably become infected with opportunistic, viral, fungal or bacterial pathogens from which they will die.

On diagnosis of SCID, treatment of any infection is instigated and patients are then commenced on prophylactic antibody replacement, the latter in an attempt to provide the patient with some capacity to fight subsequent infections. Replacement therapy (*ie* provision of replacement immunoglobulin therapy) is not appropriate in SCID.

Following their SCID diagnosis, attempts will be made to treat all patients with a definitive therapy: normally an allogeneic bone marrow transplant (HSCT). A number of major studies have documented positive outcomes following HSCT, and highlight that a history of previous infections is a significant risk factor in the mortality following transplant (Antoine 2003, Fischer 1990, Gennery 2010, Grunebaum 2006).

**Summary**

- The natural history of SCID is well understood
- Without early (within weeks to months of birth) HSCT to provide cure, patients with SCID will succumb to severe infection that may be fatal and which will compromise attempts at, and the success of, curative treatment
- The risk of death is high (90–100%) in the first few months of life

*Key reference sources*

*Antoine 2003, Fischer 1990, Gennery 2010, Grunebaum 2006*

## 8. There should be an agreed policy on whom to treat

### The supporting evidence

Current practice is to offer all children with a SCID diagnosis potentially curative HSCT. This will not change with NBS, however the earlier recognition of SCID will allow HSCT to be more effective in more patients. It is likely that NBS for SCID will allow management to be less costly.

Once SCID is diagnosed, there are dedicated, specialist treatment centres where patients are managed. Patients identified through SCID NBS will be treated according to the current protocols for care of SCID. Specialist management involves care provided at expert centres working in collaboration with transplant centre networks and according to established practices for diseases arising from inborn errors and in accord with the EBMT recommendations and guidance.

It is important to note that there are no randomised studies comparing HSCT with supportive therapy only. There is an intention to treat **all** SCID children by HSCT although some individuals will die from infection prior to transplant.

In two forms of SCID (X-SCID and ADA-SCID) (Aiuti 2009, Gaspar 2011a and b, Hacein-Bey-Abina 2010) additionally gene therapy and enzyme replacement therapy may be considered when no fully matched donors are available and patients are treated within the remit of tightly regulated clinical trials. Entry criteria for these studies are available. Enzyme replacement therapy is available for ADA-SCID and is often used as an interim measure until definitive therapy by HSCT or gene therapy is available.

**Summary**

- The policy for treatment of SCID will not alter with the introduction of SCID NBS
- However, the opportunity and success of curative options will be enhanced by earlier diagnosis from birth
- All SCID cases identified through NBS will be scheduled for HSCT, as is current practice for all SCID diagnoses

*Key reference sources*

*Aiuti 2009, Gaspar 2011a and b, Hacein-Bey-Abina 2010e*

## 9. The cost of case finding (including diagnosis) should be economically balanced in relation to possible expenditure on medical healthcare as a whole

### The supporting evidence

The cost of case finding of SCID is likely to be economically balanced in relation to the expenditure on medical healthcare as a whole. Detection of SCID at birth allows for a child to be given curative treatment. This avoids many of the high costs involved in managing disease detected later where complications require protracted and expensive intensive care management. Cure also negates the unquantifiable human, family and social costs associated with undiagnosed SCID.

A report by the EU Network of Experts on Newborn Screening (Report on the practices of newborn screening for rare disorders implemented in Member States of the European Union, Candidate, Potential Candidate and EFTA Countries) prepared in 2012 notes that epidemiological evidence and costs (and cost-effectiveness) are the main reasons to screen for a disorder at birth. This report provides insights into society's willingness to pay for NBS for rare diseases. Across Europe, annual costs for national neonatal screening programmes range from €70,000–15,000,000 according to the number of conditions screened for, such that in terms of gross domestic product this ranges from 0.00021% to 0.00323% for all NBS.

There is emerging evidence on the costs of case finding based on NBS for SCID. In the United States, the estimated cost of SCID screening is $4.22 per test based on machine usage, labour and reagents. Costs for confirmatory testing were estimated at $250 per patient including complete and differential blood counts and lymphocyte phenotyping.

In terms of the cost-effectiveness of SCID NBS there are no prospective data. However, a number of studies have attempted to model the costs of SCID NBS. These studies may significantly underestimate the true costs of managing SCID which is diagnosed late – costs that include intensive care costs, drug costs and carer costs.

Evidence from a US cost evaluation in 2005 suggested that there is an 86% likelihood that NBS for SCID would be cost-effective. The evaluation assumed a 61.2% false negative rate, a 3.2% false positive rate, test costs of $15 per screen and SCID treatment costs of $1.35 million. This US study suggested that while a nationwide SCID NBS programme would cost $23.9 million per year, it would result in 760 years of life saved per year of screening at a cost to detect one case of SCID of $485,000 (McGhee 2005).

A more recent study has formally evaluated the cost-effectiveness of screening for SCID using a Markov model (Chan 2011). The study computed that over a 70-year time horizon, the average cost per infant was $8.89 without screening and $14.33 with universal screening. The model predicted that universal screening in the US would cost approximately $22.4 million per year with a gain of 880 life years and 802 QALYs. The estimated screening cost was $4.22 per infant. This study shows that screening for SCID is likely to be cost-effective because the condition is rare, limiting the overall number of infants requiring treatment, and because of better health outcomes and lower costs associated with earlier HSCT.

Cost-effectiveness of screening for SCID compares favourably with cost-effectiveness of other health interventions: $28,000 per QALY (based on the initial assumptions) would be considered moderately or highly favourable based on the scale proposed by Weinstein et al (Weinstein 1977).

A preliminary study of the costs of SCID NBS in France has been undertaken, based on calculating the cost benefits from stem cell transplantation performed before the age of 3 months rather than delayed engraftment (Durand-Zaleski personal communication). The analysis suggests that NBS could detect around 12 cases of SCID per year among 830,000 live births, at a cost of circa €3.4million for systematic screening including phenotyping. This study suggests that the ability of screening to detect children who would otherwise be missed would save around 150 life years. The medical costs for stem cell transplantation after the age of 3 months are €195,800. Direct non-medical costs to the payer, including disability benefits, add an average €1,000 per child. Stem cell transplantation costs €86,180 when performed before the age of 3 months. An early detection of the disease would therefore be expected to reduce the cost by €110,000 per child.

* *Professor Durand-Zaleski acknowledges that this work was conducted together with Dr. C Le Bihan-Benjamin (Necker Enfants Malades Hospital, Paris, France), Dr Marie-Caroline Clément (Hôpital Henri Mondor, Paris, France) and Claudine Maurey-Forquy (Necker Enfants Malades Hospital, Paris, France)*

**Summary**

- SCID is a paediatric emergency associated with a high burden on resources and quality of life
- The burden of SCID includes high healthcare resource use and unquantifiable burden in terms of impact on children and families
- Earlier detection and diagnosis of SCID through NBS will improve prospects for curative treatment

- Preliminary health economic evaluations suggest that the cost-effectiveness of screening for SCID compares favourably with cost-effectiveness of other health interventions

*Key reference sources*

*Chan 2011, McGhee 2005, Weinstein 1977*

## 10. Case finding should be a continuing process and not a "once and for all" project

### The supporting evidence

SCID is an inherited condition. Unlike acquired conditions such as infectious diseases, this means that a screening programme to find SCID cases will not lead to a "once and for all" eradication of the condition. Babies will continue to be born with SCID. However, by detecting the disease at birth, the opportunities for cure are enhanced. As an inherited condition, SCID incidence will remain steady and therefore NBS for SCID will have long-term value.

### Summary

- Case finding will be a continuing process since SCID is an inherited condition
- SCID NBS will allow detection of the disease at birth, enhancing the opportunities for cure in individual patients
- The disease per se will not be eradicated by NBS

*Key reference sources*

## 11. The benefits of screening should be shown to outweigh the harm

### The supporting evidence

To date, screening programmes in the US have been initiated in Wisconsin, California, New York State and Massachusetts. On the basis of evidence so far, in January 2010, the Advisory Committee on Heritable Disorders in Newborns and Children voted unanimously to add screening for SCID to the core panel for universal screening of all newborns in the United States.

A systematic review undertaken and recently published concluded that 'Evidence from large case series indicates that children receiving early stem cell transplant for SCID have improved outcomes compared with children who were treated later' (Lipstein 2010).

Reports on the progress and successes of SCID NBS in US states can be found at http://idfscidnewbornscreening.org/

Data available so far highlighting the benefit of SCID screening include:

**California:**

- 265,544 babies screened in ~ 6 months
- DNA amplification failure rate 0.12%, comparable to failure rates for other screened newborn conditions
- Positive rate for TREC screen (requiring flow cytometry) in 30 of 265,544 (0.001%)
- Of those 30, 12 (40%) were SCID (8) or severe T-lymphocytopenic (4)
- PPV 40%, specificity > 99.99%
- All identified patients are alive. Those with SCID that have been transplanted are alive and well

**Wisconsin:**

- 207,696 babies (188,741 full term) screened in 36 months
- Positive rate for TREC screen (requiring flow cytometry) in 72 of 207,696 babies (0.038%)
- Of those 72, 35 (48%) were SCID or severe T-lymphocytopenic
- PPV 48%, specificity > 99.98%
- All identified SCID patients are alive and those that have been transplanted are alive and well

**Summary**

- The benefits of SCID NBS outweigh the harm

*Key reference sources*

*Lipstein 2010*

## The call to action

The authors of this White Paper consider that:

- SCID meets the criteria for clinical conditions that should be included in NBS programmes
- SCID is a life-threatening inherited condition for which an effective screening tool exists to allow NBS from standard Guthrie (DBS) samples
- Delay in recognising and detecting SCID generally has fatal consequences and reduces the success of the available curative option of HSCT
- NBS for SCID should be mandatory in all European countries

## Acknowledgements

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