UK National Screening Committee

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Newborn screening for Severe Combined Immunodeficiency (SCID) – an evidence review

Consultation comments pro-forma

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Do you consent to your name being published on the UK NSC website alongside your response?

Yes X ☐ No ☐

Do you agree with the proposal to undertake a practical evaluation of newborn screening for SCID in the NHS?

Yes X ☐ No ☐ but see comment below

Please explain why you agree or disagree with the proposal.

Comment: PID UK is very disappointed that a full national screening programme has not been recommended at this stage given that the criteria for implementing a newborn screening programme for SCID have been met as attested by the conclusions in the systematic review and

economic analyses produced by UKNSC.

However we support and welcome the recommendation to proceed with an evaluation study as the next 'best step' with the following caveats:

1. **That the proposed evaluation study is of a sufficient scale in order to pick up enough cases to make the necessary evaluations.** This is essential due to the low incidence of SCID.
2. **That the regions chosen in the study are reflective of the ethnic composition of the UK population.** This will help ensure that accurate data is obtained.
3. **That the necessary resources to carry out such a study will be made available by UKNSC.** This is essential for its success and implementation.
4. **That the exact timelines of the evaluation study are defined at its outset.** We suggest that a reasonable amount of time would be 1 year with 2 years as a maximum. An evaluation study should not be used as an opportunity to further delay implementation of a full screening programme, the evidence for which is already compelling.
5. **That the questions that the evaluation programme seeks to address are reached by expert consensus and are clearly set out in an open and transparent framework.** This will help ensure that the 'goalposts' are not changed further down the line. Clarity is needed on when enough evidence, is enough.
6. **That an interim analysis based on specific criteria is carried out at a defined time point during the evaluation study.** If certain criteria are met then we need to be assured that a full national screening programme will be implemented as quickly as possible.

On which consultation document are you commenting?

The systematic review ☐ X **The modelling and cost effectiveness evaluation ☐ X**

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Systematic review	Overall comment	The review is comprehensive and states that the key criteria for screening have been met. As such this document fully supports the implementation of a newborn screening programme for SCID. PID

		UK therefore does not understand why UKNSC are seeking to address other questions.
		A screening programme would allow early diagnostic and the start of care and treatment for ALL families, not just those for whom a prior devastating experience had made them alert to the risk in future children.
	Impact of UK NSC decision on families who have lost their child to SCID	There is bewilderment, frustration and anger among bereaved families that newborn screening for SCID has not yet been fully implemented in the UK. Bereaved families know that there is a solution ready so that other families do not have to go through the agony of seeing their child's health deteriorate in terrible circumstances and the pain of bereavement **(see below).** They are also at a loss to understand why the UK is lagging behind other countries in implementing SCID NBS (**see below)** especially when cures for the condition are proven and available.
	Public support for SCID screening	Screening for SCID has public backing. A petition, 'Stop the unnecessary deaths of babies. Include SCID in the UK new-born screening programme' set up by a mum whose child died due to SCID not being picked up early enough has received over 25,000 signatures. https://www.change.org/p/uk-newborn-screening-committee-stop-the-unnecessary-deaths-of-babies-and-include-scid-in-new-born-screening-programme.
Page 6	1. Importance of early diagnosis and curative intervention for affected children and families.	The document does not address the parent/carer perspective of the importance of an early diagnosis of SCID. We have therefore included testimonies from bereaved parents who lost their child because their SCID wasn't picked up early enough. These stories exemplify the diagnostic odyssey that parents can go through to get a diagnosis of SCID (at cost to the NHS and emotional and financial toll on parents), the importance of early intervention and the horror and anguish of losing a child when this could have been avoided through a screening test. 1. **George's story told by his mum Rachel.** 'Our family has been personally affected by SCID. Our baby son George Jack Carpenter was born with X-linked SCID, he died on 25th August 2011 at 11 months old, just 10 days before his 1st birthday. This is our sad story, please let me share it with you to give you an insight into why it is so important that this curable condition is detected at birth. George, our second son, was born on 5th September 2010. He was a huge baby weighing 10lbs

		8oz. He was very strong, alert and engaging. George had his routine heel prick test done when he was 6 weeks old and the results came back negative. George appeared very healthy, we had no concerns. He fed well, gained weight and thrived. We already had a son called Reece, who was 2 years of age. His brother had been well and healthy, we had no idea that I was a carrier of X-Linked SCID. The first few months of family life were great. We did normal everyday things. I took Reece to toddler groups and we went and visited family and friends and showed off our new smiling, happy baby to everyone. A few months later it was Christmas. We shared a happy first Christmas together with George, we were very happy, we opened presents and enjoyed the day feeling blessed that we had 2 beautiful healthy boys. Had we known it was to be George's first and last Christmas we would have been absolutely horrified. Once George reached 5 months of age, at the beginning of February, things took a dramatic turn for the worse. I can only describe what happened over the course of the next 2 and a half months as utterly nightmarish. George developed a cough and cold that he just could not get over. This developed into a chest infection. Despite going to our GP and having antibiotics prescribed George did not get better. George began to develop breathing difficulties. This was very frightening and often he would become worse at night. During the whole of February and March and half way through April we were back and forth from the GP, to the out of hours "Grab a Doc" service and multiple visits to Accident and Emergency. In total we visited A&E 6 times during those 2 months, we visited the "Grab a doc" out of hours service twice and our GP 3 times and also saw our health visitor. George was hospitalised on 4 occasions at our local hospital, Queen Elizabeth in Woolwich. Consultants were baffled; they couldn't understand why George was repeatedly ill and having lengthy stays on the ward. The first and second admission was put down to bronchiolitis and the 3rd admittance was put down to pneumonia, but on the 4th stay they really didn't know what was wrong. They thought George may have whooping cough or Cystic Fibrosis so he was tested for these conditions but both came back negative. During these 2 months of toing and froing and sitting for hours upon hours in A&E waiting room and in Grab a Doc centres and GP waiting rooms etc we were, unbeknown to us, exposing George to even more germs and viruses. George began to rapidly lose weight. He had been a good weight at birth and had been on the 98th centile, which is just as well, as by the time George was finally diagnosed at 7 months he was on the

		25th centile and weighed less than he did when he was 4 months old. Now during these 2 months of consultants trying to reach a diagnosis George was growing weaker and I could see that he was wasting away. I had asked a consultant if George was dying and he laughed off my concern and said “Children lose weight when they are ill”. I began to be afraid of the hospital discharging George home because he would become unwell within a few days of being home and I found the worry unbearable. I felt as though George was being pumped with IV antibiotics, he would perk up and then we would be discharged and then a few days later the nightmare would continue. George would struggle to breath and we would be back at A&E again. Even on our 4th admission the plan had been to get George well and send him back home while we wait for an outpatient appointment for the allergy clinic. They had also referred him as an outpatient to Kings Respiratory and GOSH immunology department, although the immunology was being pursued as a sideline. There was no sense of emergency and I was worried George didn’t have time to wait. I took it upon myself to contact Kings Respiratory and GOSH and asked if they had received the referral letters. I found out after calling them that neither had received the referral letters. So I faxed the letters over myself and rang to confirm receipt. Once GOSH had the letter they acted on it and asked for George’s bloods to be taken and couriered to them. The next day we were transferred to GOSH where we received the most shocking and devastating news, George was diagnosed with SCID. I felt my world crash around me! I had thought something was wrong but I had no idea how serious it was! It was so shocking I had a panic attack and had to leave the ward to get some air. Now during all of this my husband was still working full time and our 2 year old son was being passed from pillar to post while I was on the hospital ward or at A&E and sometimes Reece, our older son, had to come with us when we had to rush George to the Grab a Doc centre in the middle of the night. This put a huge strain and worry on the whole family. The uncertainty of it all was very stressful. Once George received a diagnosis even though it was terrible we knew that at least he would now receive the care and treatment he desperately needed and the diagnosis also confirmed to us that we were not going crazy, he really did have something wrong with him. By the time we got George diagnosed he was ravaged with infections. He had PCP Pneumonia which can be fatal in SCID patients, he had influenza and he also had to cope with a horrible common tummy bug called “Rotavirus” which in people with a functioning immune system would just be a 24hr sickness bug but with George as his body couldn’t fight it he would have to contend with it until he had his transplant. George was malnourished due to these illnesses. His lung was also partially collapsed upon arrival

		to GOSH. I had been breastfeeding George and unknown to myself my milk contained cytomegalovirus (CMV), which would be harmful to a SCID baby so I had to cease breastfeeding. Over the next 6 weeks George was an impatient at GOSH he got over the PCP Pneumonia and was given gut rest and nourished back to better health. We were discharged home to live in isolation while a donor could be found on the register. A 10/10 match was found but the donor lived in Germany and it would take time to organise. We went home. I was scared to go home and after just 3 weeks George became unwell again. He began to spike temperatures and slept for much longer than normal. He also started to cover his eyes and vomit. He was not himself, he had no energy. We went back to our local hospital they took bloods and found markers for infection and so we were transferred back to GOSH. Over the next few days Georges leg started to tremor. At first this was put down to malnutrition but it soon became clear and to our horror that it was neurological. The tremors became more pronounced. They thought he could possibly have a virus on the brain. We had no time to wait for George's 10/10 BMT match as George needed an immune system as soon as possible. So a cord was used instead that was an 8/10 match. George was too unwell for chemotherapy conditioning which is the usual procedure prior to transplant. George began to have seizures. Ironically the BMT had engrafted well but the virus was attacking George's brain. We then received the most horrific news ever that George was now profoundly brain damaged. We felt defeated, I felt as though the fight was over, we were absolutely devastated. A few weeks later George died as the virus had attacked his brain stem. He died from encephalitis. The suffering George went through was indescribable, he fitted to death in our arms and to think that this could have all been prevented from early screening and diagnosis makes me feel physically sick and very angry. SCID babies need to be identified at birth. SCID babies look completely normal unlike other genetic conditions there are no physical signs or markers. Doctors cannot identify it, this means that there are huge delays in getting these children diagnosed and by the time they are diagnosed they are in no fit state to survive a transplant. It seems crazy that there are 2 specialist centre in the UK geared up to treat SCID (GOSH & Newcastle) but no diagnostic test is in place to give these babies a chance at life. **The need for a screening programme** I feel sure that George would be alive today had he been identified as having SCID when he was born. He was so healthy the first few months of life we would have had time for him to receive a 10/10 match and we could have kept him well by keeping him isolated and away from infection. **Losing a child never leaves you**

		The psychological impact of this tragedy has been immense. Reece was 3 when George died and is still confused by what happened. The whole family have been shocked and emotionally upset, we have literally been to hell and back. Losing a child never leaves you. I would like to think that this could be prevented from happening to other families in the future. There are currently two conditions rarer than SCID that are on the heel prick test and SCID is the only condition that is curable if found at birth with a 95 percent survival rate. It is also more cost effective to screen for it than not to and would cost just £2.50 per child. We need to get this condition onto the screening programme to save lives and prevent suffering to the patients themselves and their families. If all SCID babies die before the age of 1 without treatment then George didn't stand a fighting chance having been diagnosed at 7 months. George battled bravely and smiled throughout his ordeal. If SCID is put onto the new born screening programme I would feel happy that such a great positive can come out of this awful tragedy. We were fortunate to go on to have another son a year after George died. I was able to have screening when I was pregnant to determine if he was well or not. Luckily Ethan was not affected. George was one of the fortunate babies to have been able to receive a diagnosis. How many babies die from pneumonia and other infections when really SCID is the underlying course? No family should have to endure what we have had to go through. All we ask is that you read our story and help to get this test implemented immediately.' 2. **James's story is told by his mum Susie.** 'I would like to share our story with you about our baby son James, who we tragically lost in February 2017 as he had Severe Combined Immunodeficiency (SCID). James was born a healthy baby on the 23rd February 2016, weighing in at 8lb 8oz. James was two weeks overdue and so I had to be induced to have him. Now I know why our poor little boy didn't want to come out sooner. Myself and James's dad, Justin, were so relieved when James arrived safe and well. We both have 2 boys each from a previous relationship and James just completed our family. Everything was fine until James developed a bit of a cold at 5 weeks old. I took him to our GP who checked him over and said it was just a cold and indeed he did improve over the next few days, although his weight was starting to drop off a bit and I was recommended by my Health Visitor to change his milk formula to see if that helped.

		At 8 weeks old James had his 8 week check-up with the GP and then saw the nurse for his first lot of immunisations. As soon as I got James home he started coughing. I remember thinking it was strange and thought it must be a reaction to the immunisations. The cough got worse and I was so concerned that I rang the out of hours 111 service on the Saturday for advice. As James was so little they advised me to take him to see the out of hour's doctor at our local hospital, which we did and the doctor said he had a temperature and cough probably as a result of the immunisations and to just give him some Calpol. However James didn't get any better over the following days and so I took him back to our GP. The GP didn't like the sound of James's cough and agreed that his weight was still dropping off and sent us to the Jenny Lind Children's Department at our Local Norfolk and Norwich Hospital. James was kept in for 6 days as he required oxygen and IV antibiotics as they said he had pneumonia. We were discharged home but James just didn't improve. I took him back to my GP 3 times within the next two weeks as I was concerned that he wasn't showing any signs of improvement and in fact was getting worse. My GP prescribed oral antibiotics and said it would take a while for him to get over a serious chest infection. But when I took him to the GP for the third time I was extremely concerned as James wouldn't even feed and he looked terrible. My GP said he had thrush in his mouth probably from all the antibiotics and as I expressed concern that he was breathing very fast. She sent us back to the Jenny Lind Children's Department. When we arrived at the Hospital the doctor came round and said they were really busy but that James looked ok and they would put him on a monitor and get to him as soon as they could. The nurse put him on a monitor and was shocked to see that his sats were at 47%. All of a sudden doctors and nurse came running into the room and it turned out that James was having some sort of vacant seizure and he almost stopped breathing. Doctors were concerned he may have meningitis so they performed a lumbar puncture which came back ok. James was admitted onto the High Dependency Unit and underwent a range of tests, including loads of blood tests, 3 lumbar punctures, an EEG, MRI scan of his brain and CFS monitoring and the doctors were telling us that James was still suffering from Pneumonia and that now he has epilepsy. We were devastated that James had epilepsy and I wondered how we would ever cope at home if he kept having seizures. Little did I know then about the nightmare that was about too unfold. James deteriorated every day he was in hospital over the next two weeks and despite myself and Justin expressing our frustration and concern with the doctors there, they were adamant that James just had a chest infection and epilepsy. After being in there for two weeks James was in an awful way. He required increasing amounts of oxygen, couldn't tolerate feed even through his NG tube so

		was just on fluids and he just laid there completely lifeless. It was only when James eventually had an echocardiogram which was very abnormal that the doctors said they didn't know what was going on and that James needed to be ventilated and transferred to Addenbrooks or Great Ormond Street Intensive Care Unit. Addenbrooks were the only one to have a bed on PICU and so James was transferred by the CATS team that day. The doctors repeated all of the tests that James had had done in Norwich and carried out further tests that were recommended by GOSH. After 4 days at Addenbrooks the doctors told us that they thought James had SCID and he would need to be transferred to GOSH for urgent specialist care. James was then moved again by the CATS team to GOSH on the 3rd June 2016. The doctors at GOSH were amazing but were extremely concerned about how poorly James was and told us that he may not survive as his body was being destroyed by the cytomegalovirus (CMV) virus. James had to be put on an oscillator ventilator as he was struggling on the conventional ventilator and this was a massive step backwards. We also found out from the Ophthalmologist at GOSH that James had CMV retinitis which had been present for at least 10 days earlier and that it had caused so much damage to his eyes that he would be blind. This was yet another blow and we were distraught at the thought that this had been missed at our local hospital. James was on a ventilator for three weeks but with intensive treatment did eventually come off the ventilator and after a short time on CPAP was able to breathe all by himself. He was extremely weak and couldn't move but we were so relieved to finally be able to hold him. He had lost so much weight that he had dropped right off the centile chart. The doctors from Immunology were brilliant and they told us that they felt James' only chance was to have a stem cell transplant, but that he was too weak to have a full bone marrow transplant with Chemotherapy so they would use cells from Justin who was only a half match, but with regular immunoglobulins this would be his best chance. Justin donated his T-cells to James on the 4th July 2016. We were told it could take up to six months for the cells to engraft and James would be tested regularly to check for engraftment. James perked up a lot while on the ward in GOSH. He even managed to feed through a bottle, only requiring his medication down his nasogastric tube (NG tube). He gained a little strength in his arms with regular physiotherapy and started to gain a little weight. We were transferred back to our local hospital on the 21st July 2016 to try and establish a relationship with the doctors there as they would be the first point of call if James got poorly. We were not happy about this as we feel they let James down immensely and as a result he got so poorly with lasting consequences. After only being at the Norfolk and Norwich Hospital for two days James got very sick and again couldn't tolerate any feed. His eyes then started to go yellow and

		after much pushing and complaining at the lack of care yet again from the doctors there, James was transferred back to GOSH by ambulance for review by the immunology team. They discovered that James had gallstones and a stone was blocking his bile duct. He was going to be considered for surgery at Kings Hospital London, but thankfully the stone dislodged and James returned to a normal colour and managed to start feeding again. After ten days we were able to be discharged home as we refused to go back to our local hospital. However, my twins at home had got chickenpox so we were unable to expose James to them. So we did a house swap with Justin's parents who stayed with my twins and we then stayed at their house with James while the twins got over the chicken pox. A week later we were finally able to move back home and be a family again, albeit a very different family. Because James still had no immune system he couldn't be exposed to anyone who was poorly, even with a simple cold, and we had to limit the number of people he could be around and had to be very strict with hand washing and cleanliness. After a couple of weeks at home where James seemed to be doing well, he started to have seizures again. They were different to the last ones and after another hospital admission GOSH diagnosed him with infantile spasms as a result of all the scaring on his brain which the CMV virus caused. They gave us yet more devastating news that infantile spasms were very difficult to control and meant that James would be severely disabled if he even survived. Going home with yet more bad news was horrendous and so hard to comprehend. However we weren't prepared to give up and with a change of medication the seizures stopped and with regular physiotherapy and lots of hard work James proved he was a fighter once again and gained some head control and even managed to play with his toys on his play mat. He started smiling which was amazing and I actually thought we were going to win this fight. We had regular clinic visits to GOSH where they checked for engraftment, but unfortunately it seemed that the transplant hadn't worked as there was no sign of any T-cells. In November we started talking about arranging for James to have a full BMT with chemo in the New Year, six months post last transplant as he had made such good improvement. But unfortunately just before Christmas James started having seizures again and they were constant and very damaging to James. Christmas was stressful and sad and it was so hard watching James constantly have seizures. The way he would cry out and the fear in his little eyes was horrendous. After another admission to GOSH in January where James had lots more tests, the doctors told us that the CMV virus had once again taken over James's body and that because of the infantile spasms he would be so severely disabled that they would not be able to do a BMT for James as he

		just wouldn't survive it. After long and distressing discussions with the doctors, we had to agree to take James home with palliative care. We were lucky to have the help of the East Anglia's Children's Hospice at Quidenham and the nurses were lovely, helping me to keep James as comfortable as possible at home. James died three weeks later in my arms on the 18th February 2017, five days before his first birthday. **Our famly is broken** We are absolutely heartbroken. I can't believe we have lost James when we just thought he had a chest infection. His brothers have been hugely affected by the amount of time we have been so far away from home in hospital and now to have lost James after all he went through. Our family is broken. **The need for SCID screening** We have since learnt that SCID can be tested for as part of the newborn screening programme and that it is currently being done in many states across the USA and in other countries too. To learn that the UK does not include SCID as part of the new-born screening programme is incomprehensible and frankly disgusting. And after finding out that this test would only cost £2.50, I am horrified that we have lost our son for such a tiny cost of a simple test. SCID is a life threatening condition and there is a test which can diagnose it at birth and if diagnosed early and treated, has a 95% survival rate. In fact I understand that if SCID was included in the new-born screening programme that it would be the only condition which could be diagnosed by the heel prick test that can be cured. I am horrified that my baby's life wasn't even worth £2.50 to this country. I wonder how many tests could have been carried out on babies across the UK for the cost of all of James' treatment when he was so poorly. It seems ironic that it cost us more to park our car at our local hospital when we went to have James then it does to perform a life-saving test. This test should have been available for our James. He should still be here with me. But he's not and I have to try and live with that every day. I sincerely hope that the screening committee takes some responsibility and finally does what they should have done years ago and include SCID in the newborn screening programme. With all the unrest and horrible diseases in the world which can't be cured and take so many lives, we have the opportunity to save the lives of innocent babies; why would you not take it. James certainly wishes we did much earlier. The image of my baby's still cold body will haunt me forever. Putting his precious little body into a

		casket on the day of his funeral, knowing I will never see him again. I can't even begin to describe how that feels. I hope no other baby is made to suffer the way that James did. We cannot let this carry on. Losing James has broken my heart and ruined mine and my family's lives.' 3. **Aimee's story is told by her mum Suzanne.** 'My daughter, Aimee, died in January 1997, aged 5 years. She died from B Cell Lymphoma driven by the Epstein Barr Virus as a direct result of, what could only be described at the time, as 'leaky SCID'. Aimee had been poorly almost since birth. Within 24 hours she developed a rash all over her body and would sweat profusely when she tried to feed. She also started with a cough when she was approximately 6 weeks old. At 5 months of age she was admitted to Royal Manchester Children's Hospital with what was later diagnosed as Cytomegalovirus. Within those first 12 months of her life she was admitted to hospital 6 times, each time for at least 2 weeks and it was then that a primary immunodeficiency was suspected. Unfortunately, due to there only being 2 centres in the UK with specialised paediatric knowledge of PID, Aimee was treated by a Consultant Paediatrician at our local general hospital and it wasn't until she contracted chickenpox aged 5 which then set off a chain of tragic events leading to her developing B Cell Lymphoma. Aimee was admitted to Booth Hall Hospital on November 22nd 1996, was diagnosed with Lymphoma on 29th November and admitted to ICU on 1st December. In her notes from the 1st December, Dr Will Consultant Haematologist wrote 'so much to do, so little time'. He recognised that Aimee had a very severe form of immunodeficiency and that she should be under the care of either GOSH or Newcastle, however by that time she was too sick to be moved. All of Aimee's notes were sent by taxi to Newcastle and were reviewed by [redacted] whose professional opinion was that Aimee had a 'leaky SCID' which should have treated by a bone marrow transplant (BMT) at birth. A BMT was carried out at the beginning of January 1997, however Aimee was too poorly and she never recovered. It is my strong belief that if newborn SCID screening had been in place when Aimee was born then it would have been detected that Aimee had a complex immunodeficiency and she would have received timely and appropriate treatment, possibly resulting in saving her life. Obviously for me the most important outcome that this screening could have had for my family is that my daughter could have been alive today, thus avoiding Aimee's suffering and also the devastating effects that grief have had on Aimee's father and I and also her brother.

		For the NHS and the government though, screening at birth (hopefully picking up immunodeficiencies early) would have saved hundreds of thousands of pounds and valuable resources both human and material. It does not make any financial sense to me why this newborn screening would not be implemented and it certainly does not make any humanitarian sense for it not to be implemented.'
	2. Impact of late diagnosis of ADA-SCID on child and family.	Parent testimonies from families affected by ADA-SCID provided to PID UK through a survey: 1. 'My son who is 8 years old now, got sick around 8 months old. He had been diagnosed with ada-scid when he was 14 months old. He had a bacteria called pneumococcus and that bacteria shut down both his kidneys but sometime in his life he will need a kidney transplant.' 2. '[redacted] wasn't diagnosed until she was 2 years old and by then she had suffered a lot through infections/pneumonia and other complications. This has had an impact on her future health and treating her by the usual means of BMT was not possible initially and was still not the preferred option later on. ' 3.'[redacted] struggled at school due to time off for weekly infections and other appointments. She ended up repeating her last year of primary school to catch up. Due to her ADA not being picked up early enough she has been left with life-long lung issues and serious kidney problems, as well as the issue SCIDs bring. Emotionally, especially as getting older she struggled with what had to happen to her.' 4. 'Exposed my son to a life of serious risk. As stated my son's weakened state meant staying in a laminar flow room. We wore gowns over aprons, hairnet/hat, covers on shoes and had to scrub. My son had to be in a head box for 100% oxygen then induced coma and ventilated for few weeks. I was told to prepare for my son's death!. Drains were needed for burst air sacs by the ventilator followed by suction for mucus. A permanent line put in chest for meds and to take blood. Fluid retention from ventilator. Around 3 weeks the last thing to try was nitric gas which after 4 hours his oxygen levels altered. Eventually coming of the ventilator, still he needed to be treated for pneumonia. 5 weeks of no touching between mother and son, trying to avoid his hands near my face.' 5. 'Massive impact on all my families lives. Financial issues'. 6. 'My wife almost has a total breakdown due to the strain and worry. I almost lost my job due to the time needed to support my wife and to be present in hospital with [redacted].'

		7. 'Husband and I both had to stop work. Huge impact on our daughter who was 2 at the time. Living in isolation and often in separate rooms.'
Page 6	Screening programmes outside of the UK. In the USA	48 states in the USA are now screening for SCID. 92% of all newborns in the US are receiving SCID screening. Source: Immune Deficiency Foundation https://primaryimmune.org/idf-advocacy-center/idf-scid-newborn-screening-campaign/
	Use of NBS for SCID, outside of the USA	Canada, Israel, Qatar, Taiwan, the Netherlands, Sweden, Norway and New Zealand now have screening programmes. Pilot studies are underway in Germany, France, Italy, Spain, Iran, Saudi Arabia, Brazil and Japan.
	Comment	The information above indicates how far the UK is lagging behind the rest of the world!
Page 6	Use of NBS for SCID	The government is pledged to improve the diagnosis of rare conditions through Rare Disease Strategy Implementation plans. Implementation of a full screening programme for SCID would be a concrete demonstration of that commitment.
Page 8	Key question 1	The review provides solid data that criterion 1 is met (page 27). We agree that SCID should be treated as 'an important health condition'. Indeed it is treated as a paediatric emergency because it is a fatal condition if not detected early enough as our patient stories above indicate. Early detection through a NBS screening programme that has been demonstrated to be able to pick up all SCID cases would ensure curative options can be offered to affected children.
Page 10	Detecting children with DiGeorge (22q11 deletion syndrome) by SCID screening	McDonald-McGinn et al., 2015 report that '*early diagnosis, preferably prenatally or neonatally could improve outcomes, thus stressing the importance of universal screening*'. Nat Rev Dis Primers. 2015 Nov 19;1:15071. doi: 10.1038/nrdp.2015.71.This emphasises that the detection of these children should be viewed in a positive way. Furthermore a UK consensus of care document on 22q11 deletion syndrome is available http://www.maxappeal.org.uk/knowledge/consensus_document and care for affected children is covered by the NHS contract service specification B04/S (HSS)/b for severe immunodeficiency and related disorders service (children).
Page 10	Detecting children with Ataxia telangiectasia	Note that medical guidelines for AT are available at https://www.ataxia.org.uk/clinical-guidelines and that the UK has Specialist Ataxia clinics to care for AT affected children https://www.ataxia.org.uk/Pages/News/Category/ataxia-centres.
	Detection of non-SCID T cell lymphopenia	We understand that the TREC test may pick up non-SCID T cell lymphopenia. This should be seen as an opportunity to understand the incidence and prognosis of T cell lymphopenia in the newborn

		population. Such information would add valuable data for the PHE NCARDRS initiative https://www.gov.uk/guidance/the-national-congenital-anomaly-and-rare-disease-registration-service-ncardrs. Although there is doubt over the guidelines for the treatment of non SCID TCL, detection would provide an opportunity to intervene in a child's care where possible. It would also drive the development of guidelines by the clinical community. Centres in the USA are already using this an opportunity to drive research.
Page 24	Section 4.1.3. Incidence of SCID	It is only through a large-scale, well-planned evaluation study that the true incidence of SCID will be determined in the UK.
Page 34/36	TREC test cut off and specificity	The review confirms that a suitable cut off for the TREC test can be defined and that the test has high specificity for detecting SCID.
Page 36	Number of false positives	We agree that it is only through a population wide pilot screening programme will a more accurate picture of the rate of false positives be obtained. Please see comment above on detection of non-SCID TCL.
Page 58	Key question 3 Efficacy of early vs late treatment using HSCT	The review confirms that early HSCT for SCID substantially improves outcomes for affected children. It also confirms that there are established guidelines for the treatment of SCID {see ESID EBMT HSCT GUIDELINES 2017} and the NHS has specialist commissioned services for SCID HSCT.
Page 62	Other curative treatment options: Gene therapy for SCID	The recent decision by NICE on Strimvelis confirms gene therapy offers an alternative curative therapy for ADA-SCID when an HSCT is not considered a viable option. Successful clinical trials for ADA-SCID have also been conducted at GOSH. See also publications by Kohn and Gaspar; J Clin Immunol. 2017 May;37(4):351-356. doi: 10.1007/s10875-017-0373-y. Epub 2017 Feb 14. Ferrua and Aiuti; Hum Gene Ther. 2017 Nov;28(11):972-981. doi: 10.1089/hum.2017.175. Gene therapy clinical trials for X-SCID are also on going at GOSH with good success rates. See also the publication by Ravin et al., Sci Transl Med. 2016 Apr 20;8(335):335ra57. doi: 10.1126/scitranslmed.aad8856.
		This evidence confirms that SCID is a condition for which there are two curative options available. So the necessary criteria 9 and 10 have been met.

Economic review	Overall comment	There is bias around the emphasis of the cost analysis: NOT taken into account are the 'opportunity lost' costs i.e. cost of NOT identifying babies with SCID at birth – diagnostic odyssey, cost of ER/referrals to get diagnosis, impact of children's deaths on family, an holistic view of societal gain. **Please read the patient testimonies given above.**
	Page 3 treatment of SCID by gene therapy	NICE have recently recommended the use of STRIMVELIS, a gene therapy treatment for ADA-SCID, be made available on the NHS. This approval, along with the highly successful clinical trials carried at GOSH, indicates that gene therapy is an accepted form of curative treatment for SCID when a haematopoietic stem cell transplant (HSCT) is not possible.
	Page 14: incidence rate in UK affecting economics	It is only through a large-scale, well-planned evaluation study that the true incidence of SCID will be determined in the UK.
	Page 14: point 5 productivity costs	The impact of SCID is on the whole family and much broader than loss of earnings for caring: see patient testimony.
	Page 24: Babies identified by screening rather than family history	The document acknowledges results from a 5-year UK study showing approximately 30% of babies with SCID are identified as a result of family history. The economics analysis suggests that this figure has to rise to over 40% before the QALY threshold rises above £20,000**.** It seems that this issue has been effectively answered without having to undertake an evaluation study.
	Page 28 treatments options for ADA-SCID	See comment on NICE recommendation of Strimvelis
	Page 30, 31 Quality of life of SCID patients	A recent paper by Hamid et al., 2017 https://www.ncbi.nlm.nih.gov/pubmed/28209722# reports that the current approach of low-toxicity myeloablative regimens for transplanting patients have better B-lymphocyte/myeloid chimerism and are free from immunoglobulin replacement therapy. IL2RG/JAK3 SCID survivors free from immunoglobulin replacement have normal QoL.
	Page 38 Costs of screening	The price of the screening test is being reduced to £2.50 per infant screened, and the modelling of screening shows that probability of SCID screening being cost effective at a QALY threshold of £20,000 is 96%. There is therefore little doubt based on this modelling that SCID screening is cost-effective.
	Page 41 Costs of late diagnosis versus early	The figures quoted speak for themselves: £128k for an early-diagnosed child with SCID and £231K for care for late diagnosis. Whilst compelling these figures do not tell the full story of the costs associated with the impact of a late diagnosis on the wider family unit. These include the financial

		burden of care in terms of lost earnings, necessary changes needed to the home in caring for an affected child, costs of travel to hospital and clinics through the diagnostic odyssey, over night stays near hospital when a child is severely ill as well as the emotional toll on parents, relationships and wider family. **Please read the testimonies given above from affected families.**
	Page 39 - 42. Evidence or questions omitted by the review that might contribute to the recommendation	There is bias in the analysis. Considerable emphasis is placed on the psychological effect of screening on parents with babies identified as false positives and non-SCID conditions, but there is no mention or analysis of psychological effect on parents who have lost a child with SCID and the huge impact this has. **Please read the testimonies given above from affected families.** The death of a child is a traumatic life-changing event for any parent to have to deal with. The loss of a child for a condition for which there is a simple test available and that would enable an early curative intervention to be given is even harder to live with. The cost and psychological impact of bereavement on affected parents such as funeral expenses; impact on mental health, relationships, need for counseling etc MUST be taken into account. We ask the panel to read the following document 'How to calculate the economic impact of grief' by Professor Van der Berg, Professor of Economics, University of Bristol http://theconversation.com/how-to-calculate-the-economic-impact-of-grief-68936 We urge the panel to redress the balance in the analysis with regard to the above.
	Page 57 Scenario analysis – impact of discount rate	We suggest that a lower discounting rate of 1.5% be used. This would make the probability even greater and there is an argument that this lower discount rate should be used given that the intervention has a substantial and sustained positive outcome.

Please return to the UK NSC Evidence Team at screening.evidence@nhs.net by **Saturday 4th November 2017**.