NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency

Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: Dr Susan Walsh

Name of your organisation: Primary Immunodeficiency UK (PID UK)

Brief des*crip*tion of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

PID UK supports individuals and families affected by a primary immunodeficiency in the UK. Our aims are to be the first port of call for those in the UK seeking information on all aspects of having a PID; to promote awareness and understanding of PID; to provide direct support to individuals and families affected by PID; act as an advocate and campaigner for the needs and rights of people affected by PID. We have over a thousand members representing approximately one fifth of the population affected by PID (approx 4,800 patients are registered on the UK PIN registry). PID UK is funded by a mixture of income from donations, fundraising activity, legacies, grants from foundations and sponsorship from pharma. No funding has been received from GSK.

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- √ an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc). Director

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NONE
http://www.piduk.org/aboutus/sponsorsandfunders

How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

a diagnosis

Babies with SCID may seem well at birth and first signs usually occur within the first three – six months. The baby is likely to suffer infections more frequently than other infants, and ordinary problems, such as coughs and colds, will seem more severe and last longer than would be expected, requiring repeated and prolonged courses of treatment.

Unless here is a family history of ADA-SCID, parents often have a long diagnostic odyssey due to it being a very rare disorder and it not being recognised by healthcare professionals. Families may seek help from their family doctor (GP) or local A&E because of repeated infections, poor weight gain or feeding problems, and the baby may be referred to a local paediatrician. However, the first indication that something is wrong can be a serious infection that causes rapid deterioration in the baby's condition, requiring urgent admission to hospital, and sometimes to an intensive care unit. As a result of routine investigations, SCID may be suspected, usually because of a low lymphocyte count in the blood. As soon as the possibility of SCID is suspected, the infant will be referred to a specialist immunology centre, and further investigations are then necessary to confirm the diagnosis, and subsequently to determine the type of SCID. Infants with typical early onset ADA-SCID have poor growth and frequent, severe and unusual infections, such as pneumonia with an organism called *Pneumocystis jirovecii* (a yeast-like fungus) that does not usually cause illness in healthy individuals. Breathing difficulties can also occur in infants with ADA-SCID without any detectable infection. Central nervous system: development may be slower than in healthy children and there may be behavioural and psychological problems, such ashyperactivity and poor social behaviour. Deafness may also be a problem and there may also be problems with other body systems, including the kidneys, liver and lungs.

A typical story of the diagnostic odyssey of a child affected by SCID

'xxx our second son, was born on xxx. He was a huge baby weighing 10lbs 8oz. He was very strong, alert and engaging. He fed well, gained weight and thrived. At 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. He 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 he did not get better. He 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. He was hospitalised on 4 occasions at our local hospital. Consultants were baffled, they couldn't understand why he was repeatedly ill and having lengthy stays on the ward. The first and second admission was put down to Broncilitous and the 3rd admittance was put down to Pneumonia , but on the 4th stay they really didn't know what was wrong. They thought he 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 him to even more germs and viruses.
My son 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 he 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 he was growing weaker and I could see that he was wasting away. I had asked a consultant if he 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 him home because he would become unwell within a few days of being home and I found the worry unbearable. I felt as though he 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. He would struggle to breath and we would be back at A&E again. Even on our 4th admission the plan had been to get my son 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, although the Immunology was being pursued as a side line. There was no sense of emergency and I was worried that he 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 his 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, My son was diagnosed with a SCID. I felt my world crash around me!'

'We nearly lost him twice' – Kelly, mother to her son Zeus, diagnosed with ADA-SCID at 10 weeks old.

Implementation of a national newborn screening programme for SCID (under consideration) would mean that this costly diagnostic odyssey is avoided and appropriate infection preventative treatments e.g. prophylactic antibiotics, antifungals etc can be given with the option of curative therapy at a later date.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency

- appropriate treatment

Once diagnosed a referral to a specialist centre (GOSH and Newcastle) is made and appropriate treatments are given. This is the time that parents feel that they are in the best hands with experts that understand the condition and know what to do. This can be a relief to parents but comes with the bewilderment and panic of the seriousness of the condition [see ii below}.

The immediate priority is to provide an environment that protects the child from infection. Possible treatments that can correct the defect such as GT and HSCT [if a suitable match is available] are then discussed with the family. The first stages of treatment and precautions are the same as in all forms of SCID. In ADA-SCID it is possible to replace the missing enzyme using PEG-ADA. It is given as a weekly injection into a muscle, for instance, the thigh muscle. PEG-ADA treatment corrects the ADA and adenosine levels in the blood. Treatment usually leads to gradual improvement and partial correction of immune function. It is used until a more definitive therapy is available.

Kelly *'He was given synthetically produced ADA-SCID every week, which kept him alive while doctors searched for a bone marrow donor.' Our lives were turned upside down. No one could come round and see us if they had colds and coughs. Basically our family was on lockdown for a whole year.'*

- helpful information about the condition

Both GOSH and Newcastle have information on the condition, HSCT, and gene therapy available for affected families. This is currently being updated in collaboration with PID UK. Booklets available are SCID [available at http://www.piduk.org/static/media/up/SCID.pdf] and ADA-SCID [in production].

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:

- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)

other impacts not listed above (any impact the condition has had on carers and family members, specifically the ability to work and requirements to update the family home)

Prolonged hospitalisation, separation from extended family, blood tests and uncomfortable procedures will contribute to a great deal of stress and anxiety and even guilt for parents of a child with ADA- SCID. It may be possible for the affected child to go home for a period of time before he or she goes ahead with corrective treatment. Most parents are delighted to get home, but it can be a worrying time. Anxiety about catching or passing on an infection can make life very stressful. The hospital team, nurses and support groups provide guidance

on protecting a child from infection, keeping the house clean and coping with diet and any medication.
The impact is on the whole family including unaffected siblings who may experience anxiety and stress and feelings of jealousy and exclusion as the affected child gets more attention.

One parent giving up work to become a fulltime carer is not uncommon. Loss of income in conjunction with paying for travel for hospital visits and or time off work puts a financial strain on the family. The psychological impact on the family of a diagnosis is profound and can often put a strain on a marriage.

'Our lives were turned upside down. No one could come round and see us if they had colds and coughs. Basically our family was on lockdown for a whole year.'

'This all put a huge strain and worry on the whole family. The uncertainty of it all was very stressful. Once xxx 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. 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.'

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages
(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

Technology will result in a child developing a functional immune system – less worry about getting infections, ability to have a normal childhood, less concern about being made to feel different, less dependence on medication, able to have vaccinations.

Families – a cure for their child, less stress and concern about their child's future, less worry about infections, removal of feelings of isolation about having a child with a rare condition, not having to explain constantly about their child's condition and need for time off work and hospital appointments, potential to re-enter job market as caring needs are less, improving financial stability of family, reestablishment of normal family life.

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:
- the course and outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends and employers)
- other issues not listed above

A cure through the technology offers a improvement of quality of life for the child and their families. See above.

3. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:
- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

It is our understanding that gene therapy will not reverse any neurological problems associated with ADA-SCID in children who may already have damage due to late diagnosis and not being put on PEG-ADA replacement therapy. Deafness will still persist after gene therapy. We understand that HSCT will also not impact on these complications.

Families travelling to receive STRIMVELIS may have to set up supportive care for other members of the family. This may include care for siblings, care for elderly parents etc and may be have to be covered by a paid carer. Parents will have to take time off work to access treatment for their child and this will have a big financial impact. Employers might not be understanding of the need for time and there may be anxiety of how having time off may influence promotion opportunities for the parent employee.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

Children with ADA-SCID who are unable to find a suitable matched donor for HSCT or for whom a HSCT is deemed too risky will benefit more from this technology.

6. Comparing the technology with alternative available treatments or technologies
NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

Management of condition - ADA-PEG enzyme replacement therapy – twice weekly into thigh. Antibiotics, antiviral and antifungal medicines to protect against serious infection.

Curative therapies - Allogeneic HSCT
And
Gene therapy clinical trials using lentiviral ADA vector – GOSH.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

Management of ADA-SCID is not enough to ensure good outcomes for children with ADA-SCID affected. Curative therapies either by GT or by HSCT offer a definitive treatment of ADA-SCID.

Gene therapy is a relatively straightforward procedure compared to HSCT and does not require chemotherapy. Those treated with GT spend less time in hospital and as it uses the child's own stem cells there is less risk of GvHD.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

We are unaware of any health disadvantages to affected patients and families. The only disadvantage is having to have STRIMVELIS treatment in Milan – see section below.

7. Research evidence on patient, family or carer views of the technology

(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions. Were there any unexpected outcomes for patients?

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

PID UK is not aware of any.

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

No.

8. Availability of this technology to patients

(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

Chance of a cure for their child with a life threatening condition, having a child with a functional immune system removing the stress and anxiety of living in constant fear of infection, less dependence on prophylactic medication, having a child who can feel different and enable them to have a normal and healthy school life and to grow up contributing to society.

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

STRIMVELIS gene therapy is an important part of the armoury for the curative treatment of children affected by ADA-SCID when a suitable matched donor is not available for HSCT. Because the technology uses autologous blood stem cells there is a reduced risk of graft versus host disease. These children would be left without the life-line of this treatment option and the chance of a cure and therefore the potential of leading a normal productive life.

(iii) Are there groups of patients that have difficulties using the technology?

No, not to our knowledge.

(iv) Are there any situations where patients may choose not to use this technology?

It is our understanding that STRIMVELIS treatment involves travel to Milan. This would represent a huge upheaval for a family and may have cost implications in terms of family income and having on hand support from family and friends. Cultural differences such as language, approach to healthcare, different foods, dealing with a new healthcare team may be too daunting for some families to handle. For some families this may not present a challenge and they may decide this route to a cure is in the best interest of the child.

For others having gene therapy through clinical trials at GOSH may be a more attractive option as nearer home and more culturally aligned to their needs in an environment where they have already built up a trusting relationship with health professionals. Supportive networks are closer, there may be more potential for one parent still to work and 'normal life' may be easier to maintain.

The important thing is patient choice based on good information and having as many available options as possible.

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

The UK PIN REGISTRY has 28 reported cases of ADA-SCID in England although this is known to be an underestimate due to underreporting.

Based on current knowledge of incidence 6-10 children will present with ADA-SCID per annum, of these most will be eligible for this technology.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which strimvelis is/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency

Other Issues

Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.