UK National Screening Committee
Screening for Severe Combined Immunodeficiency - an evidence review

Consultation comments pro-forma

Organisation:	Primary Immunodeficiency UK (PID UK; Part of Genetic Disorders UK)		
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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.*	
Criterion 1, page 3 **Criterion met**.	The condition should be an important health problem	PID UK supports the conclusion of the review indicating that SCID is an important health problem and one worthy of implementation of a newborn screening programme. The impact of SCID if undiagnosed is a high rate of mortality with babies dying before their first birthday because of common and opportunistic infections.	
		Treatment and a cure are available. These are unnecessary deaths because SCID can be cured and lives can be saved if it is picked up and treated early enough. Successful treatments such as haematopoietic stem transplants, gene therapy and enzyme replacement therapy have been developed to treat these patients.	
		In common with other primary immunodeficiencies and other rare conditions, SCID is under diagnosed. Presentation is variable and it needs both a gene defect and exposure to infection for overt disease. Repeated infections are a hallmark but infections are common in all infants, not just those with SCID so non-specialists often do not consider a diagnosis of a primary immunodeficiency. Hence, diagnosis of SCID is far from straightforward and usually involves many hospital visits and lots of tests before a firm diagnosis is made. These place a	

		cost burden on the NHS. It is worth noting approximately 70% of cases are sporadic, with no family history to inform diagnosis.
		Early diagnosis ensures the best outcome for treatment: the review cites convincing evidence that early diagnosis and treatment, within 3.5 months of life, is associated with the highest survival rates (>90%) in contrast to 40% survival rates for those without a family history with median diagnosis age of 5 months (range 1 to 455 days).
		Early diagnosis ensures that precautions can be taken to protect children from infection. This reduces the chances of complications and increases the chances of successful treatment.
		Considerable costs are involved in caring for SCID children who are not diagnosed as they become very seriously ill and need lots of expensive, specialised hospital treatment. A SCID newborn screening programme would reduce this burden on the NHS.
		PID UK offers this personal story from a member of our patient panel to highlight SCID as an important health problem; the consequences of not treating early enough and the devastating personal tragedy of losing a child to SCID: **Patient story statement from Mrs Suzanne Fox, date 14th January.** **29 Bentside Road, Disley, SK12 2AJ.** *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 GOS 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 Dr Andrew Cant whose professional opinion was that Aimee had a 'leaky SCID', which should have treated by a Bone Marrow Transplant 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.*

		Conclusion: Newborn screening for SCID would ensure that all infants identified would be offered the best chance of survival by allowing measures to be taken to prevent infection, enabling optimal timing of treatment and a chance to live full lives and contribute to society.
Criterion 2, page 10 **Criterion met**.	The true prevalence of SCID in the UK	**Criterion met**. PID UK fully supports and endorses this statement and believes a tangible benefit of implementing SCID newborn screening includes gaining much needed evidence on the incidence and true spectrum of SCID.
Criterion 5, page 10 **Criterion partly met.**	There should be a simple, safe, precise and validated screening test	The results from seven pilot studies in the USA and preliminary data from Europe has provided convincing evidence indicate that TREC analysis on Guthrie cards fits this criteria. Importantly the test has demonstrated high sensitivity with no reported cases of SCID having been missed by screening. Further evidence and opinion supporting this is documented in • Puck JM. J. Allergy Clin Immunology 2012 Mar;129(3):607-16. **Laboratory technology for population-based screening for severe combined immunodeficiency in neonates: the winner is T-cell receptor excision circles.** • Verbsky, J, Thakar M, Routes J. J Allergy Clin Immunol. 2012 Mar;129(3):622-7. **The Wisconsin approach to newborn screening for severe combined immunodeficiency.** • Borte S, von Döbeln U, Hammarström L. Curr Opin Hematol. 2013 Jan;20(1):48-54.**Guidelines for newborn screening of primary immunodeficiency diseases.** • Borte S, von Döbeln U, Fasth A, Wang N, Janzi M, Winiarski J, Sack U, Pan-Hammarström Q, Borte M, Hammarström L. Blood. 2012 Mar 15;119(11):2552-5. **Neonatal screening for severe primary immunodeficiency diseases using high-throughput triplex real-time PCR.** http://bloodjournal.hematologylibrary.org/content/119/11/2552.full.html
		Newborn screening by TREC would eliminate the chances of a missed diagnosis such as a leaky SCID as described above in criterion 1 and other unnecessary deaths of children.
	the positive predictive value of the test is poor, identifying	PID UK believes that this should be weighed against the positive value of early diagnosis of SCID for those identified. It enables children to have prompt and appropriate treatment to

	only 14 infants with SCID from 364 screen positives.	save their lives from opportunistic infections and increases their chance of successful treatment. The stark reality is that without early diagnosis and proper treatment most babies with SCID will die within 1 year of life.
	the test identifies children with other T-cell deficiencies or lymphopenias.	PID UK believes this is a positive and not a negative outcome of testing since early detection and correct management of other rare conditions, T-cell deficiencies or lymphopenias is vital to avoid infectious complications and may lead to better outcomes and quality of life for those affected. Of recent note is: Mallott J, Kwan A, Church J, Gonzalez-Espinosa D, Lorey F, Tang LF, Sunderam U, Rana S, Srinivasan R, Brenner SE, Puck J. **Newborn Screening for SCID Identifies Patients with Ataxia Telangiectasia.** J Clin Immunol. 2012 Dec 20.
	Harms from false positive screening results	Harm from false positive results from SCID newborn screening would be minimised by further diagnostic investigation which might lead to a recognised diagnosis. Infants with false positive results could also be followed up prospectively as some primary immunodeficiencies can develop in later life.
	Consequences of testing	In the absence of UK based information on the consequences of testing evidence could be drawn from the extensive studies in the USA and in Europe.
	Consequences of testing: false positives in premature babies	Evidence indicates that false positives with the TREC assay can occur in premature babies. Further research as indicated in the review is clearly needed. Coordination of research and aggregation of results from the different centres may help elucidate the normal range of TRECs in premature babies and would help validate further the test.
Criterion 6, page 23 **Criterion partly met.**	Validation of test and definition of cut-off level.	Although the range of TREC values seen and the cut-off used varies depending on the exact assay used, in the US the test has shown excellent analytical validity. There will certainly be a need to be an agreed cut-off value and validation of tests prior to implementing screening in the UK. PID UK understands that work is currently underway at Great Ormond Street Hospital to address this.
Criterion 7, page 29	The test should be acceptable to the population	PID UK fully supports and endorses this statement. TREC analysis can utilise the dried blood samples collected routinely as part of newborn screening programme for other disorders. Therefore there is no additional need for a blood sample and the test can be

Criterion met.		performed quickly. No further suffering or harm would be caused to the child. The TREC test has already been applied in health programmes in the USA without controversy.
Criterion 8, page 29 **Criterion met**.	Agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals	PID UK fully supports and endorses this statement. PID UK notes that expert guidance on the recognition; diagnosis and management of PID diseases including SCID have already been published. Standards of care have been developed in the UK by UKPIN.
Criterion 10, page 58 **Criterion met**.	There is an effective treatment with evidence that early treatment improves prognosis.	PID UK fully supports the evidence in the report and its conclusion. As noted in responses concerning criterion 1 above, early identification of SCID through a newborn screening programme would allow preventative measures to be taken so that infections can be avoided and this could potentially allow treatment to occur earlier.
	Recent evidence for the effectiveness of treatment of SCID by HSCT includes	• **A single-center study of hematopoietic stem cell transplantation for primary immune deficiencies (PIDD).** Dinardo L, Brown V, Perez E, Bunin N, Sullivan KE. *Pediatr Transplant. 2012 Feb;16(1):63-7.* This paper reports overall survival rates of 88% for SCID using allogeneic HSCT. • **Transplantation in patients with SCID: mismatched related stem cells or unrelated cord blood?** Fernandes JF, Rocha V, Labopin M, Neven B, Moshous D, Gennery AR, Friedrich W, Porta F, Diaz de Heredia C, Wall D, Bertrand Y, Veys P, Slatter M, Schulz A, Chan KW, Grimley M, Ayas M, Gungor T, Ebell W, Bonfim C, Kalwak K, Taupin P, Blanche S, Gaspar HB, Landais P, Fischer A, Gluckman E, Cavazzana-Calvo M; Eurocord and Inborn Errors Working Party of European Group for Blood and Marrow Transplantation. *Blood. 2012 Mar 22;119(12):2949-55.* This paper documents mismatched related-donor transplantation or unrelated-donor umbilical cord blood transplantation as valuable treatment options for SCID when an HLA-identical hematopoietic stem cell donor is not available. • **Hematopoietic Stem Cell Transplantation Outcomes in Primary Immunodeficiency: A report from the Australian and New Zealand Children's Haematology Oncology Group and the Australasian Bone Marrow Transplant Recipient Registry.**

		Mitchell R, Nivison-Smith I, Anazodo A, Tiedemann K, Shaw P, Teague L, Fraser C, Carter T, Tapp H, Alvaro F, O'Brien T. *Biol Blood Marrow Transplant. 2012 Dec 7.* Paper summarises a retrospective analysis of HSCT outcomes in 1992 and 2008 and quotes a 5 year overall survival rate for SCID of 70%. • **Outcome of hematopoietic stem cell transplantation for adenosine deaminase-deficient severe combined immunodeficiency.** Hassan A, Booth C, Brightwell A, Allwood Z, Veys P, Rao K, Hönig M, Friedrich W, Gennery A, Slatter M, Bredius R, Finocchi A, Cancrini C, Aiuti A, Porta F, Lanfranchi A, Ridella M, Steward C, Filipovich A, Marsh R, Bordon V, Al-Muhsen S, Al-Mousa H, Alsum Z, Al-Dhekri H, Al Ghonaium A, Speckmann C, Fischer A, Mahlaoui N, Nichols KE, Grunebaum E, Al Zahrani D, Roifman CM, Boelens J, Davies EG, Cavazzana-Calvo M, Notarangelo L, Gaspar HB; Inborn Errors Working Party of the European Group for Blood and Marrow Transplantation and European Society for Immunodeficiency. *Blood. 2012 Oct 25;120(17):3615-24.* Describes HSCT outcomes from 106 patients with 86% survival rate for matched sibling donors compared with 66% from matched unrelated donor.
	Recent evidence for treatment of ADA-SCID and X-SCID by gene therapy includes:	• Rivat C, Santilli G, Gaspar HB, Thrasher AJ. **Gene therapy for primary immunodeficiencies**. Hum Gene Ther. 2012 Jul;23(7):668-75. • Montiel-Equihua CA, Thrasher AJ, Gaspar HB. **Gene therapy for severe combined immunodeficiency due to adenosine deaminase deficiency**. Curr Gene Ther. 2012 Feb 1;12(1):57-65. • Candotti F, Shaw KL, Muul L, Carbonaro D, Sokolic R, Choi C, Schurman SH, Garabedian E, Kesserwan C, Jagadeesh GJ, Fu PY, Gschweng E, Cooper A, Tisdale JF, Weinberg KI, Crooks GM, Kapoor N, Shah A, Abdel-Azim H, Yu XJ, Smogorzewska M, Wayne AS, Rosenblatt HM, Davis CM, Hanson C, Rishi RG, Wang X, Gjertson D, Yang OO, Balamurugan A, Bauer G, Ireland JA, Engel BC, Podsakoff GM, Hershfield MS, Blaese RM, Parkman R, Kohn DB. **Gene therapy for adenosine deaminase-deficient severe combined immune deficiency: clinical**

		comparison of retroviral vectors and treatment plans. Blood. 2012 Nov 1;120(18):3635-46. Paper describes the results from a clinical trial of 10 patients and shows importance of providing non-myeloablative pre-transplantation conditioning to achieve therapeutic benefits with gene therapy.
Criterion11, page 58. **Criterion met**.	Agreed evidence based policies covering which individuals should be offered treatment	PID UK fully supports and endorses this statement. PID UK notes that the reports states there are several sources of evidence based policies covering the treatment of SCID including standards of care from UK PIN and guidelines on HSCT for primary immunodeficiencies including SCID from the EBMT Inborn Errors Working Party.
	Availability of appropriate treatment	Centres for the treatment of SCID and the facilities needed are already available in the UK at Great Ormond Street Hospital and Newcastle. The centres have been instrumental in the development and publication of agreed evidence policies for the treatment of SCID.
	Treatment options for patients with low TREC numbers but without classical SCID	A newborn screening programme would allow these patients to be followed prospectively as they may develop problems in later life. This close monitoring would be in the patient's interest and the knowledge and experience gained would be invaluable for the understanding of non-classical SCID.
	Identification of patients with abnormal TREC results .	This should be viewed as a positive outcome of screening for SCID as it will prompt clinicians to explore further the underlying defects leading to the abnormal screening results. As noted in the review these infants would not be picked up if there were no screening. These children may need as urgent and prompt treatment as classical SCID. This would also allow treatment options such as immunoglobulin therapy, antibiotic prophylaxis and HSCT to be considered, as noted in the review. These interventions may prevent needless of life for larger numbers of children.
	Treatment options for patients with low TREC numbers but without classical SCID	This outcome of SCID newborn screening may also provide further impetus and rationale for the primary immunodeficiency international community to derive treatment standards for the very rare conditions encompassed by non-classical SCID.
Criterion 12, page 59 **Criterion not**	Clinical management of the condition and patient outcomes should be	The review notes that Great Ormond Street Hospital and Newcastle Hospital are two recognised specialised centres for the management of SCID. As the condition is rare, care is best centred at specialised centres. Recommendations in standards of care for SCID by UK

assessed.	optimised in all health care providers	PIN state that these are the centres that should be consulted and where patients should be referred to, when a diagnosis of SCID is being considered within the UK.
	Ditto	As noted by the review, UK PIN has developed standards for the management of SCID. www.ukpin.org.uk/home/standards-SCID.htm As indicated above this document makes the key recommendation that patients with SCID are discussed and referred to either GOSH and Newcastle centres as a matter of urgency.
Criterion 13, page 60 **Criterion not met.**	There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.	In the absence of RCT trials it is important to note that: 1. Without appropriate treatment, SCID is often fatal. 2. Early recognition is vital as an increased infective burden is a significant negative prognostic factor in the success of definitive therapy. 3. SCID is a curable condition if diagnosis is made early. There is a narrow window of opportunity to ensure the highest probability of the successful outcome of saving a child's life. PID UK would consider it immoral and unethical to set up RCT trials when a huge wealth of evidence indicates that implementation of the newborn screening programme would prevent needless deaths from SCID.
	The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened	PID UK will work with all stakeholders to ensure development of patient friendly information about the implications of testing and its value. This can be done through our patient panel.
Criterion 14, page 61 **Criterion not assessed.**	There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.	As stated in response to criterion 13 and in agreement with the personal story above PID UK believes it would not be clinically, ethically or socially acceptable NOT to screen newborn babies for SCID. The fact that SCID newborn screening will prevent needless suffering, save children's lives and allow swift access to life-saving treatment SCID newborn screening should be viewed as an absolute social, ethical and clinical requirement.
Criterion 15, page 61	The benefit from the screening programme should	As evidenced in the report and highlighted above not diagnosing and treating SCID children early results in loss of life. The benefit gained from implementing the screening programme

Criterion partly met.	outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)	in saving children's lives would outweigh any potential harm caused by the test, diagnostic procedures and treatment.
Criterion 16, page 84 **Criterion uncertain.**	The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource	Newborn screening would be cost effective as babies would be detected and treated early reducing the need for the multiple hospital visits often needed before a definitive diagnosis is currently made and the substantial costs involved in caring for children who are not diagnosed and become seriously ill and need specialised hospital treatment such as ICU. Costs in the care of SCID also include the high costs of antimicrobial drugs to treat and stave off infection to stabilise children so that they can receive treatment. A SCID newborn screening programme would help to significantly reduce this considerable burden on the NHS. The cost of the test is cheap - evidence indicates that screening costs are £3/case. Assuming live births of 750,000/year this equates to about £2.1m for screening all live births in the UK. PID UK believes this cost is far outweighed by the savings described above. PID UK believes the opportunity cost should also include the societal and economic contribution that will follow by allowing children, who would die otherwise, to live, so they can become net contributors to society.
Criterion 17, page 67/68 **Criterion uncertain.**	All other options for managing the condition should have been considered: boosting awareness.	Raising awareness will never be as effective as a newborn screening programme at preventing children dying from SCID. SCID is very rare and presentation can be variable making diagnosis difficult. Newborn screening would eliminate 'missed cases' and prevent the sometimes inefficient, costly and dangerous 'diagnostic Odyssey' that is often associated with diagnosing rare conditions.
	Optimisation of HSCT protocols	PID UK notes that extensive collaboration already exists between many centres with Europe to ensure optimisation of HSCT. The Inborn Errors working party of the European Group for Blood and Marrow Transplantation (EBMT), chaired by Dr Gaspar is dedicated to improving the outcome of transplantation for severe congenital immunodeficiencies such as SCID.

		The centres at GOSH and in Newcastle collaborate fully to ensure optimisation of protocols for HSCT.
Criterion 18, page 68 **Criterion not met.**	There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.	PID UK does not believe this should be a barrier to implementing the screening programme. The pilot studies in the USA provide good models on which to base management, monitoring and QA standards.
Criterion 19, page 69 **Criterion not met.**	Implementation of TREC as the first DNA-based screen, rather than tandem mass spectrometry to the newborn screening programme: transfer of expertise and speed of implementation	This should not be an issue. Evidence from the USA newborn screening programme has indicated that TREC analysis from dried blood spots can be successfully integrated into public health programs and that the expertise can be successfully transferred between centres. The UK NSC review also cites evidence supporting the feasibility and speed at which a fully operational screening system could be established. 'The authors estimate that with 3 to 4 weeks hands-on training in the Wisconsin laboratory, another state newborn screening program could become fully operational within 6 months and is 'is compatible with a high-throughput, automated environment". The programme if implemented could also become a template for other screening programmes based on DNA.
	Requirement for equipment for and expertise in RT-qPCR.	This is not an issue. The equipment needed is commercially available and finding staff with expertise in qPCR will not be a problem.
	Impact on service capacity	This would have to be reviewed during the programme. Any increase in capacity needed for diagnostic and treatment will be significantly outweighed by the reduced burden on the NHS as indicated above in comments on criterion 16.
Criterion 20, page 70 **Criterion not met.**	No UK evidence-based information explaining the consequences of testing was identified.	This should not be considered as a barrier to adopting the screening programme. As indicated in the review, information could be based and adapted on that available in the USA.
	No UK evidence-based information explaining the	This information can be developed. PID UK will endeavour to work with the major centres and UKPIN to develop information on SCID and the processes and consequences of testing.

	consequences of testing was identified.	Dr Gaspar is a member of our medical panel along with representatives from UKPIN and our patient panel has one member who has experience of the trauma of losing a child to SCID (see her personal story below).
Criterion 21, page 70/71 **Criterion not met.**	The International Patient Organisation for Primary Immunodeficiencies (IPOPI) has been campaigning for the implementation of SCID Newborn Screening in the European Union.	PID UK fully endorses the IPOPI campaign for the implementation of SCID newborn screening in the EU and its desire for this to done swiftly so as to prevent needless loss of life due to SCID.
	Issue of 'public pressure'	Public pressure for the support of people with rare conditions is growing. Rare Diseases UK, Genetic Alliance UK and Genetic Disorders UK are now drawing attention to the needs and challenges faced by people affected by rare conditions. Last year, The Department of Health in the UK launched the UK Plan for Rare Diseases to improve outcomes for those affected and included the statement *'Earlier diagnosis of a rare condition and better co-ordinated care will help improve the quality of life for people with rare diseases and their families'.* PID UK fully endorses this statement and would see implementation of the screening programme as a concrete step forward in fulfilling this goal.
	Issue of 'public pressure'	Public pressure does exist in the UK: In 2011 the Primary Immunodeficiency Association (now disbanded) held a parliamentary reception and launched a wide Call for Action headed by Dr Gaspar.
	Issue of 'public pressure'	Other examples of public pressure include: • Tabling of written questions to European Parliament by Glenis Willmott MEP (East Midlands) on screening for SCID (2011 Jul 11). www.europarl.europa.eu/sides/getDoc.do?type=WQ&language=SL&reference=E-2011-007151&secondRef=0 • www.gleniswillmott.eu/an-emotional-meeting-with-sufferers-of-scid/ • International Patient Organisation for Primary Immunodeficiencies. News [2011 Dec 8]. www.ipopi.org/index.php?mact=News,cntnt01,detail,0&cntnt01articleid=164&cntnt01returnid

		=38 • International Patient Organisation for Primary Immunodeficiencies. News [2012 Mar 27]. www.ipopi.org/index.php?mact=News,cntnt01,detail,0&cntnt01articleid=193&cntnt01returnid=38 • International Patient Organisation for Primary Immunodeficiencies. News [2012 Dec 12]. www.ipopi.org/index.php?mact=News,cntnt01,detail,0&cntnt01articleid=279&cntnt01origid=113&cntnt01detailtemplate=detalj&cntnt01returnid=63
	Issue of 'public pressure'	PID UK, as a new organisation supporting individuals and families affected by primary immunodeficiencies, will be working actively with patients, patient groups and professional medical bodies to lobby support for newborn screening for SCID.
Page 71	'Pilot SCID screening trials are reportedly taking place in Germany and Sweden.'	Results from this pilot study have now been published: Borte S, von Döbeln U, Fasth A, Wang N, Janzi M, Winiarski J, Sack U, Pan-Hammarström Q, Borte M, Hammarström L. Neonatal screening for severe primary immunodeficiency diseases using high-throughput triplex real-time PCR. Blood. 2012 Mar 15;119(11):2552-5. http://bloodjournal.hematologylibrary.org/content/119/11/2552.full.html

Please return to Adrian Byrtus, UK NSC Administrator (on behalf of John Marshall, Projects and Programmes Manager): adrian.byrtus@imperial.nhs.uk by 14th January 2013