Newborn screening for severe combined immunodeficiency (SCID) in the NHS Newborn Blood Spot (NBS) screening programme: A rapid evidence review

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PLAIN ENGLISH SUMMARY

When a new population screening programme is proposed, in the UK, it is assessed using the UK National Screening Committee (UK NSC) criteria for appraising its viability, effectiveness and appropriateness. The overall goal of population screening programmes is to provide early treatment or intervention to someone identified as having a condition or risk factor before they have symptoms. Ideally this should lead to better outcomes than if the person were to present later with symptoms. In the UK, the current newborn screening programme looks for nine rare, but serious conditions. Screening uses drops of blood, collected from an infant's heel onto a special card (also known as the 'heel prick test'). In the rare event that laboratory tests on this blood find an abnormal result, the child undergoes further testing to confirm whether they definitely do have one of the conditions screened for. If a child is then diagnosed with one of the conditions, they are referred for treatment.

Severe combined immunodeficiency (SCID) is a rare, inherited condition that results in low numbers of white blood cells and prevents the body from fighting infection properly. There are usually no symptoms of SCID when an effected baby is born, however, a diagnosis of SCID is considered an emergency because the condition almost always results in death in the first year, unless the child receives treatment. Treatment usually involves haematopoietic stem cell transplantation (HSCT), also known as a bone marrow transplant. This transplant uses stem cells taken from a suitable donor (often a relative). These healthy, donated cells are then given to the child through an intravenous (IV) infusion. The stem cells travel to the bone marrow where they multiply over time. In this way, they can provide the child with a working immune system that is able to fight infection.

There is a test that can be used to screen for SCID, which involves counting the numbers of a specific product in the blood, called 'T-cell receptor excision circles (TRECs)'. TRECs are used to indicate how many working white blood cells of a particular type (T-cells) that a person has. Below a certain number (cut-off point), the test is considered to be an abnormal (or 'positive') test result. However, it is important to note that the TREC test does not only identify SCID; a large number of other conditions that effect the immune system and result in very low levels of T-cells will also result in a positive TREC test.

The UK NSC does not currently recommend screening newborn babies for SCID. This is because it is not known:

- how many well babies may be told they are ill incorrectly (false positives)
- the best way to care for babies with low numbers of white cells caused by other conditions
- how many babies are born into families who are already aware they have SCID
- how well laboratories will cope with the increase in testing and more ill babies

This project will form part of a review of the evidence, by the UK NSC, following completion of a trial of screening for SCID in the English NHS.

BACKGROUND

Severe combined immunodeficiency (SCID) is an inherited form of severe primary immune deficiency, which arises from mutations in at least 19 known genes and hence has a large number of subtypes. It is characterised by T-cell lymphopenia (TCL), i.e. absence or significant reduction in the number of functioning T-cells.[1] Depending upon the genotype, SCID can also affect B cells and Natural Killer (NK) cells. Hypomorphic mutations in SCID genes (mutations which result in reduced levels of activity of the gene product) result in particular forms of SCID known as atypical SCID and Omenn syndrome. Most subtypes of SCID have autosomal recessive inheritance and there is an X-linked, recessive form of SCID that arises from mutations in the IL2RG gene. The proportions of different SCID subtypes vary widely geographically; e.g. the proportion of SCID cases accounted for by ADA-SCID has been reported as 9.6% for the USA, 11.6% for the Netherlands, 26.8% for the UK and 51.9% for the republic of Ireland where 13 of the 14 ADA-SCID cases in the sample were associated with Irish Traveller ethnicity.[1]

SCID may be identified through screening, family history (cascade testing) or upon clinical presentation. SCID is usually asymptomatic at birth and presents, in infancy, as recurrent and frequently severe infections (e.g. bacterial and viral infections such as *Streptococcus pneumoniae*, cytomegalovirus and adenoviruses, and opportunistic organisms such as *Pneumocystis jirovecii*), failure to thrive, persistent diarrhoea, and or oral thrush.[1] In the absence of treatment SCID is almost always fatal in the first year of life. Early identification of SCID is also important in the context of childhood immunisation; children with the condition should not receive live vaccines due to the potential for severe illness and mortality.

The most widely used method of newborn screening for SCID involves the quantification of T-cell receptor excision circles (TRECs). A recently completed assessment for the Health Information and Quality Authority, Republic of Ireland (HIQA Ireland), noted that (as at September 2022) newborn screening for SCID had been implemented in seven European countries, the USA and New Zealand, with regional or ongoing implementation, piloting or assessment being noted in nine further countries including Canada and the UK; the majority of programmes used TREC-based screening, with four countries using combined TREC- and kappa-deleting excision circles (KREC)-based screening. This review included a summary of the current newborn screening landscape for SCID, describing screening programmes and pilots currently in place both nationally and internationally.[1]

The TREC assay is performed using DNA extracted from a dried blood spot (DBS) sample and involves the use of PCR. There are currently two commercially available TREC assay kits, the Perkin Elmer EnLite Neonatal kit™ and the Immuno IVD SPOT-it™ screening kit, both of which are CE marked.

TRECs are a DNA by-product, generated during normal T-cell maturation; blood levels of TRECs are a surrogate marker of thymic output of newly formed T-cells, with an absence or low level of TREC being indicative of TCL. Originally developed to assess thymic output in relation to aging and HIV infection, the TREC assay has been adapted for use in newborn

screening. In this context, it is important to note that the results from a TREC assay are indicative of the presence or absence of TCL, for which there are a large number of possible causes, and are not specific for SCID. TREC-based screening for SCID is, therefore, different from the other tests and target conditions included in the UK NHS DBS newborn screening programme (sickle cell disease, cystic fibrosis, congenital hypothyroidism, a six inborn errors of metabolism [phenylketonuria PKU, medium-chain acyl-CoA dehydrogenase deficiency MCADD, maple syrup urine disease MSUD, isovaleric acidaemia IVA, glutaric acid urea type 1 GA1 and homocystinuria HCU])[2] in that it is associated with high rates of incidental findings (screen positive results caused by conditions other than the target condition, SCID). The rate and diversity of incidental findings is likely to complicate the process of obtaining informed consent for TREC-based screening for SCID in that it may be argued that a truly informed parent should be aware of the purpose and process of screening, as well as all possible outcomes of the screening test and their subsequent impact (e.g. further testing, treatment options, potential for identification of untreatable conditions). A recent systematic review of the acceptability of blood spot screening and genome sequencing in newborn screening, conducted for the UK NSC,[3] included one study of newborn screening for SCID.[4] However, this review only considered assessments of acceptability that were made antenatally or within one month of birth and may therefore not have captured potential effects on parental attitudes of the unique aspects of TREC-based screening for SCID described above. Our review will consider, specifically, studies which examine the acceptability of screening for SCID and will additionally include studies that assess acceptability at later time points and/or retrospectively.

Immune reconstitution using allogeneic haematopoietic stem cell transplant (HSCT) is the primary treatment for SCID.[1] Gene therapy may be an additional treatment option for some SCID sub-types (e.g. adenosine deaminase deficiency severe combined immunodeficiency [ADA-SCID], a subtype that is associated with neurological impairments not resolved by HSCT and which accounts for a relatively high proportion of SCID cases in the UK and Republic of Ireland.[5, 6] This review will include an evidence map/horizon scanning document describing developments in gene therapy for SCID as an alternative or adjunct to HSCT.

The HIQA Ireland report listed 21 non-SCID-related congenital conditions that may result in an abnormal TREC result at screening: 22q11.2 Deletion Syndrome (DiGeorge syndrome); combined immunodeficiency; ataxia telangiectasia; DOCK 8 deficiency; Anhidrotic ectodermal dysplasia with immune deficiency; Trisomy 21; Trisomy 18; Kabuki syndrome; CHARGE syndrome; Noonan syndrome; Jacobsen syndrome; Fryns syndrome; CLOVES syndrome; Renpenning syndrome; TAR syndrome; VACTERL syndrome; Dandy Walker syndrome; Barth syndrome; Schimke immuno-osseous dysplasia; cartilage hair hypoplasia; cytogenetic abnormalities.[1] The report also identified eight secondary causes for low TREC values: prematurity (typically TCL in those born before 37 gestational weeks which progressively normalises over time); congenital heart disease; chylothorax; gastrointestinal anomalies; vascular leakage; hydrops; neonatal leukaemia; maternal causes (such as

autoimmune disease, HIV infection, and immunosuppression).[1] Two recent USA publications noted the absence of established consensus guidelines or algorithms for non-SCID TCL cases detected through screening programmes for SCID,[7, 8] and the review of internation screening programmes for SCID, included in the HIQA Ireland report, also identified no clinical guidelines or pathways. This review will include guidelines searches to identify any published guidelines or algorithms for the management of non-SCID TCL. Our report will also include a set of vignettes (e.g. as provided, for DiGeorge syndrome, in Appendix 2.3 of the HIQA Ireland report) describing conditions (to be confirmed by UK NSC) which may be detected as incidental findings from TREC-based screening for SCID, including the potential effects of TREC-based screening on the rates/timing of detection of these conditions, management options and outcomes.

Newborn screening for SCID is not currently recommended in the UK[9] The UK NSC reviewed the evidence for newborn screening for SCID, against its programme appraisal criteria, in 2012[10] and up-dated this review in 2017.[11, 12] An in-service evaluation (ISE) of newborn screening for SCID is ongoing in English NHS services and is due to complete in March 2024.[13] A more recent (2023) HTA has been conducted by HIQA Ireland.[1] However, this assessment was conducted in the context of a pre-exiting, tandem mass spectrometry-based screening programme for ADA-SCID (implemented in Ireland in May 2022) and is, therefore not directly applicable to the UK context. The accumulation of metabolic substrates associated with ADA-SCID is detectable in DBS samples using tandem mass spectrometry, a method that is already used in both the UK and Republic of Ireland NBS programmes to screen for a number of different inborn errors of metabolism and which does not result in the high rates of incidental findings associated with TREC-based screening; more than half of SCID cases in the republic of Ireland are ADA-SCID and can be detected using tandem mass spectrometry-based screening. Tandem mass spectrometry cannot be used to screen for other forms of SCID.

This rapid evidence review will provide an up-date to the to the 2017 UK NSC review,[11] and will focus on UK NSC criteria,[14] which were deemed to be not fully met at the 2017 review:

Criterion 4 - There should be a simple, safe, precise and validated screening test.

Criterion 5 - The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

Criterion 6 - The test, from sample collection to delivery of results, should be acceptable to the target population.

Criterion 9 - There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered.

Because our review will focus on previously identified evidence gaps, some of our inclusion criteria (particularly in relation to acceptability) differ from those used by previous assessments. For this reason, new literature searches will be conducted from 2011 to present, rather than relying upon up-dates to previous searches. We will also seek data from the UK NHS ISE.

OBJECTIVES

The overall aim this project is to summarise the available evidence relevant to newborn screening for SCID in the NHS NBS screening programme. The following research questions have been defined to address specific project objectives:

1. What is the accuracy of the TREC test in population studies of screening for SCID?
    - Accuracy will be considered in term babies, pre-term babies and sick babies
    - The rate and type of incidental findings (non-SCID TCL) will be considered
2. Does HSCT (or gene therapy or thymic transplant, if appropriate) in SCID cases detected during the asymptomatic period lead to improved outcomes?
    - Detection in the asymptomatic period might include universal newborn screening, familial cascade detection or in individuals detected by other means
3. Is the experience of population screening for SCID acceptable to parents and carers of newborn babies?
    - The acceptability of screening for SCID, when assessed pre-screening, during the screening phase and post-screening, will be considered

In addition to summarising the available evidence to inform the above questions, our report will include:

- A set of vignettes describing conditions (conditions of interest to be confirmed by UK NSC) which may be detected as incidental findings from TREC-based screening for SCID
- An evidence map/horizon scanning document describing developments in gene therapy for SCID as an alternative or adjunct to HSCT
- A summary of the current newborn screening landscape for SCID, describing screening programmes and pilots currently in place both nationally and internationally

METHODS

The systematic review will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care,[15] and the Cochrane Handbook[16] and Cochrane Handbook for Diagnostic Test Accuracy Reviews.[17]

INCLUSION CRITERIA

Separate inclusion criteria have been developed for each of the three research questions and these are summarised in Table 1.

Studies published in languages other than English will be excluded. Only studies reported in peer reviewed publications will be included; conference abstracts will be excluded.

Table 1: Inclusion criteria

Research question	**1. What is the accuracy of the TREC test in population studies of screening for SCID?**	**2. Does HSCT in SCID cases detected during the asymptomatic period lead to improved outcomes?**	**3. Is the experience of population screening for SCID acceptable to parents and carers of newborn babies?**
Population	Newborns Where possible, data will be extracted and reported by population subgroup: • Term babies • Pre-term babies • Sick babies	Newborns, infants or children with SCID	Parents and carers of newborns/infants or children to whom SCID screening was offered
Intervention	PCR-based measurement or TEC in dried blood spots	Treatment (HSCT, gene therapy or thymic transplant) where: 1. SCID has been detected through population screening 2. SCID has been detected early (e.g. incidentally or through cascade testing) 3. SCID which remains symptom-free (could include both screening-detected and early-detected)	Newborn population screening programme for SCID
Comparator	NA	Treatment (HSCT, gene therapy or thymic transplant) where:	Current offer and delivery of newborn population screening programme for SCID (as

		1. SCID has been detected without population screening 2. SCID has been detected late 3. SCID has been detected following the development of symptoms	suggested to the screening programme that it is examined)
Reference standard	Flow cytometry, genetic testing and/or subsequent clinical detection of SCID	NA	NA
Outcomes	Sensitivity, specificity, PPV, NPV, of the intervention (by screening test, e.g. test kit used, and threshold) for the target condition SCID Incidental findings (type and incidence of non-SCID TCL)	Survival, safety (e.g. incidence of AE associated with HSCT), freedom from immunoglobulin substitution (with consideration to the potential confounding factors related to treatment and complications), CD3+ T-cell and IgA recovery, cognitive behavioural or neurological outcomes	Overall: • Stated parental acceptability/perceptions of screening Parents or carers characteristics of acceptability / experience including: • Logistic measures of acceptability (e.g. convenience, accessibility) • Procedure related measures of acceptability (e.g. pain / physical discomfort for the baby, information confidence in result,)

			• Psychosocial measures of acceptability (e.g. anxiety, fit with values) • Knowledge related measures (e.g. understanding of the intervention and its effectiveness)
Study design	Studies in randomly assigned or consecutively enrolled populations (diagnostic cohort studies) and systematic reviews will be prioritised. Diagnostic case-control studies will be considered if no studies or a low volume of other types of studies are identified.	Any comparative study design, in humans.	RCTs, cohort studies, feasibility studies, mixed methods studies, surveys and / or focus groups, qualitative interview studies, systematic reviews

AE: adverse events; CD3+: cluster of differentiation 3 positive; HSCT: haematopoietic stem cell transplantation; IgA: immunoglobulin A; NA: not applicable; NPV: negative predictive value; PPV: positive predictive value; RCTs: randomised controlled trials; SCID: severe combined immunodeficiency; TCL: T-cell lymphopenia

LITERATURE SEARCHES

Search strategies will be developed to identify studies on newborn screening for SCID, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[15] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[17]

Candidate search terms will be identified from target references, browsing database thesauri (e.g. MEDLINE MeSH and Embase EMTREE), existing reviews and initial scoping searches. Strategy development will involve an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search strategies will be developed specifically for each database and the keywords and thesaurus terms will be adapted according to the configuration of each database.

- MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily (Ovid)
- EMBASE (Ovid)
- CINAHL (EBSCO)
- PsycInfo (Ovid)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- International HTA Database (Internet) (https://database.inahta.org/)
- KSR Evidence (KSR Ltd) (Internet) (https://ksrevidence.com/)

Additional searches

A search of the following resources will be conducted to identify the latest background, guideline and policy documents on SCID and to present an evidence map/horizon scanning document to describe therapeutic developments in the field.

- Trip Database (Internet) (https://www.tripdatabase.com/)
- Guidelines International Network (GIN) (Internet) (https://g-i-n.net/international-guidelines-library/)
- National Institute for Health and Care Excellence (NICE) (Internet) (https://www.nice.org.uk/)
- NIHR Health Technology Assessment (HTA) (Internet) (https://www.nihr.ac.uk/)
- ECRI Guidelines Trust (Internet) (https://guidelines.ecri.org/)
- Policy Commons (Internet) (https://policycommons.net/)
- ScanMedicine (Internet) (https://scanmedicine.com/)
- Orphanet Newborn Screening Bibliographical Knowledgebase (Internet) (https://nbs.orphanet.app/)

In order to maintain relevance to current clinical practice and update existing research, searches will be date limited to 2011 - present. An example search strategy is presented in Appendix 1. This may be adapted following consultation with clinical experts.

The main Embase strategy for each search will be independently peer reviewed by a second Information Specialist based on the CADTH Peer Review checklist.[18]

Reference checking

The bibliographies of included primary studies and systematic reviews will be checked for relevant studies.

Handling of citations

Identified references from the bibliographic database searches will be downloaded into Endnote bibliographic management software for further assessment and handling. Individual records within the Endnote libraries will be tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enables the information specialist to track the origin of each individual database record, and its progress through the screening and review process.

STUDY SELECTION AND DATA EXTRACTION

Two reviewers will independently screen titles and abstracts of all reports identified by the searches and any discrepancies will be resolved by discussion or consultation with a third reviewer. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following: study design/details; study setting (country); population (e.g. details of screening program/numbers screened, details of parents/carers from whom acceptability data were elicited, any subgroups reported); details of TREC assay methods (e.g. including details of sample collection, threshold, manufactures of any commercial kits used, PCR methods); details of screening protocol; screening test performance outcome measures (sensitivity and specificity, positive and negative predictive values, details of SCID findings and incidental findings); details (including timing) of treatment (e.g. HSCT) in intervention and comparator groups; follow-up duration (treatment studies only); treatment outcomes; summary of main findings, frameworks and theories, and constructs of acceptability (acceptability studies only). Data will be extracted by one reviewer, using piloted data extraction forms. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

ASSESSMENT OF METHODOLOGICAL QUALITY

The methodological quality of included RCTs of treatment will be assessed using the revised Cochrane Risk of Bias Tool for Randomised Trials (RoB 2)[19] and cohort studies of treatment will be assessed using the ROBINS-I tool.[20] Diagnostic accuracy studies will be assessed using QUADAS-2.[21] In line with the recently completed systematic review of acceptability,[3]

quantitative and qualitative studies reporting acceptability data will be assessed using the Mixed Methods Appraisal Tool (MMAT).[22] The MMAT is a seven-item multi-dimensional checklist comprising of two screening questions, and then five questions evaluating different features according to the study design.[22]

DATA SYNTHESIS

Based on the between study heterogeneity observed in recent systematic reviews,[1, 11] we do not anticipate that any meta-analyses will be undertaken. A narrative synthesis of results will be presented, structured by research question, using the UK NSC Report template. This will involve the use of text and tables to summarise data. Where appropriate, graphical representations (e.g. ROC space plots) may also be used. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Findings from studies of the acceptability of SCID screening to parents and carers will be mapped to previously identified domains of acceptability (support for screening; level of anxiety, information and knowledge; consent; views of the procedure; and support after screening);[3] particular attention will be paid to information about the views of parents and carers in respect of the high rates of incidental findings associated with TREC-based screening for SCID, the lack of clarity about post-screening care pathways for non-SCID TCL and the implications for information provision, weighing up risks and benefits and informed consent.

TIMETABLE

The final report will be submitted to NSC by 28th November 2024 and to NIHR by 12th December 2024.

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APPENDIX 1 Draft Embase search strategy

Embase (Ovid): 1974 to 2024 February 27
Date searched: 28.2.24
Records found: 3295 (2011+)

SCID

1 exp severe combined immunodeficiency/ 8090
2 (severe combined adj2 (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab,ot,hw. 11583
3 ((SCID or SCIDs) and (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab,ot,hw. 10164
4 bare lymphocyte syndrome$.ti,ab,ot,hw. 525
5 familial reticuloendothelios$.ti,ab,ot,hw. 4
6 Omenn$ syndrome$.ti,ab,ot,hw. 816
7 Swiss-type agammaglobulin?emia.ti,ab,ot,hw. 5
8 Alymphocytosis.ti,ab,ot,hw. 11
9 (severe mixed adj2 (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab,ot,hw. 1
10 Glanzmann-Riniker syndrome$.ti,ab,ot,hw. 0
11 Thymic alymphoplasia.ti,ab,ot,hw. 10
12 (adenosine deaminase deficiency or ADA deficiency).ti,ab,ot,hw. 1806
13 (purine nucleoside phosphorylase deficiency or PNP deficiency).ti,ab,ot,hw. 335
14 Reticular dysgenesis.ti,ab,ot,hw. 150
15 JAK3 deficiency.ti,ab,ot,hw. 108
16 (DCLRE1C or PRKDC).ti,ab,ot,hw. 1421
17 (bubble boy disease or bubble baby disease).ti,ab,ot,hw. 6
18 (x linked adj3 (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab,ot,hw. 1880
19 (XSCID or SCIDX or SCIDX1).ti,ab,ot,hw. 178
20 ("immunodeficiency 4" or "immunodeficiency 6").ti,ab,ot,hw. 59
21 or/1-20 19106

SCREENING

22 newborn screening/ 23643
23 exp infant/ and exp screening/ 42314
24 ((neonatal$ or newborn$ or infant$ or baby or babies) adj3 (screen$ or test$ or diagnos$)).ti,ab,ot,hw. 63780
25 (heelprick$ or heel prick$).ti,ab,ot,hw. 641
26 dried blood spot testing/ 6520
27 (blood spot$ or bloodspot$ or NBS).ti,ab,ot,hw. 22848
28 ((dried or dry) adj1 (blood test$ or blood sampl$)).ti,ab,ot,hw. 727
29 Guthrie.ti,ab,ot,hw. 1095
30 t-cell receptor excision circle test kit/ 35
31 (T-cell receptor excision circle$ or TRECs or TREC).ti,ab,ot,hw. 2131

32 (EnLite$ or PerkinElmer or Eonis$ or "Immuno IVD SPOT-it$" or "SCREEN-ID").ti,ab,ot,hw. 1459
33 (Kappa deleting recombination excision circle$ or KREC or KRECs).ti,ab,ot,hw. 315
34 (genetic adj3 (screen$ or test$ or diagnos$)).ti,ab,ot,hw. 188007
35 or/22-34 283286
36 21 and 35 1807

TREATMENT

37 exp hematopoietic stem cell transplantation/ 91397
38 (h?ematopoietic stem cell therap$ or HSC therap$).ti,ab,ot,hw. 207
39 (h?ematopoietic stem cell transplant$ or HSC transplant$).ti,ab,ot,hw. 104226
40 (HPSCT or HSCT).ti,ab,ot,hw. 40207
41 exp bone marrow transplantation/ 71699
42 (bone marrow adj2 (transplant$ or transfer$ or graft$ or transfusion$)).ti,ab,ot,hw. 83213
43 or/37-42 183682
44 21 and 43 3721
45 36 or 44 4894

ANIMAL EXCLUSION & DATE LIMIT

46 animal/ 1650806
47 animal experiment/ 3116751
48 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. 7771476
49 or/46-48 7771476
50 exp human/ 26197570
51 human experiment/ 654730
52 or/50-51 26200103
53 49 not (49 and 52) 5808702
54 45 not 53 4613
55 limit 54 to yr="2011 -Current" 3295