Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Repatriation of paediatric haematopoietic stem cell transplant services to Ireland: a Health Technology Assessment

Published: 9 February 2023

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

Foreword

Allogeneic haematopoietic stem cell transplantation (HSCT), otherwise known as bone marrow transplantation, is the internationally recognised standard of care for several rare paediatric conditions. In Ireland, this treatment is available to paediatric patients with certain conditions such as haematological malignancies, bone marrow failure syndromes and a number of other rare conditions at the paediatric transplant unit at Children's Health Ireland at Crumlin, Dublin. Treatment involves the transfer of healthy stem cells from a compatible donor to the patient, with the aim of new and healthy blood cells being produced by these donor cells. When successful, HSCT stops disease progression and can be curative in certain conditions.

Other notable paediatric conditions that can be treated by HSCT include inborn errors of immunity, inborn errors of metabolism, and certain haemoglobinopathies. Currently, patients with these conditions, requiring HSCT, must travel abroad to receive this treatment. Funding for these procedures is provided through the Treatment Abroad Scheme operated by the Health Service Executive. However, the requirement to travel abroad can place a significant burden on patients and their families, while capacity in the host country may represent a risk to access to care.

Work on the health technology assessment (HTA) was undertaken by an Evaluation Team from the HTA Directorate in HIQA. A multidisciplinary Expert Advisory Group was convened to advise the Evaluation Team during the course of the HTA. HIQA would like to thank the Evaluation Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.

Dr Máirín Ryan

Deputy Chief Executive and Director of Health Technology Assessment

Contents

Acknowledgements

HIQA would like to thank all of the individuals and organisations who provided their time, advice and information in support of this health technology assessment.

We would like to express our gratitude to a number of other individuals and organisations for their time, advice and contributions to this assessment. These include:

- the Treatment Abroad Scheme
- medical social workers and clinical nurse specialists at Children's Health Ireland at Crumlin and at Temple St
- Dr Mary Wingfield and colleagues from the Merrion Fertility Clinic.

We especially would like to thank the patient representatives including those from the following organisations who provided insights into the experiences of families:

- the Irish Society for Mucopolysaccharide Diseases
- Pavee Point
- the Irish Primary Immunodeficiencies Association
- Sickle Cell and Thalassaemia Ireland.

Particular thanks are due to the Expert Advisory Group (EAG) and the individuals within the organisations listed in the table below who provided advice and information.

Expert advisory group membership

The membership of the EAG was as follows:

Dr Mary Boushel	Patient Representative, Irish Society for Mucopolysaccharide Diseases
Ms Helen Byrne*	Assistant National Director, Acute Operations, HSE
Dr Abigail Collins	National Clinical Lead in Child Health Public Health, HSE
Dr Ellen Crushell	Clinical Lead, National Clinical Programme for Paediatrics and Neonatology, HSE
Ms Catherine Donohoe	General Manager, Treatment Abroad Scheme, HSE
Dr Pamela Evans#	HSCT and Cellular Therapy Director, Children's Health Ireland at Crumlin
Mr Colm Foy	Office Manager, Treatment Abroad Scheme, HSE
Ms Eilish Hardiman	Chief Executive, Children's Health Ireland
Dr Patricia Harrington	Deputy Director, HTA Directorate, HIQA
Dr Louise Hendrick	Deputy Chief Medical Officer, Department of Health
Ms Carol Ivory#	Acting Assistant National Director Acute Operations, HSE
Ms Lynsey Kavanagh#	Traveller Health Programme Manager, Pavee Point Traveller and Roma Centre
Dr Ronan Leahy	Consultant in Paediatric Immunology and Infectious Diseases, Children's Health Ireland at Crumlin
Dr Ciara Martin	National Clinical Advisor and Group Lead for Children and Young People, HSE
Prof Corrina Mc Mahon	Consultant in Haematology, Children's Health Ireland at Crumlin
Ms Jane McMenamin#	Senior Medical Social Worker, Children's Health Ireland at Temple Street
Prof Ahmad Monavari	Director, National Centre for Inherited Metabolic Diseases, Children's Health Ireland at Temple Street
Ms Mairéad O'Brien	HSCT/CAR-T Co-ordinator, Children's Health Ireland at Crumlin
Dr Helen O'Donnell	Senior HTA Analyst, HTA Directorate, HIQA
Ms Anne Marie O'Dowd	Patient Representative, Pavee Point

Ms Kathy Quinn	Patient Representative, Irish Primary Immunodeficiencies Association
Dr Máirín Ryan (Chair)	Director of HTA and Deputy CEO, HIQA
Prof Owen Smith	National Clinical Lead for Children, Adolescent and Young Adult Cancers at National Cancer Control Programme, HSE
Dr Susan Spillane	Head of Assessment, HTA Directorate, HIQA
Dr Conor Teljeur	Chief Scientist, HTA Directorate, HIQA
Ms Lora Ruth Wogu	CEO and Board Secretary, Sickle Cell and Thalassaemia Ireland

Key: *Ms Helen Byrne left the EAG after the first meeting and was replaced by Ms Carol Ivory.
[#] Joined the EAG after the first meeting.
[†] Alternate for Ms Lynsey Kavanagh, Pavee Point.

Members of the Evaluation Team

Dr Helen O'Donnell, Mr David Byrne, Dr Susan Spillane, Ms Joan Quigley, Dr Simona Paone, Mr Éanán Finnegan, Ms Karen Jordan, Dr Laura Comber, Dr Arielle Weir, Mr Paul Carty, Ms Michelle O'Neill, Dr Patricia Harrington, Dr Conor Teljeur, and Dr Máirín Ryan.

Conflicts of interest

There were no reported potential conflicts of interest declared for any members of the Expert Advisory Group or Evaluation Team.

Key Findings and Advice to the Minister for Health and the Health Service Executive

Following a request from the HSE's National Clinical Lead, Child Health and Public Health, with support from specialist clinicians at Children's Health Ireland (CHI), the Health Information and Quality Authority (HIQA) agreed to undertake a health technology assessment (HTA) of the repatriation of paediatric haematopoietic stem cell transplant (HSCT) services for children with inborn errors of immunity (IEI), inborn errors of metabolism (IEM), and haemoglobinopathies.

The key findings of this HTA, which informed HIQA's advice to the Minister for Health and the HSE, were:

- HSCT is a process by which haematopoietic stem cells (that is, immature cells with the capacity to develop into different blood cells) are transplanted to the patient with the overall aim being the long-term production of healthy blood cells. There are two main types of HSCT, autologous and allogeneic. Allogeneic HSCT, where donor stem cells are transplanted to the patient by infusion, is of most relevance to this HTA.
- IEI, IEM and haemoglobinopathies represent broad groups of genetic disorders. Many of these disorders display a higher incidence in the Irish Traveller and some ethnic populations, for example those of sub-Saharan African descent. While HSCT is the standard of care for many patients with these conditions, it is not a treatment option for every patient. The decision regarding the provision of HSCT to treat these conditions depends on the form and severity of the disease, individual patient characteristics, and the availability of a suitable donor.
- While HSCT is available in Ireland to paediatric patients with haematological malignancies and certain benign conditions, HSCT for most paediatric patients with IEI, IEM and haemoglobinopathies is provided in the UK under the HSE Treatment Abroad Scheme (TAS). To date, treatment has generally been accessed in Manchester (for patients with IEM) and Newcastle (for patients with IEI) with patients transferred back to CHI for post-treatment care. Historically, children in Ireland with haemoglobinopathies have rarely undergone HSCT. However, in 2022 an agreement for service provision was established with St. Mary's Hospital, London. As of November 2022, a small number of patients (<5) had started treatment on this pathway; no patient had yet completed treatment.

- Under the current arrangements, the child undergoing HSCT and one or both parents remain abroad for the treatment duration (which typically varies from two to six months). If the stem cell donor is a relation, this donor and their carer, where applicable, are also required to travel abroad for a number of days. The transplant journey is a period of substantial stress and uncertainty for patients, parents and families. If HSCT services for these patient groups were repatriated, the transplant episodes themselves would take place in Ireland, which would be expected to result in a large reduction in the logistical, financial and emotional burden experienced by families.

- CHI at Crumlin is accredited by the Joint Accreditation Committee of the International Society of Cellular Therapy and the European Society for Blood and Marrow Transplantation (JACIE). The HSCT service is provided by the hospital's HSCT and Cellular Therapy Unit for patients with malignant and selected benign indications. Between 2014 and 2021, a total of 93 allogeneic and 148 autologous HSCTs were performed at CHI, equivalent to an average of 12 allogeneic and 19 autologous HSCT procedures per year.

- While the number of HSCT procedures that would be repatriated is relatively low, repatriation would represent a large increase in the annual number of allogeneic transplants conducted at CHI's HSCT and Cellular Therapy Unit. It is estimated that repatriation would result in between 10 and 13 additional allogeneic transplants, on average, each year in CHI, potentially doubling the number of such procedures provided.

- The projected total demand for allogeneic HSCT under a scenario of repatriation at CHI was estimated using clinical opinion, historical data and projected national population estimates. The results suggest an average of 21 to 25 allogeneic transplants per year up to 2030. However, random variation associated with small patient numbers means this range would vary from year to year.

- In considering repatriation of the HSCT service for cohorts of relevance to this HTA, a key consideration is the number of available dedicated 'transplant' beds (single ensuite rooms with antechambers and high efficiency particulate air (HEPA) filtration systems) to accommodate the additional allogeneic HSCTs and the competing demand for these beds.
    - The HSCT and Cellular Therapy Unit at CHI at Crumlin has four dedicated transplant beds which accommodate patients receiving autologous HSCT, allogeneic HSCT and CAR–T therapy. On average,

there would be spare capacity to repatriate four transplants annually in 2023 and 2024.

  - At the new children's hospital (expected to open in late 2024 at the earliest) the number of transplant beds will increase from four to six. If all six transplant beds are available, in a year of average demand, there would be sufficient capacity to accommodate both existing patient groups and those for whom care is being repatriated.
  - The estimates above do not account for the expected variation in demand every year. When this is taken into account, if all six beds were available, the probability of meeting all demand would be 90% in 2030, based on modelled assumptions. The potential expected shortfall would equate to an average of one patient over five years.

- However, demand for transplants may also increase under a scenario where the age limit for treatment of patients with cancer increases to include patients up to the age of 20 years (currently 16 years), as alluded to under the National Cancer Strategy 2017-2026. If this group is also accommodated in the new children's hospital, in a year of average demand there would be sufficient capacity. However, taking into account years where there is increased demand, the potential expected shortfall equates to an average of nine patients over five years.
- As the impact of time to transplant may differ between the indications for HSCT, and capacity for transplant will be finite under a scenario of repatriation, careful consideration would need to be given to the process and criteria applied for the prioritisation of patients for transplant, and the use of contingencies at times where demand exceeds capacity. Examples of potential contingencies include:
  - accommodating some patients undergoing autologous HSCT in a non-dedicated transplant bed with similar facilities where there is sufficient staff capacity, and contingent on this not displacing other necessary clinical care
  - the continuation of agreements with centres abroad.
- Several factors may impact future demand for HSCT and cellular therapies, and this may impact the unit's ability to meet all demand. Such factors include changing epidemiology in Ireland, the potential for changes in clinical and age indications, and the availability of alternative treatment options to HSCT.

- Additional skilled nursing staff would be required in the HSCT and Cellular Therapy Unit, given the increased number of patients undergoing HSCT. Additional support staff across a range of disciplines would also be required. These staff will be required in CHI Crumlin if services are repatriated prior to the opening of the planned additional transplant beds in the new children's hospital.
    - Recruitment challenges have been identified for many disciplines. In particular, the limited and fluctuating number of trained HSCT nurses available to the unit has been identified by nursing management as a risk to the expansion of the service.
- If a decision is made to repatriate the service, consideration should be given to ensuring data management resources are sufficient to support the recording of patient outcome data and key performance indicators, and the engagement with international disease and transplant registries. The availability of such data supports quality management and ongoing accreditation.
    - These data would also facilitate ongoing monitoring and evaluation to ensure that access (as reflected by time to transplant) and outcomes are maintained for the repatriated patient cohorts.
- Special consideration is required in relation to the provision of extracorporeal photopheresis (ECP) and procedures aimed at preserving fertility, neither of which are currently provided in Ireland by the HSE for paediatric patients receiving HSCT:
    - ECP is used to treat graft-versus-host disease. Currently, this treatment is available to those who receive HSCT in the UK. Some patients who have received treatment abroad return to the UK for additional ECP treatment after their initial return home. This has important cost and resource implications for both the patient and the HSE. For an equivalent repatriated service, ECP would need to be available as a treatment option in Ireland.
    - Conditioning (for example, chemotherapy) is a common component of pre-transplant care. Patients receiving conditioning are at increased risk of subfertility or infertility. Procedures may be performed prior to the administration of conditioning with the aim of preserving future fertility. As part of HSCT provided in the UK, pre-pubertal patients are given the option of such procedures, with uptake reported to be high. The provision of these procedures should be evidence-based and take

into account the benefit-harm balance for individual patients. Furthermore, any service providing procedures aimed at preserving fertility would need to comply with national legislation.

- Any decision to introduce ECP and procedures which aim to preserve fertility could also have implications beyond the HSCT repatriated cohort.

- The budget impact of HSCT repatriation was examined from several different perspectives, including the HSE, the Department of Defence, and the provider of accommodation to families of patients undergoing HSCT in Ireland. From the perspective of the HSE, while subject to substantial uncertainty, the estimated five-year incremental budget impact is expected to result in cost reductions. Over a five-year time horizon, depending on whether costs arising from ECP and procedures aimed at preserving fertility are excluded or included, the reduction is estimated as €2.3 million (95% CI -€5.8m to +€1.1m) or €1.5 million (95% CI -€5.0m to +€1.9m), respectively. From the perspective of the Department of Defence, the estimated cost saving is €100,000 over a five-year time horizon. From the perspective of the Irish family accommodation provider, the estimated five-year budget impact is an increase of €370,000.

- If repatriation of HSCT services for the cohorts under consideration were deemed to be unfeasible, an alternative approach could involve attempting to alleviate some of the challenges posed by the existing model of care being delivered abroad.

- The transplant journey is a period of substantial stress and uncertainty for patients, parents and families, irrespective of the requirement to travel abroad. The requirement to travel abroad, however, places the following additional stress on families:

  - Parents need to manage a significant administrative and logistical burden.

  - There is a considerable financial burden placed on families due to incurring up-front costs and living expenses. In addition, there may be a disruption to or a reduction in family income given the requirement for a parent to travel abroad with the child for an extended duration.

  - The experience of living abroad for an extended period of time can be isolating and emotionally burdensome for parents. The separation of siblings and family members can be very difficult for these families.
  - Some ethnic minority groups may find these burdens additionally challenging due to issues such as financial insecurity, language, literacy or numeracy difficulties, and cultural values.

- In Ireland, family-centred integrated care is a core consideration of the national model of care for paediatric healthcare services. Currently, the separate delivery of care across the two healthcare jurisdictions of Ireland and the UK may make it challenging for Children's Health Ireland to ensure that continuity of family-centred care to the patient, parents and siblings is provided. Repatriation of HSCT services may improve the delivery of family-centred care for those receiving these services.

- There are several important ethical considerations relating to the child and their family:
  - The requirement to travel abroad places considerable strain on the parents of the child. Factors such a low income, single parent families, additional needs or specific cultural values may exacerbate the burden on individuals, thereby increasing inequity.
  - In Ireland, HSCT is available and provided for children with selected indications. In the absence of clear clinical rationale for the difference in treatment pathways for conditions requiring HSCT, the distinction may appear arbitrary and unjust from the patient perspective.

HIQA's advice to the Minister for Health and the HSE is as follows:

- Allogeneic haematopoietic stem cell transplant (HSCT) is the recognised standard of care for paediatric patients with particular inborn errors of metabolism (IEM), inborn errors of immunity (IEI) and certain haemoglobinopathies (depending on the form and severity of the disease). Compared to the general Irish population, patients who required HSCT for these conditions are more likely to be Irish Travellers or of non-Irish ethnicity.

- HSCT is provided by Children's Health Ireland (CHI) for paediatric patients with haematological malignancies and certain benign conditions. However, paediatric patients with IEM, IEI and haemoglobinopathies must travel abroad to obtain HSCT. This is associated with a significant administrative, logistical, financial and emotional burden for families given a treatment period abroad of between two to six months.

- Repatriation of HSCT services for these conditions would necessitate an additional 10 to 13 allogeneic HSCTs, on average, each year at CHI, potentially doubling the number of such procedures currently undertaken (average of 12 per year). From the perspective of the HSE, while subject to substantial uncertainty, the estimated five-year incremental budget impact is expected to result in cost reductions. Over a five-year time horizon, depending on whether costs arising from ancillary procedures are excluded or included, the reduction is estimated as €2.3 million (95% CI -€5.8m to +€1.1m) or €1.5 million (95% CI -€5.0m to +€1.9m), respectively.

- Additional considerations relevant to a decision to repatriate HSCT services for these conditions, include the following:

    - While there will be potential fluctuation in demand, on average, there would be sufficient capacity for all patients when services move to the new National Children's Hospital and the number of dedicated transplant beds increases from four to six.

    - The ability to accommodate any increase in HSCT activity would be contingent on the recruitment of additional staff, such as skilled nursing staff and support staff across a range of disciplines.

    - Repatriation would reduce the burden on ethnic minority groups who are both disproportionately represented in this cohort and who are disproportionately impacted by challenges associated with travelling abroad for care.

    - Patients undergoing HSCT in the UK have access to procedures not currently provided in Ireland by the HSE; these include extracorporeal photopheresis for the treatment of graft-versus-host disease and the provision of procedures aimed at preserving fertility. The provision of such services in Ireland for paediatric HSCT patients would have considerable organisational and resource implications.

- In the event of a decision to repatriate HSCT services for these conditions:
    - A phased approach to implementation may be required to support the build-up of sustainable capacity within the service.
    - Given the potential fluctuation in demand, there may be a requirement for contingencies at times when there are multiple high-priority patients for transplant and demand exceeds available capacity. This could include continued agreements with centres abroad.
    - Careful consideration of the process and criteria applied for the prioritisation of patients for transplant (including criteria to determine which patients are referred abroad for treatment when demand exceeds capacity), would be required to ensure equity and fairness.
    - Consideration should be given to ongoing monitoring and evaluation to ensure that access (as reflected by time to transplant) and outcomes are maintained for these patient cohorts.

Executive summary

A health technology assessment (HTA) is intended to support evidence-based decision-making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given finite healthcare budgets and increasing demands for services provided.

1 Background to the request

Allogeneic haematopoietic stem cell transplant (HSCT), otherwise known as a bone marrow transplant, is the internationally recognised standard of care for paediatric patients with particular inborn errors of metabolism (IEM), inborn errors of immunity (IEI) and haemoglobinopathies (depending on the form and severity of disease). While HSCT is available in Ireland to paediatric patients with haematological malignancies and certain benign conditions, paediatric patients with other conditions requiring HSCT must travel abroad to avail of this treatment. Funding for these procedures is provided through the Treatment Abroad Scheme (TAS) operated by the Health Service Executive (HSE). However, the requirement for travel can place a significant financial and logistical burden on patients and their families. The long duration of treatment, ranging from two to six months, means that families of patients undergoing HSCT may be separated for extended periods of time.

In light of the issues described above, a request was received by HIQA from the National Clinical Lead; Child Health, Public Health in the HSE, with support from specialist clinicians in Children's Health Ireland (CHI), to carry out a health technology assessment (HTA) of the repatriation of paediatric HSCT services for these non-malignant indications.

The overarching aim of this HTA was to describe the current and proposed HSCT treatment pathways and to identify the implications of the choice of treatment location both for patients and for the Irish healthcare system. The HTA did not assess the clinical effectiveness, safety, or the cost effectiveness of repatriation of HSCT services. These domains were omitted under the assumption of equal effectiveness of the UK and Irish service. That is, it was assumed that clinical outcomes would be equivalent whether patients are treated in the UK or Ireland. This HTA will advise on the potential impact of providing HSCT in Ireland for these patients.

2 The treatment pathway

HSCT is a process by which haematopoietic stem cells (that is, immature cells with the capacity to develop into different blood cells) are transplanted to the patient with the overall aim being the long-term production of healthy blood cells. There are two main types of HSCT, autologous and allogeneic. Allogeneic HSCT is of most relevance to this HTA. This is where donor stem cells are transplanted to the patient by infusion (primarily indicated in genetic disorders such as those under consideration within this HTA). In an autologous HSCT, a person is reinfused with their own stem cells after high dose chemotherapy (primarily indicated in malignant conditions).

The steps in the allogeneic HSCT process include donor identification and selection, prioritisation and patient evaluation, donor cell harvesting, graft processing, conditioning, transplant, engraftment, monitoring and treatment of complications (such as graft failure), and long-term follow-up. There are some differences in where some of the steps of the pathway take place between the groups of genetic disorders of relevance to this HTA. Of note, under the current pathway, a proportion of donor and candidate tests performed in Ireland are duplicated in the UK for governance reasons. To date, treatment has generally been accessed in Manchester (for patients with IEM) and Newcastle (for patients with IEI). Historically, children in Ireland with haemoglobinopathies have rarely undergone HSCT; however, an agreement for service provision is now in place with St. Mary's Hospital, London. Post-treatment, care for all three patient groups is transferred back to CHI.

If HSCT services for these patient groups were repatriated, the transplant episodes themselves would take place in Ireland without the requirement for the child, their family, or, where relevant, the familial donor to travel abroad. Given a current requirement to remain abroad for the treatment duration (which varies from two to six months), repatriation would reduce the logistical and cost burden for families in relation to travel, accommodation, and sustenance. For patients who are not in a position to travel abroad to access HSCT, repatriation would improve access to treatment. Repatriation would allow greater continuity of care, with management of all aspects of care being performed within the same service and reduce the administrative burden associated with referrals abroad. However, a number of associated procedures and therapies (for example, procedures aimed at preserving fertility and extracorporeal photopheresis (ECP) for graft-versus-host disease) that are offered as part of standard care in the HSCT services accessed through the UK, may not be included or available in a repatriated service.

3 Epidemiology and burden of disease

IEI, IEM and haemoglobinopathies represent broad groups of genetic disorders. While HSCT is the standard of care for many patients with these conditions, it is not a treatment option for every patient. The decision regarding the provision of HSCT to treat these conditions is dependent on the form and severity of the disease, individual patient characteristics, and the availability of a suitable donor.

Between 2013 and 2021, patients with severe combined immunodeficiency (SCID) comprised 9 of 37 IEI cases referred abroad for HSCT, while patients with Hurler syndrome comprised 25 out of 27 IEM cases referred abroad. The burden of the disease associated with each of these conditions was noted to be considerable, with both displaying higher incidence in the Irish Traveller population. Both conditions are associated with early morbidity and mortality in the absence of appropriate treatment, with HSCT considered the primary intervention for both. Sickle cell disease represents the most common form of haemoglobinopathy internationally, with a rising prevalence in Europe owing to an increase in inward migration. The clinical presentation, and overall outcomes, associated with HSCT for sickle cell disease is heterogeneous, with HSCT typically reserved for more severe cases for whom the clinical benefit is considered to outweigh potential harm.

While the number of allogeneic HSCT that would be repatriated is relatively low, repatriation would represent a large increase in the annual number of allogeneic transplants conducted at CHI's HSCT and Cellular Therapy Unit. HSCT is already performed in CHI at Crumlin for patients with malignant and selected benign indications. Between 2014 and 2021, a total of 93 allogeneic and 148 autologous HSCTs were performed at CHI, equivalent to an average of 12 allogeneic and 19 autologous HSCT procedures per year. It is estimated that repatriation would result in between 10 and 13 additional transplants, on average, each year in CHI. The projected total demand for allogeneic HSCT under a scenario of repatriation at CHI was estimated using clinical opinion, historical data and projected national population estimates. The results suggest an average of 21 to 25 allogeneic transplants per year up to 2030. However, random variation associated with small patient numbers means this range would vary from year to year. These estimates do not account for a proposed increase in the upper age limit from 16 to 20 years at CHI for patients with cancer which may further increase demand for allogeneic HSCT.

It should be noted that the information and estimates outlined are likely to be influenced by a number of factors including a changing epidemiology in Ireland (for example, increased inward migration), the potential for changes in clinical and age

indications for HSCT, and the availability of alternative treatment options. Factors include both potential for an increase in the range of HSCT indications for IEI given improvements in the benefit risk balance associated with the advancement of techniques for HSCT, but also potential reductions in HSCT requirements due to introduction of gene therapy. CHI also provides autologous HSCT and chimeric antigen receptor (CAR) T-cell therapy within its HSCT and Cellular Therapy Unit; changes in clinical indications for these procedures may further influence overall capacity within the unit.

4 Organisational considerations

The organisational considerations associated with the potential repatriation of HSCT services to Ireland are important given the high care needs of patients in the peri-transplant phase. A description was provided of the organisational considerations associated with the TAS, the resources required to enable the repatriation of the HSCT service, the resilience of the current and prospective service, considerations relating to quality assurance, and opportunities to improve the existing arrangements.

Under the current system there is a considerable administrative and logistical burden on both the system and families availing of the service. Treatment abroad involves travelling with a sick child to another country. Children who are medically unstable may travel with the Irish Air Corps, which is resource intensive. In terms of the resilience of the current service, there is a risk to access to HSCT for these cohorts should there be a change to the current agreements in place, or a scenario in which demand in the host country exceeds available capacity. Additionally, while patients are travelling to centres of excellence for HSCT, this necessitates a concession of clinical oversight and management from the local treating team to an external team abroad, interrupting the continuum of care.

To facilitate the provision of HSCT in Ireland for the cohorts of relevance to this HTA, and to preserve resilience in such a service, a number of key resources and organisational changes would be required. These are summarised in the following sections.

With regard to bed capacity, standard care in HSCT involves accommodating patients undergoing allogeneic HSCT in single rooms comprising antechambers, ensuite facilities and high efficiency particulate air (HEPA) filtration systems (also known as transplant beds) during the peri-transplant period until engraftment is achieved. An important consideration therefore is the number of these transplant beds that are available. The current HSCT and Cellular Therapy Unit at CHI at Crumlin has four dedicated transplant beds. Currently, these accommodate patients

receiving allogeneic HSCT, autologous HSCT and CAR-T therapy. Based on expected demand, it was estimated within this assessment that there would be capacity to repatriate four HSCT procedures annually in 2023 and 2024. At the new children's hospital (expected to open in late 2024 at the earliest) the number of transplant beds will increase to six. In years of average demand, there would be sufficient transplant capacity for repatriation if all six transplant beds are available for all groups and if future demand is in line with historical demand. However, these capacity estimates do not account for variation in demand every year. Under model assumptions, if all six transplant beds are available following repatriation, the probability of meeting demand is estimated to be 90% in 2030. Taking into account years where there is increased demand, the potential expected shortfall equates to an average of one patient over five years.

Demand for transplants may further increase under a scenario whereby the age limit for treatment of patients with cancer increases to include patients up to the age of 20 years (currently 16 years), as alluded to under the National Cancer Strategy 2017-2026. If this group is also accommodated in the new children's hospital, in a year of average demand there would be sufficient capacity. However, taking into account years where there is increased demand, the potential expected shortfall would equate to an average of nine patients over five years.

A number of options are available to maximise the probability of having adequate capacity while still maintaining required standards of care. These include accommodating patients receiving autologous HSCT in non-dedicated transplant beds, maintaining agreements with centres abroad, and or referring patients aged 16 years and older to the adult HSCT services in St. James's Hospital as appropriate. If autologous HSCT procedures were provided in non-dedicated transplant beds, the probability of meeting demand across all years to 2030 is estimated to be 100% if six transplant beds are available. This option would be contingent on this not displacing other necessary clinical care.

Given that a proportion of patients undergoing HSCT require admission to the intensive care unit (ICU), repatriation would increase demand for ICU bed days. Additional skilled nursing staff would be required in the HSCT and Cellular Therapy Unit given the increased number of patients undergoing HSCT as well as additional support staff across a range of disciplines. Furthermore, repatriation would increase demand for family accommodation. An inability to sufficiently increase any of these resources would adversely impact on the ability to successfully repatriate the service.

In the event of a decision to repatriate care, consideration would also need to be given to ensuring data management resources are sufficient to support the recording of patient outcome data and key performance indicators, and the engagement with

international disease and transplant registries. The availability of such data would support quality management and ongoing accreditation.

Special consideration is also required in relation to the provision of extracorporeal photopheresis (ECP), which is used to treat graft-versus-host disease. Currently, this treatment is available to those who receive HSCT in the UK. Some patients who have received treatment abroad return to the UK for additional ECP treatment after their initial return home; this has important cost and resource implications for both the patient and the HSE. For an equivalent repatriated service, ECP would need to be available as a treatment option in Ireland.

Conditioning (for example, chemotherapy) is a common component of pre-transplant care. Patients receiving conditioning are at increased risk of subfertility or infertility. Procedures may be performed prior to the administration of conditioning with the aim of preserving future fertility. As part of the HSCT care provided in the UK, pre-pubertal patients are given the option of this procedure with uptake reported to be high. At present, the HSE does not provide procedures aimed at preserving fertility for paediatric patients receiving HSCT in Ireland. The provision of these procedures should be evidence-based and take into account the benefit-harm balance for individual patients.

It is important to note that any decision to introduce ECP and procedures which aim to preserve fertility could also have implications beyond the HSCT repatriated cohort.

If repatriation of HSCT services for the cohorts under consideration were deemed to be unfeasible, an alternative approach could involve attempting to alleviate some of the challenges posed by the existing model of care being delivered abroad. For example, initiatives could be taken around improvement of the model of subsistence, financial and logistical support for the transport, accommodation and living expenses of patients and families who travel abroad for treatment.

5 Budget impact analysis

A budget impact analysis was carried out to assess the financial consequences of providing HSCT in Ireland for the additional indications of IEM, IEI and haemoglobinopathies for which treatment is currently provided abroad.

The BIA only considers aspects of the service that are expected to change in a repatriated service, that is, it does not include any of the services that are already provided to the patient in Ireland before they leave or when they return to Ireland. Therefore, the figures presented here are incremental and should not be interpreted as the full cost of care.

From the perspective of the HSE, while subject to substantial uncertainty, the estimated five-year incremental budget impact is expected to result in cost

reductions. Over a five-year time horizon, depending on whether costs arising from ECP and procedures aimed at preserving fertility are excluded or included, the reduction is estimated as €2.3 million (95% CI -€5.8m to +€1.1m) or €1.5 million (95% CI -€5.0m to +€1.9m), respectively. From the perspective of the Department of Defence, the estimated cost saving is €100,000 over a five-year time horizon. From the perspective of the Irish family accommodation provider, the estimated five-year budget impact is an increase of €370,000. All budget impact analyses were sensitive to changes in the number of patients receiving treatment. Given the small patient population, and historical variation in numbers of patients, small fluctuations are likely to have a significant impact.

The budget impact associated with repatriation under the patient perspective is especially complex. The extent of the financial burden depends on family circumstances. Significant accommodation, travel and sustenance costs will be incurred by families regardless of treatment location. It is difficult to quantify how treatment abroad affects all of these costs. The patient perspective in the formal budget impact analysis only considers the costs associated with the minimum level of transport and accommodation required. In this analysis, the estimated additional cost per family associated with repatriation is €120. This was driven by the co-pay for patients staying in family accommodation in Ireland. Supports are available that may alter the budget impact for families associated with repatriation.

Given the complexity, the costs associated with going abroad for treatment were also considered in two vignettes representing hypothetical families. While the families are fictional, the types of financial challenges documented have been described to the review team as lived experiences by families who have travelled abroad for treatment and by medical social workers who assist such families. Under these assumptions, repatriation would reduce the financial burden on families.

6 Patient and social considerations

The transplant journey is a period of substantial stress and uncertainty for patients, parents and families, irrespective of the requirement to travel abroad. The focus of this chapter was the additional burden that travelling abroad placed on them. This chapter was informed by meetings with parents, clinicians, specialist nurses, and medical social workers.

Parents need to manage a significant administrative and logistical burden arising from the requirement to travel abroad for the patient to receive a transplant. There is a considerable financial burden on families due to up-front costs and living expenses incurred while abroad. In addition, there may be a disruption of, or a reduction in, family income given the requirement for a parent to travel abroad with the child for an extended duration. This may exacerbate the financial burden. The

impact of this burden will vary depending on the individual circumstance of each family. If HSCT services were repatriated to Ireland there would be a very large reduction in the logistical burden and there would be a reduction in the up-front costs that families are required to pay. This, in turn, may reduce families' reliance on charitable sources of funding and offer them more certainty and control over their financial resources.

The experience of living abroad for between two and six months in another country, separated from the support network of family and friends, can be isolating and emotionally burdensome for parents (and the patient, depending on their age). The current separation of siblings and other family members can be very difficult for families. The repatriation of HSCT services to Ireland may allow greater scope for the immediate and wider family to provide support to the patient and parents, which may help to reduce the emotional impact on families during this time. For families in a position for the patient to recover at home during the outpatient phase, the duration for which the primary caregiver would be separated from the rest of their family or support network would be reduced.

In Ireland, family-centred integrated care is a core consideration of the national model of care for paediatric healthcare services. Currently, the separate delivery of care across the two healthcare jurisdictions of Ireland and the UK may make it challenging for Children's Health Ireland to ensure that continuity of family-centred care to the patient, parents and siblings is provided. Repatriation of HSCT services may improve the delivery of family-centred care for those receiving these services.

The above-described burden associated with receipt of HSCT treatment abroad may be distributed unequally across population groups. Certain minority or ethnic groups may find the burden of travelling abroad to access HSCT services additionally challenging beyond that of the general population. Issues such as financial insecurity, language, literacy or numeracy difficulties, and the impact of cultural values, may mean that they are disproportionately affected by challenges associated with travelling abroad to access transplant services.

It is important to note that if the service were repatriated, there may be a change in the availability of ancillary or follow-up treatment options such as fertility-related procedures and extracorporeal photopheresis therapy for the treatment of graft-versus-host disease. As noted, such services are not currently available within the publicly-funded healthcare system in Ireland. However, some parents felt strongly that procedures intended to preserve fertility should be offered to children in Ireland. It would be important that appropriate information is provided to parents in relation to the indications for these procedures, and their associated benefits and risks.

7 Ethical issues

The impact of repatriation on the family of children who receive this service abroad was noted to be a key consideration. Under the current pathway, there is the potential for considerable employment, financial and administrative strain on the parents of the child, which may not be equitable in terms of resilience when considering families on lower incomes. The need to travel is associated with a separation of the family unit, and reduced support from wider family and community networks. This burden is likely exacerbated when considering single parent families.

HSCT is available and provided in Ireland for children with selected indications. In the absence of clear clinical rationale for the difference in treatment pathways for conditions which require HSCT, the distinction may appear arbitrary and unjust from the patient perspective.

The requirement to engage with healthcare systems abroad for the provision of HSCT services necessitates that clinical responsibility and oversight is transferred to the host country. The HSE is furthermore reliant on the capacity and prioritisation of care in that country, with a risk to care provision should current agreements change. There are further ethical considerations relating to the child and their family in this context. The protection of autonomy and variations in processes of information provision and obtaining of informed consent internationally should be considered. It is also important to consider differences in respect for persons in terms of a family being unfamiliar with a healthcare system outside of Ireland, and the potential for privacy challenges with the sharing of data with host countries and, in particular, those outside of the European Union.

The sustainability and benefits of a repatriated service would depend on the investment in staff resources and availability of clinical facilities. As HSCT is already provided in Ireland for certain indications, repatriation of the remaining indications would increase demand for such services in Ireland. The unpredictable nature of when transplants will be required makes it challenging to project demand. If periodic demand exceeds capacity in a repatriated service, then some patients may still be required to access treatment abroad. To ensure equity and fairness, a transparent system would be required to determine which patients are referred abroad for treatment. In the event of a decision to repatriate, consideration should be given to ongoing monitoring and evaluation to ensure that access (as reflected by time to transplant) and outcomes are maintained for these patient cohorts.

In terms of the ethical consequences of the HTA itself, given the rarity of the genetic conditions under consideration, there are challenges relating to the availability of

data to inform these types of assessments. Moreover, the findings of the HTA may be impacted by prospective changes in elements such as the availability of alternative treatments, service level agreements, and family support packages. Lastly, the approach of the assessment was based on the assumption that the procedure as delivered in Ireland would be equivalent to that delivered in the UK. However, there may be distinct differences such as the availability of publicly funded options for fertility-related procedures.

8 Conclusions

The results of this assessment suggest that repatriation would reduce the financial, logistical and emotional burden on families at a time that is already unavoidably stressful for families. In total, it is estimated that repatriation would mean an average of between 10 and 13 additional allogeneic HSCT procedures each year, potentially doubling the number of such procedures currently provided by CHI. While there will be potential fluctuation in demand, on average, there would be sufficient capacity for all patients when services move to the new National Children's Hospital and the number of dedicated transplant beds increases from four to six. From the perspective of the HSE, provision of the service in Ireland is unlikely to cost more than the current arrangement of travelling abroad for treatment and may be cost saving. It would also reduce demand for air ambulance services provided by the Department of Defence, but would increase demand for family accommodation close to CHI. If a decision were made to repatriate HSCT services for these conditions, it would be necessary to ensure appropriate resources are in place before changes are made to the existing provision of services. A decision to repatriate HSCT services for these conditions may warrant a phased approach to implementation, which would support the build-up of sustainable capacity within the service.

Plain language summary

Allogeneic haematopoietic stem cell transplant (HSCT), sometimes known as a bone marrow transplant, is a procedure in which a patient receives healthy stem cells (a type of cell than can develop into all types of blood cells) from a compatible donor to replace their own damaged or defective stem cells. HSCT is the internationally recognised standard of care for some children with particular inherited (that is, passed to them from their parents) health conditions. These three groups of conditions are broadly referred to as inborn errors of immunity (IEI), inborn errors of metabolism (IEM), and haemoglobinopathies (that is, a group of disorders that affects red blood cells and reduces the amount of oxygen carried by the blood). For some of these conditions, the suitability of HSCT depends on how the disease affects the patient and whether the patient has a suitable donor. In Ireland, currently, children with these types of conditions who need a HSCT must travel abroad to access this treatment. This is funded through the Treatment Abroad Scheme (TAS) operated by the Health Service Executive (HSE). This is in contrast to arrangements for children with diseases such as cancer and certain bone marrow failure syndromes; HSCTs for these patients are done in Ireland.

The Health Information and Quality Authority (HIQA) was asked by the HSE to carry out a health technology assessment (HTA) of providing HSCT in Ireland for children who currently need to travel abroad to access this procedure. This assessment looked at organisational, social and ethical issues, and the budget impact of providing HSCT procedures for these conditions in Ireland rather than abroad.

There are many steps involved in donor-provided (allogeneic) HSCT. These include finding a suitable donor, prioritising the patients, and taking, storing and treating the stem cells before the transplant happens. After the transplant, the patient is monitored closely to make sure the treatment went well and that they are recovering appropriately. For the conditions this HTA is considering, usually the child, and one or both of their parents, have to travel to the UK for the HSCT procedure. Typically this means staying in the UK for between two to six months. This need to travel and stay abroad for a long time is difficult for families as they have to cope without the support of the rest of their family and friends at a challenging time. There may also be extra work for the family to organise transport and accommodation while away, as well as extra costs and potentially a loss of household income. Given that children with other health conditions receive HSCT in Ireland, being required to travel to the UK for treatment may seem unfair.

The groups of conditions this HTA is considering are rare diseases in the general population. However they occur in greater numbers in specific groups. In Ireland,

some of the conditions classed as "inborn errors of immunity" and some classed as "inborn errors of metabolism" are more common in the Irish Traveller Community. Also in Ireland, haemoglobinopathies occur in higher numbers in those who are of non-Irish ethnicity, for example those of sub-Saharan Africa descent. While rare, these conditions are very serious and children with these conditions will often have significant health problems. For some patients with very severe forms of these conditions, a child will die if they do not receive early treatment by HSCT.

Given the rare nature of these conditions in the general population, the number of donor-provided HSCT procedures that would need to be performed in Ireland instead of the UK is relatively low. It is estimated that bringing this care back to Ireland would result in an extra 10 to 13 transplants per year at Children's Health Ireland (CHI). The transplant unit in CHI already performs donor-provided transplants each year for patients with other conditions, such as cancers. In total, if all HSCT were performed at CHI, on average, between 21 and 25 total donor-provided transplants would be needed per year up until 2030. These numbers are estimates, however, and may vary from year to year. Other factors that might influence the number of HSCT procedures that are required include changes in the make-up of the Irish population and changes to what other treatments might become available.

Children who have a HSCT have high care needs. If all the donor-provided HSCT procedures were to be done in Ireland, a number of important organisational issues would need to be considered. First, there needs to be enough capacity to accommodate all of the patients. The CHI centre uses dedicated transplant beds for HSCT procedures. These are single bed, ensuite rooms that are designed to reduce the risk of infection for patients who need HSCT and which are only used for this purpose. Children's Health Ireland at Crumlin has four dedicated transplant beds. This will increase to six dedicated transplant beds when the new National Children's Hospital opens. If only four transplant beds are available, it will not be possible to accommodate all of the children who currently travel abroad for treatment. If six beds are available, it is estimated that, in most years, there will be enough transplant bed capacity to accommodate all of these children. However, the number of children needing HSCT for these conditions can change a lot from year to year. In some years, there may not be enough capacity in Children's Health Ireland when there are multiple patients who urgently need HSCT. If this happened, it is possible that a small number of children would still need to go abroad for their HSCT.

There are other important considerations that will affect transplant services for these patients. Extra skilled nursing staff would be required by the transplant unit, as well as extra support staff across a range of medical services. Since there would be an

increase in children travelling to Dublin for transplant services, there would be an increase in the demand for family accommodation in Dublin. These points will need to be carefully considered to ensure a high standard of treatment experience for patients and families.

The report also considered the cost of providing HSCT in Ireland for children who currently travel abroad to get treatment. While there is substantial uncertainty in relation to costs, it was estimated that providing these services in Ireland could save the HSE between €1.5 million and €2.3 million over five years. As each family's situation is different, it is difficult to calculate how costs would change for families if the service was provided in Ireland. However, it is expected that the financial burden on families would be substantially reduced if transplant services were provided in Ireland.

It was important to look at the impact of travelling abroad to get transplant services on families. This was done by meeting with medical professionals, support staff and parents of patients. The experience of travelling abroad and being separated from family and friends in Ireland can be an isolating and a very emotional experience for parents. Having to travel abroad also means there is a lot of planning, preparation and paperwork for parents to manage during an already difficult time. Other concerns, such as the cost of living abroad for two to six months and a person's ability to take time off work or to organise care for other dependents, can make this experience more difficult for families. Removing the need to travel abroad is likely to help reduce many of these concerns, although some issues will remain.

This report has also identified many issues that will need to be carefully considered when deciding whether to provide these transplant services in Ireland for children who currently travel abroad for treatment. It is important to make sure there will be enough beds for patients and appropriately trained staff available to provide high quality care. Removing the need to travel may reduce some of the difficulties and concerns for parents of patients and family members, but also increase the demand for family accommodation in Dublin. There are certain treatments available to patients in the UK that are not currently provided in Ireland. These include procedures aimed at preserving fertility in children, and also a procedure called "extracorporeal photopheresis" which is sometimes used to manage one of the complications that can happen following a donor transplant. Future access to these types of procedures may need to be considered.

List of abbreviations

AITHS	All-Ireland Traveller Health Study
ADA-SCID	adenosine deaminase severe combined immunodeficiency
AYA	adolescents and young adults
BCG	Bacillus Calmette-Guérin
BIA	budget impact analysis
BMT	bone marrow transplant
BSBMTCT	British Society of Blood and Marrow Transplantation and Cellular Therapy
CAR-T	chimeric antigen receptor T-cell
CHI	Children's Health Ireland
CI	confidence interval
CID	combined immunodeficiencies
CMV	cytomegalovirus
CNS	central nervous system
CPI	consumer price index
CSO	Central Statistics Office
DRG	diagnosis-related group
EBMT	European Society for Blood and Marrow Transplantation
ECP	extracorporeal photopheresis
ESID	European Society for Immunodeficiencies
EUnetHTA	European Network of HTA
FACT	Foundation for the Accreditation of Cellular Therapy
GAG	glycosaminoglycan
G-CSF	granulocyte colony stimulating factor
aGvHD	acute graft-versus-host disease
GvHD	graft-versus-host disease
Hb	haemoglobin
HEPA	high-efficiency particulate absorbing
HIPE	Hospital In-Patient Enquiry
HIQA	Health Information and Quality Authority
HLA	human leukocyte antigen
HPO	Healthcare Pricing Office
HPRA	Health Products Regulatory Authority

HSCT	haematopoietic stem cell transplant
HSE	Health Service Executive
HTA	health technology assessment
ICU	intensive-care unit
IEI	inborn errors of immunity
IEM	inborn errors of metabolism
IPC	infection prevention and control
ISCT	International Society of Cellular Therapy
IUBMR	Irish Unrelated Bone Marrow Registry
IUIS	International Union of Immunological Societies
IUI	intrauterine insemination
IVF	in vitro fertilisation
JACIE	Joint Accreditation Committee ISCT-Europe & EBMT
LOS	length of stay
MDT	multidisciplinary team
MMUD	mismatched unrelated donor
MOU	memorandum of understanding
MPS	mucopolysaccharidoses
MRD	matched related donor
MSD	matched sibling donor
MUD	matched unrelated donor
NBS	newborn screening
NHS	National Health Service
NNBSP	National Newborn Bloodspot Screening Programme
NSAC	National Screening Advisory Committee
PCRS	Primary Care Reimbursement Service
PPP	purchasing power parities
PRSI	Pay-related social insurance
PSA	probabilistic sensitivity analysis
SLA	service level agreement
SCD	sickle cell disease
SCID	severe combined immunodeficiency
SCETIDE	Stem CEll Transplant for ImmunoDeficiencies in Europe
TAS	treatment abroad scheme
TCL	T-cell lymphopenia
TREC	T-cell receptor excision circle

VAT	value added tax
WHO	World Health Organization
WMDA	World Marrow Donor Association

1 Introduction

1.1 Background to the request

Allogeneic haematopoietic stem cell transplant (HSCT), otherwise known as a bone marrow transplant (BMT), is the internationally recognised standard of care for paediatric patients with particular inborn errors of metabolism (IEM), inborn errors of immunity (IEI) and certain haemoglobinopathies (depending on the form and severity of disease). In Ireland, the most prevalent genetic conditions for which HSCT is indicated are Hurler syndrome (an inborn error of metabolism), severe combined immunodeficiency (SCID) (an inborn error of immunity) and sickle cell disease (a haemoglobinopathy).[1-3]

Haematopoietic stem cells are immature cells which are found in the peripheral blood and in the bone marrow and which have the capacity to develop into different types of blood cells.[4] Allogeneic HSCT is a process by which donor haematopoietic stem cells are transplanted to the patient by infusion.[5] The goal of treatment is the acceptance of donor stem cells by the patient (engraftment), and the sustained long term production and release to the peripheral blood of healthy red blood cells, white bloods cells and platelets (haematopoiesis).[6] As these donor cells are free of the underlying genetic mutations giving rise to the disease, HSCT, if successful, prevents disease progression and may in some conditions be curative.[6]

There is a single paediatric HSCT centre in Ireland, located in Children's Health Ireland (CHI) at Crumlin, Dublin. As a transplant unit, CHI is accredited by the Joint Accreditation Committee of the International Society of Cellular Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT) (JACIE), demonstrating adherence to international standards of HSCT.[7, 8] Clinical care of children undergoing HSCT currently is delivered under the supervision of the haematology consultants.[9]

While HSCT is available in Ireland to paediatric patients with certain conditions such as bone marrow failure syndromes and haematological malignancies, paediatric patients with other conditions requiring HSCT must travel abroad to avail of this treatment.[1-3, 10] Funding for these procedures is provided through the Treatment Abroad Scheme operated by the Health Service Executive (HSE).[10] However, the requirement for travel can place a significant financial and logistical burden on patients and their families.[1, 2] The long duration of treatment, ranging from two to six months, means that families of patients undergoing HSCT may be separated for extended periods of time. For others, the logistical challenges associated with travelling to receive HSCT represent a prohibitive barrier to accessing this care; as

such, some patients are not able to access HSCT treatment.[1] Furthermore, HSCT performed outside Ireland is subject to available capacity in the host country, representing a risk to access.

In light of the issues described above, a request was received by Health Information and Quality Authority (HIQA) from the National Clinical Lead Child Health Public Health in the HSE, with support from specialist clinicians in Children's Health Ireland, to carry out a health technology assessment (HTA) of the repatriation of paediatric HSCT services for these non-malignant indications. This request was prioritised for inclusion in the HIQA HTA work plan.

1.2 Terms of reference

The overarching aim of this HTA is to describe the current and proposed HSCT treatment pathways for paediatric patients with certain inborn errors of metabolism, inborn errors of immunity and haemoglobinopathies, and to identify the implications of the choice of treatment location for both patients and for the Irish public healthcare system. This HTA will advise on the potential impact of providing HSCT services in Ireland for these patients to inform decision-making by the Minister for Health and the HSE. In establishing which domains should be examined within the HTA, it was noted that HSCT is already recognised as the standard of care for the patient cohorts under consideration. However, there are social and ethical issues arising from the location in which HSCTs are provided for these patients. Furthermore, it was noted that there may be significant organisational and resource implications associated with repatriation of the HSCT service. As such, it was concluded that the assessment should focus largely on domains relating to social, ethical, organisational and resource implications.

With consideration to paediatric patients with certain inborn errors of metabolism, inborn errors of immunity and haemoglobinopathies requiring HSCT, the terms of reference of this HTA are to:

- describe the epidemiology of these conditions in Ireland and the associated burden of disease
- provide a high-level description of HSCT and the outcomes associated with its use for these indications
- describe the current standard of care and treatment pathway for these patients and the proposed pathway if HSCT treatment for all paediatric conditions were to be repatriated to Ireland

- assess the governance and organisational implications for the HSE of repatriating HSCT services as well as the implications for the resilience of the service
- assess the budget impact of providing HSCT in Ireland
- consider the social, ethical and legal implications that the provision of HSCT for these indications in Ireland may have for patients, their families, the general public and the healthcare system in Ireland
- based on the evidence in this assessment, advise on the impact of the alternative approaches to the provision of HSCT for these patients.

1.3 Overall approach

Following initial scoping of the available evidence, the terms of reference for this assessment were agreed between HIQA and the HSE. HIQA appointed an Evaluation Team comprising staff from the HTA Directorate to carry out the assessment. A detailed protocol outlining the methodological approach to this HTA has been published (available here).

HIQA convened an Expert Advisory Group comprising representation from key stakeholders including the Health Service Executive, Department of Health, clinicians with specialist expertise, and patient representation. The role of the Expert Advisory Group is to inform and guide the process, provide expert advice and information, and to provide access to data, where appropriate.

The Terms of Reference of the Expert Advisory Group are to:

- contribute to the provision of high quality and considered advice by the Authority to the Health Service Executive
- contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate
- be prepared to provide expert advice on relevant issues outside of group meetings, as requested
- provide advice to the Authority regarding the scope of the analysis

- support the Evaluation Team led by the Authority during the assessment process by providing expert opinion and access to pertinent data, as appropriate
- review the project plan outline and advise on priorities, as required
- review the draft report from the Evaluation Team and recommend amendments, as appropriate
- contribute to the Authority's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment
- notify the project lead if a nominee can no longer participate or contribute to the process, as non-participation may require alternative EAG membership to be sought.

The Terms of Reference of the HTA were reviewed by the Expert Advisory Group at its first meeting. Draft chapters were circulated to the Expert Advisory Group for review and were discussed at two formal meetings of the group, with amendments made, where appropriate. The final version will be submitted to the Board of HIQA for approval. Upon approval, the completed assessment will be submitted to the Minister for Health and the HSE as advice, and published on the HIQA website.

2 The treatment pathway

Key points

- Haematopoietic stem cell transplant (HSCT) is a process by which haematopoietic stem cells (that is, immature cells with the capacity to develop into different blood cells) are transplanted to the patient with the overall aim being the long-term production of healthy blood cells. There are two main types of HSCT, autologous and allogeneic, with allogeneic HSCT being of most relevance to this HTA:
    - Autologous: where a person is reinfused with their own stem cells after high dose chemotherapy (primarily indicated in malignant conditions)
    - Allogeneic: where donor stem cells are transplanted to the patient by infusion (primarily indicated in genetic disorders such as those under consideration within this HTA).
- In the majority of cases referred for treatment, HSCT for inborn errors of immunity (IEI), inborn errors of metabolism (IEM), and haemoglobinopathies (that is, the collective disorders of interest to this HTA) is provided in the UK under the HSE's Treatment Abroad Scheme (TAS).
- The steps in the allogeneic HSCT process include donor identification and selection, prioritisation and patient evaluation, donor cell harvesting, graft processing, conditioning, transplant, engraftment, monitoring and treatment of complications (such as graft failure), and long term follow-up.
- To date, the HSCT procedure has generally been accessed in Manchester (for patients with IEM) and Newcastle (for patients with IEI). Historically, children in Ireland with haemoglobinopathies have rarely undergone HSCT. However, in 2022 an agreement for service provision was established with St. Mary's Hospital, London. While a number of patients have started on this pathway, no patient has completed treatment as of November 2022. Post-treatment, care for all three patient groups is transferred back to CHI. Of note, under the current pathway, a proportion of donor and candidate tests performed in Ireland are duplicated in the UK for governance reasons.
- If HSCT services for these patient groups were repatriated, the transplant episodes themselves would take place in Ireland without the requirement for the child or their family to travel abroad for the treatment duration (which

typically varies from two to six months). Additional impact associated with such repatriation may include:

- elimination of the need for familial donors and their carers, where applicable, to travel outside Ireland for donor cell harvesting
- reduced logistical and cost burden for families in relation to travel, accommodation, and sustenance
- improved access to treatment for patients who may not be in a position to travel overseas to access the treatment
- greater continuity of care, with management of all aspects of care being performed within the same service
- reduced administrative burden for referrals abroad
- associated procedures and therapies (for example, extracorporeal photopheresis (ECP) and procedures aimed at preserving fertility) that may be provided as part of standard HSCT care in the UK may not be included or available in a repatriated service.

2.1 Introduction

The HSCT treatment pathway, which is indicated in certain patients with inborn errors of metabolism, inborn errors of immunity, and, haemoglobinopathies, (hereafter, 'genetic conditions') is the technology under assessment in this HTA. This chapter describes the current pathway available to patients under the HSE's Treatment Abroad Scheme, and outlines how this treatment pathway would differ if HSCT for these conditions were repatriated to Ireland. This chapter begins with a brief description of the Treatment Abroad Scheme, followed by a description of HSCT and a review of the main international standards associated with HSCT. This review focuses on recommendations which are of increased importance for the genetic conditions of relevance to this HTA, and which relate to transplant volumes, types of procedures and patients.[11]

Given that there is already a HSCT service in Ireland provided to patients with conditions such as bone marrow failure and haematological malignancies, which meets international accreditation standards, a detailed service specification of HSCT is beyond the scope of this overview.

2.2 Treatment Abroad Scheme (TAS)

The purpose of the Treatment Abroad Scheme (TAS) is to enable a public patient to seek public funding for a treatment not available in Ireland. The TAS provides financial assistance towards the cost of treatment in public health facilities in another EU/EEA member state, the UK or Switzerland, for treatments within Irish law and either:

- not available in Ireland, or
- not available within the time normally necessary to receive the treatment in Ireland, taking into account the patient's current health and the likely course of the patient's condition or disease.

The legislative basis of the TAS is further detailed in chapter 4 (section 4.2.1).

To apply for treatment of a patient abroad, the patient's Irish-based referring hospital consultant must submit the TAS application form, and provide details of the patient's condition, the specific treatment being applied for, and the provider of the treatment abroad (including a copy of the consultant's referral letter). Generally within TAS, a decision on the application is usually made within 15 to 20 working days of its receipt.[10] Once the patient has availed of the approved treatment abroad, the care of the patient reverts immediately to the referring Irish consultant.

Costs covered under TAS

The TAS provides for the cost of the treatment to be received abroad, but does not cover travel or subsistence expenses for the patient or their relatives. However, it is stated within the Travel Policy for TAS applicants, that assistance may be provided towards reasonable economic air or sea travel fares for the patient and 'a travelling companion' where appropriate and subject to available funding.[12] Where the patient is under the age of 18, the air or sea fares of two accompanying adults will also be provided, subject to available funding. The air or sea fares are restricted to the cost of the airline or ferry ticket charge and the government and airport/sea port charges only. Other costs, for example, luggage charges or travel agent fees, are excluded.[12] In order for eligible travel costs to be reimbursed, documentation, including booking confirmations and boarding passes, must be submitted to the HSE following completion of the air or sea journey. The impact of costs associated with treatment abroad, versus under a repatriation scenario, is explored in detail in chapter 5.

2.3 Description of HSCT

Haematopoietic stem cells are immature cells found in the peripheral blood and in the bone marrow, which have the capacity to develop into different types of blood cells.[4] HSCT is a process by which haematopoietic stem cells are transplanted to the patient by infusion.[5]

There are two main types of HSCT: autologous and allogeneic. Autologous HSCT is where a person is reinfused with their own stem cells after high dose chemotherapy. This is primarily indicated in malignant conditions and is not an appropriate treatment for the patients of relevance to this HTA. The subject of this HTA, allogeneic HSCT, is a process by which donor haematopoietic stem cells are transplanted to the patient by infusion.[5] The goal of treatment is the acceptance of donor stem cells by the patient (engraftment), and the sustained long-term production and release to the peripheral blood of healthy red blood cells, white bloods cells and platelets (haematopoiesis).[6] As these donor cells are free of the genetic mutations that give rise to the underlying disease, HSCT, if successful, prevents disease progression and may in some conditions be considered curative.[13]

2.4 Donor identification and selection

The first step in the HSCT process is the identification of potential donors. Factors for donor selection include cytomegalovirus (CMV) status, blood group, sex, parity and age. However, the most important factor for transplant success is the degree of match between donor and recipient.[14] Matching is evaluated through human

leukocyte antigen (HLA) typing.[5] HLA describes markers which enable the body to differentiate between its own cells and foreign cells. There are a number of donor types: matched sibling donor, matched related donor, matched unrelated donor, mismatched unrelated donor, haplo-identical, and cord blood transplantation.[14] These are described in more detail below.

The ideal donor is a matched sibling donor. Patients have a 25% chance of each sibling being fully HLA matched. Other relations may also be considered as a potential matched related donor. Although this increases the potential donor pool, compared to siblings, the probability of each person being a full match is lower.[14] It is also possible that unrelated donors may be a full HLA match (that is, a matched unrelated donor). However, despite being a full HLA match, the probability of a successful transplant outcome is lower than with a matched sibling donor.[11]

Nonetheless, outcomes obtained with matched unrelated donors have improved over time and are now approaching those of matched sibling donors.[11] Matched unrelated donors may be identified from the Irish Unrelated Bone Marrow Registry (IUBMR) at the Irish Blood Transfusion Service.[15] This registry is also the World Marrow Donor Association (WMDA) national hub for the request of donors from international registries. The WMDA holds over 38 million donors and cords on its database, which includes the IUBMR.[15] It is the responsibility of the IUBMR to process requests for donors originating from within the country or coming from abroad and to co-ordinate activities in the respective countries.[15]

Transplantation with mismatched unrelated donors is also possible where there is a partial incompatibility with HLA typing. An HLA haplo-identical donor is one who shares, by common inheritance, exactly one HLA haplotype with the recipient, but is mismatched for other HLA genes.[16] The haplo-identical donor may be a parent, brother, sister or other relative.[16] High incidence of graft rejection and graft-versus-host disease (GvHD) because of the mismatched disease make these transplants challenging (see 2.11 for more information on GvHD).[14] Graft engineering and pharmacological prophylaxis of GvHD have reduced the incidence of these complications.[11] Some guidelines recommend that transplantations with a mismatched donor should only be performed in centres with experience in these types of procedures and patients.[11]

Another donor option is unrelated donor umbilical cord blood unit transplantation. Advantages of this form of transplantation, which uses cryopreserved units at cord blood banks, include the ready availability of cord blood, a lower incidence of GvHD, and comparable transplant outcomes to those occurring in matched unrelated donor or mismatched unrelated donor transplants.[14] Disadvantages include the greater

treatment cost and the slower time to haematopoiesis.[14] In recent years, umbilical cord has been a preferred graft source for patients with Hurler Syndrome in some centres.[17]

The importance of time to transplant depends on the individual genetic condition. However, in general, HSCT outcomes are better the earlier in the disease course that the transplant occurs.[13] The search for an unrelated matched donor normally takes six to eight weeks.[17, 18] Therefore, while matching is the most important factor for donor selection, a balance may need to be struck between the use of mismatched family donors, which may be quicker to identify, versus the time taken to find a matched donor.[14] For the treatment of some conditions, the donor should not be a carrier of the underlying genetic disease mutation. However, for others, carrier status does not impact survival.[19, 20]

The donor selection process is complex. For some conditions, especially patients with haemoglobinopathies, the benefit-risk balance may no longer lie in favour of HSCT if a matched sibling donor is unavailable.[21] For ADA-SCID, a particular form of SCID, gene therapy may be a preferable treatment option in the absence of a suitable donor and a decision may be made to not proceed to transplant;[11] several children in Ireland have received gene therapy for ADA-SCID thus far as part of clinical trials taking place in Great Ormond Street Hospital, London.[3]

2.5 Donor Cell Harvesting

There are three graft sources for HSCT: bone marrow, peripheral blood stem cell, and umbilical cord blood. While the use of peripheral blood and cord blood is increasing, bone marrow is the principal graft source in paediatric patients.[22]

Bone Marrow

Bone marrow is collected from the pelvic bones using needles and syringes under general anaesthesia.[23] The typical hospital stay is one night.[9] It normally takes the body around one week to replace the bone marrow.[23]

Peripheral blood

The concentration of haematopoietic stem cells is lower in the peripheral blood than in the bone marrow.[23] To increase the concentration available for transplant, an infusion of granulocyte colony stimulating factor (G-CSF) may be given to the donor on each of the four days before the donation procedure; G-CSF stimulates the bone marrow to produce stem cells and release them into the bloodstream. The donor is admitted for a day case procedure which lasts around six hours. The procedure first

involves placing sterile needles in both arms. Blood is removed from a vein in one arm. Next, the blood is passed through plastic tubing into a cell separator machine, which separates the blood stem cells from the rest of the donor's blood. The stem cells are collected and the remainder of the blood is returned to the donor via a tube placed in the donor's other arm. In most cases, one harvesting session is sufficient. Sometimes, donors are given a fifth injection and undergo a further collection procedure the following day to collect a sufficient sample to proceed with the transplant.[23]

Umbilical Cord blood

Umbilical cord blood may be collected from consenting mothers who wish to donate to a cord blood bank. Following the birth of a baby, the umbilical cord is cut and the placenta is delivered.[24] At this point, the process of cord blood collection may begin; the placenta is taken to a dedicated cord blood collection room, the cord is cleaned, and blood is collected from a needle inserted into the cord. The donated blood is screened, HLA typed, frozen and stored at a core blood bank for future use.[24]

Directed cord blood banking was previously undertaken by the IBTS but service ceased due to a lack of demand for banked blood and the extent of resources required to store blood.[17] However, if a cord is chosen as the optimal donor choice for a transplant recipient, it will be sourced from an accredited cord bank internationally.[9]

2.6 Graft Processing

CD34+ is a cell surface marker used to identify haematopoietic stem cells. The dose of transplanted cells for the recipient is measured as the number of CD34+ T-cells by kilogram of body weight.[25] As such, the number of CD34+ cells in the graft is counted. The graft quality is also assessed, and graft manipulation is performed to optimise the volume and the cellular composition of the sample. If there will be a time delay between graft harvesting and transplant, or if the sample will be transported to a distant transplant centre, the graft is cryopreserved within 48 hours or less of donor harvesting.[25]

2.7 Conditioning

Conditioning involves the administration of combinations of chemotherapy, radiotherapy, and or serotherapy, to the transplant recipient for up to ten days prior to transplant.[26] In the non-malignancy setting, as is the case for conditions of relevance to this HTA, the aim of the conditioning therapy is to create space in the

recipient bone marrow for donor cells to engraft, and to suppress the immune system to decrease the risk of rejection of donor cells by the recipient.[26] There are three types of conditioning approaches: full conditioning (also known as myeloablative conditioning), reduced intensity conditioning, and no conditioning. The choice of conditioning approach depends on the condition being treated, patient characteristics, and the level of the HLA match between donor and recipient. The advantages of avoiding full conditioning include reduced incidence of toxic side effects (such as subfertility or infertility). On the other hand, full conditioning allows better stem cell engraftment and reduced incidence of GvHD.[27] Full conditioning is recommended for inborn errors of metabolism and is suggested for sickle cell disease,[20, 21] but guidelines for some SCID subtypes recommend no conditioning where the donor is a full HLA match.[27] For some conditions, full consensus has not been reached among clinicians regarding the optimal approach and research into reduced intensity regimens is ongoing in many disease areas.[20, 27]

2.8 Transplant

The stem cells are infused into the transplant recipient via a Hickman line.[13]

2.9 Engraftment

Engraftment is a process in which transplanted donor stem cells travel through the blood to the bone marrow, where they begin to make new white blood cells, red blood cells and platelets (haematopoiesis). It normally happens within two to four weeks following transplant.[28] Prior to engraftment, patients require blood product support (including red cells, platelets, and sometimes granulocyte infusions) and antibiotic, antifungal and antiviral drug prophylaxis and treatment of infection, where applicable.[29] Complications that may occur include mucositis, fluid overload, GvHD, haemorrhagic cystitis, veno-occlusive disease, pneumonitis, renal failure and acute neurological problems. Intensive-care unit (ICU) stay may be required for severe complications.[29]

Engraftment may lead to the patient showing a “complete chimerism”, where all of the haematopoietic cells produced are of donor origin, or “mixed chimerism”, where the haematopoietic cells produced by both donor and recipient origin co-exist.[30] In the genetic conditions of relevance to this HTA, it is not always necessary to replace the recipient haematopoiesis completely. Often, it is sufficient to implement a state of mixed haematopoietic chimerism to improve the patient's well-being; in these cases, a reduced intensity conditioning regimen may be used, which reduces toxic side effect, but increases the likelihood of graft rejection or failure.[30]

2.10 Graft failure and rejection

In some cases, treatment with HSCT may not achieve the desired outcomes; there may be ineffective recovery of haematopoiesis or ineffective immune reconstitution (the rebuilding of the immune system post-transplant). The unsuccessful outcomes may be due to graft failure, where the donor cells have not engrafted, or rejection where the donor cells initially engrafted but at some point, the patient's body rejected the cells.[31] In such cases, patients may be treated with an additional dose of donor cells (stem cell boost) or undergo a full additional transplant. Here, stem cell boosts typically refer to an additional infusion of stem cells from the same donor without conditioning, whereas an additional transplant involves HSCT from a different donor with or without conditioning or from the same donor with conditioning.[32, 33]

2.11 Graft-versus-host disease (GvHD)

A commonly reported complication experienced by patients following HSCT is acute or chronic GvHD, where donor T-cells cause pro-inflammatory responses in the host. This occurs when donor T-cells encounter host cells that these donor T-cells regard as hostile.[34] Common symptoms of acute GvHD include a rash, usually initiating at the extremities such as the palms of the hands or the soles of the feet (also commonly manifesting on the shoulders or the ears), jaundice, swelling of the liver, and diarrhoea.[35] Other symptoms include anaemia, thrombocytopenia, and fever.[35] GvHD is more common with reduced-intensity conditioning regimens. Complications of GvHD within the first 100 days following HSCT are classified as acute, while those that arise after this time period are considered chronic.[35] Acute GvHD is graded in severity from I (mild) through IV (very severe) according to the modified Seattle Glucksberg Criteria; these criteria are based on the type and number of organ systems affected and the severity of symptoms.[36]

For Grade II to IV acute disease, systemic corticosteroids are indicated for first-line therapy. In the UK, the National Health Service (NHS) commissioning guidelines recommend extracorporeal photopheresis (ECP) as a second-line treatment. ECP is a form of apheresis, and is a therapeutic procedure in which the buffy coat (fraction of an anti-coagulated blood sample that contains most of the white bloods cells and platelets following centrifugation) is separated from the patient's blood, treated extra-corporeally with a photoactive compound (for example, psoralens) and exposed to ultraviolet A light, and is then subsequently infused into the patient during the same procedure. This is a highly specialised treatment with important resource implications.[36]

2.12 Service standards

JACIE, the Joint Accreditation Committee of the International Society of Cellular Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT), is a non-profit body established for the purposes of accreditation in the field of HSCT.[37, 38] The primary aim of JACIE is to promote high-quality patient care and laboratory performance in cellular therapy.[38] In collaboration with the Foundation for the Accreditation of Cellular Therapy (FACT), JACIE develops and maintains global standards for the provision of quality medical and laboratory practice in HSCT and other cellular therapies. The standards are extensive and comprehensive and cover all phases of cell collection, processing, storage, transportation and administration.[39] An accreditation manual accompanies the standards, which explains the intent and rationale for specific standards, provides examples of how to meet the standards, and details the type of documentation that may verify compliance.[36] Centres can demonstrate that they are performing at these standards and that they operate an effective quality management system by obtaining JACIE accreditation.[7] This involves a JACIE review of relevant documentation submitted by the centre and an onsite inspection. Renewal of accreditation is required after four years or if there are substantial changes to personnel or infrastructure within the centre.

In Ireland, CHI at Crumlin is JACIE accredited to perform autologous and allogeneic transplantation in paediatric patients, including cell processing (minimally manipulated CD34+ selection only) and collection of stem cells (apheresis and marrow).[8] This is a rolling process. Assessment for reaccreditation is due to take place in 2023.[17] In 2020, CHI at Crumlin performed 12 allogeneic transplants, the number of which is greater than the minimum number of allogeneic transplants (minimum being 10 transplants) required to maintain JACIE accreditation.[40] As ECP is not provided in CHI at Crumlin at present, JACIE Standards, which state that there should be policies addressing indications for and safe administration of ECP if utilised by the clinical program, have not applied to date.[36]

The NHS has published minimum service specifications for the provision of paediatric HSCT in England, as outlined in its clinical commissioning policy[41] and detailed in its standard contracts for paediatric HSCT[29], including the following:

- All centres should be JACIE accredited or in the process of renewing JACIE accreditation.[41]

- All transplant units are required to register transplants in the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) registry and to participate in a national retrospective audit of outcomes.(41)

- The standards recognise that research and involvement in clinical trials is an important element of providing a high-quality service in stem cell transplantation. Providing patients meet the commissioning policy criteria and that there are no excess treatment costs to commissioners, treatment provided as part of the National Cancer Research Institute (NCRI) approved clinical trials is commissioned.(41)

- The importance of comprehensive multi-disciplinary team care for the optimisation of patient selection and all aspects of care is outlined.(29)

- The minimum data collection requirements include capture of the indication, donor stem cell source, stem cell manipulations, conditioning therapy, and outcomes and complications, with detailed description of serious morbidities and mortality.(29)

- The standards aspire that all centres would contribute to a weekly teleconference to discuss patient selection, transplantation approach, management of complications and waiting lists.(29)

The NHS commissioning policy for allogeneic HSCT for primary immunodeficiencies also outlines how decisions on patient treatment are undertaken by regional paediatric HSCT multidisciplinary teams.(42)

- To ensure shared practice and expertise, the policy states that all providers will participate in an 'all ages annual confidential audit meeting' where the outcomes of all transplanted patients are discussed.

- Complete datasets are required to be submitted to the European Society for Blood and Marrow Transplantation's Registry and to Stem Cell Transplant for ImmunoDeficiencies in Europe (SCETIDE); this is the comprehensive database for HSCT in patients with IEI, which is held in Paris and linked with the EBMT and European Society for Immunodeficiencies (ESID) registries.

2.13 Mapping of the treatment pathway

2.13.1 The current pathway: HSCT abroad

Patients with haemoglobinopathies, IEI and IEM are managed in the national tertiary referral centres of CHI. These are the Red Cell and Haemoglobinopathy Service and the Department of Paediatric Infectious Diseases and Immunology at CHI at Crumlin,[3, 43] and the National Centre for Inherited Metabolic Disorders at CHI at Temple Street.[44] A few patients with sickle cell disease are managed at Cork University Hospital.[1]

Before 2012, patients with Hurler syndrome, a form of IEM, received HSCT in CHI at Crumlin, but the service ceased on the retirement of the consultant providing treatment.[2] This service did not extend to other IEM or the other conditions under consideration in this HTA. Since 2012, all Irish patients (with limited exception) who have undergone HSCT for these indications have been treated in England under the Treatment Abroad Scheme.[2]

Patients with IEI and IEM are referred to the Great North Children's Hospital in Newcastle upon Tyne and the Royal Manchester Children's Hospital, respectively, and all patients referred have been able to access treatment thus far.[2, 3] As of December 2022, both centres are JACIE accredited.[8] While treatment is provided by the HSE under the TAS for patients with haemoglobinopathies, past efforts to firmly establish referral pathways to European centres including the UK have not been successful.[1] HSCT for sickle cell disease is a relatively newer indication and is only indicated when patients have experienced significant morbidity. The difficulty in sourcing suitable family accommodation for the long duration of outpatient treatment post-transplant was described by clinicians as a major obstacle.[1] Until 2022, most patients were not in a position to access this treatment due to the logistical challenges involved; in the ten years preceding 2022, only one patient with a haemoglobinopathy accessed treatment.[1] In 2022, a new pathway for patients with haemoglobinopathies was established allowing referral of eligible patients to St Mary's Hospital, London for HSCT. As of November 2022, a small number of patients (<5) patients have started on this pathway; no patient had yet received a transplant.[9]

Depending on the patient's underlying condition, the HSCT treatment pathway differs slightly due to organisational differences in the referring centre, and differences in the patient's underlying demographic and clinical response to treatment. HSCT treatment steps are similar across patient groups regardless of the indication for treatment. The common treatment pathway available to Irish patients

is outlined below. Where applicable, differences in the pathway between patient groups are outlined.

Table 2.1. Current HSCT Treatment Pathway under Treatment Abroad Scheme - Pre Transplant

Step in HSCT process	Location		Notes
	Ireland	UK	
Potential HSCT candidate identified	✓		▪ The timing of candidate identification within the disease course depends on the form of disease and severity of disease. ▪ For patients with very severe disease such as SCID and Hurler syndrome, HSCT is the standard of care (provided there is a suitable donor). In these cases, the patient is identified as a potential HSCT candidate at the time of diagnosis.[11, 20] ▪ For patients with haemoglobinopathies, HSCT is usually not indicated at the time of diagnosis given that the benefit risk balance of HSCT depends on the disease course. Potential candidates are identified by clinicians if the patient experiences severe disease such as CNS involvement or cardiopulmonary events.[21] ▪ The patient's Irish-based referring hospital consultant must submit the treatment abroad application form to the TAS section of the HSE. Approval from the HSE must be received before the patient receives treatment, except in the emergency cases.[45]
Donor identification	✓	✓	▪ Donors are identified by performing HLA typing on blood samples collected from relatives.[14] ▪ If available, sibling donors are considered first due to high likelihood of a successful match. Matched sibling donors provide the best prognosis after transplants.[14] ▪ If a matched related donor is unavailable, international bone marrow registries are searched.[14] For traceability and accreditation purposes, it is mandatory for the centre performing the transplant to carry out and take responsibility for HLA typing and the donor search.[9] ▪ Other donor types need to be considered if a full match is not found.[14]

Step in HSCT process		Location		Notes
		Ireland	UK	
				▪ If a matched sibling donor is not available, the search for an unrelated donor usually takes between six and eight weeks.[9]
Candidate evaluation	Outpatient appointments	✓	✓	▪ The HSCT candidate is evaluated to ensure they are suitable for transplant.[46] ▪ The exact work-up will vary depending on the indication for treatment and individual patient characteristics.[46] ▪ Common tests include: standard blood tests, urea and electrolytes, liver function, viral serology, coagulation, tissue typing, serum ferritin, kidney, liver and lung function, ECHO and ECG.[46] **IEM** ▪ Candidate evaluation takes place at Children's Health Ireland between Crumlin and Temple Street.[2] ▪ Consultant from Manchester conducts a virtual meeting with the family of the transplant recipient in Ireland.[9] ▪ Patients do not have to travel to UK. **IEI and Haemoglobinoapthies** ▪ For stable patients, evaluation occurs in England over three days on an outpatient basis.[1, 3] ▪ Before travel, the Irish referring consultant must apply to the HSE for coverage under the Treatment Abroad Scheme.[3] ▪ Patients with very severe IEI disease do not travel to the UK for evaluation at this stage. A preliminary evaluation is conducted in Ireland and further tests are conducted by the transplant team in the UK just prior to transplant.[2]

Step in HSCT process		Location		Notes
		Ireland	UK	
	Transport and Accommodation		✓	**IEI and Haemogobinopathies** ▪ For stable patients, commercial travel is usually appropriate and hotel accommodation sufficient.(3) ▪ Patients are responsible for organising their own flights and accommodation.(3)
Donor evaluation		✓	✓	**Related Donors** ▪ Donors should be medically evaluated to ensure they are medically fit to undergo the donation process. Common tests include liver, heart and kidney function, viral serology, chest x-rays and ECG. Other tests may also be indicated depending on donor characteristics.(14) ▪ Evaluation of related donors generally occurs in Ireland by clinicians independent of the HSCT candidate with no requirement for the donor to travel to the UK at this stage.(9) ▪ IEI donor samples are sent to UK for repeat HLA typing to confirm the type of match. (3) **Unrelated donors** ▪ Unrelated donors are sourced through international bone marrow registries.(15) ▪ Donor evaluation takes place in an international clinic where the donor resides.(15)
Decision made regarding transplant and donor source			✓	▪ In some cases, there may be a decision not to transplant after donor and candidate evaluation because of the altered benefit risk balance associated with mismatched donors or complications identified during the candidate and donor evaluation.(1)

Step in HSCT process		Location		Notes
		Ireland	UK	
				▪ For referred patients, the final decision about whether to proceed to transplant and the choice of graft source is made by the UK accepting clinician as clinical governance for the treatment will lie with them.[2, 3, 9] ▪ Funding approval from the HSE's Treatment Abroad Scheme is required to proceed for transplant.[1-3]
Prioritisation for transplant		✓		▪ The urgency of HSCT depends on the patient's condition. ▪ Prioritisation for transplant by UK centres with whom a treatment pathway has been established is based on their capacity and clinical need.[2, 3] ▪ Crumlin HSCT team and Temple Street IEM Nurse specialist are invited to attend UK IEM HSCT multidisciplinary meetings.[2] [46] Frequency of meetings varies depending on the number of patients waiting for transplant. ▪ Crumlin IEI team attend multidisciplinary meetings with the UK IEI HSCT multidisciplinary team.[3]
Pre-transplant assessment			✓	▪ Parents and child travel via commercial transport and stay in hotel / hospital-affiliated family accommodation immediately prior to admission.[2, 3] ▪ HSCT candidate is treated in hospital as an outpatient or day case.[2, 3] **Patients with IEI or IEM and very severe disease** ▪ Patients with very severe forms of IEI may travel via chartered air ambulance and are admitted as an inpatient upon arrival.[3]

Key: CNS – central nervous system; CHI – Children's Health Ireland; ECG – electrocardiogram; ECHO – echocardiogram; HLA - human leukocyte antigen, HSCT - haematopoietic stem cell transplantation; HSE – Health Service Executive; IEI – inborn errors of immunity; IEM – inborn errors of metabolism; SCID – severe combined immunodeficiency; TAS – treatment abroad scheme.

Table 2.2. Current HSCT Treatment Pathway Treatment Abroad – Transplant Episode

Step in HSCT process		Location		Notes
		Ireland	UK	
Donor	Transport		✓	▪ If a related donor, the donor must also travel to the UK.
	Graft Harvesting		✓	▪ The related donor is treated in the UK hospital. The length of stay depends on the type of graft. Peripheral blood stem cell collection is a day case procedure, but additional harvesting for a second day may be required. ▪ Bone marrow harvesting requires an inpatient stay of 1-2 nights.
	Graft Processing		✓	▪ Harvested donor cells are prepared for transplant in the clinic laboratory.
Inpatient episode	Transport			▪ Commercial transport is usually appropriate – patients often travel by ferry. Very rarely, patients with an IEM require an air ambulance transfer.[3]
	Accommodation			▪ Accommodation is normally available in hospital-affiliated accommodation. If capacity is unavailable, medical social workers attempt to source charitable funding to cover accommodation costs.
	Preparation		✓	▪ Patients are admitted to a single occupancy HEPA-filtered room to reduce the risk of infection.[26] ▪ Prophylactic medicines are given to reduce the risk of infection and graft-versus-host disease.[26] ▪ A short length of theatre time is required to place a central line.[22] Ovarian or testicular tissue cryopreservation is a procedure which aims to preserve future fertility. If indicated, this procedure is also performed in the same theatre episode to reduce the risk of additional anaesthesia.[17] A longer amount of theatre time is required if a testicular or ovarian procedure is being performed to retrieve tissue for cryopreservation. Further information regarding gonadal tissue cryopreservation is presented in chapter 4.
	Conditioning		✓	▪ This may involve 5 to 10 days treatment prior to transplant; some patients with SCID do not require any conditioning.[26]

Step in HSCT process		Location		Notes
		Ireland	UK	
	Transplant		✓	▪ The donor stem cells are transfused to the HSCT recipient through the central line.[22]
	Post-Transplant		✓	▪ Recovery from transplantation typically takes four to eight weeks as an in-patient.[29] Patients remain in hospital until there is evidence of engraftment, the patient is well and IV therapy and infusions are no longer required.[29] ▪ This timeframe may be extended if the complications outlined below occur.[29]
Potential pertinent inpatient complications	ICU Admission		✓	▪ Some patients require admission to ICU due to critical complications such as severe acute GvHD or complications arising from infections such as septic shock or respiratory failure. The length of stay and underlying treatments required will vary depending on the nature of the complication.[29] ▪ A small proportion of HSCT recipients will not survive transplant. For the 2014-2018 UK paediatric cohort, point estimates of overall survival at one year for a paediatric cohort were 87%, 84% and 90% for patients with IEI, other inherited disorders (including IEM) and haemoglobinopathies, respectively. [47]
	Infection		✓	▪ Inpatient admissions requiring antifungal therapy are considered complex admissions given the cost of therapy and risk to the patient.[29]
	Acute Graft-versus-Host Disease		✓	▪ 37% of paediatric patients in the UK registered from 2009 to 2014 who received HSCT for non-malignant indications experienced GvHD with 7% of patients experiencing Grade 3 or 4 disease. This complication extends the length of hospital stay.[48] ▪ ECP is a second line treatment for acute GvHD. Treatment regimens vary depending on the treating clinicians. The UK Photopheresis Society recommend one cycle of treatment (which consists of a 1.5 hours ECP session on two consecutive days) weekly for a minimum of eight weeks. Some patients receive three treatments per week for the first four weeks.[49] ▪ Following the initial treatment block, experts recommend that ECP treatment schedules are continued, tapered, or stopped at this point, depending on the treatment response, manifestation of disease and use of co-medications.[49]

Step in HSCT process		Location		Notes
		Ireland	UK	
				▪ Patients may require ECP treatment but are otherwise well enough to be discharged home to Ireland. Because ECP treatment is not available in Ireland to paediatric patients, this extends the time spent abroad.
	Graft Failure		✓	▪ Rarely, graft failure may occur. In the BSBMTCT report of the 2014 to 2018 cohort, this occurred in 1%, 5% and 3% of patients with IEI, other inherited disorders (including IEM) and haemoglobinopathies, respectively.[47] In these cases, stem cell boosts may be provided. Rarely, a second allogeneic transplant may be considered after extensive discussions and external expert review.[29]

Key: BSBMTCT - British Society of Blood and Marrow Transplantation and Cellular Therapy; ECP - extracorporeal photopheresis; GvHD – graft-versus-host disease; HEPA - high efficiency particulate absorbing [filter]; HLA - human leukocyte antigen; HSCT - haematopoietic stem cell transplantation; HSE – Health Service Executive; ICU – intensive-care unit; IEI – inborn errors of immunity; IEM – inborn errors of metabolism; SCID - severe combined immunodeficiency; TAS - treatment abroad scheme.

Table 2.3. Current HSCT Treatment Pathway Treatment Abroad - Post Transplant

Step in HSCT process		Location		Notes
		Ireland	UK	
Post-transplant	Outpatient Care		✓	▪ Following discharge from hospital, the HSCT recipient must stay close to the transplant centre for close monitoring for signs of infection and GvHD. Patients with IEM return to Ireland post discharge and receive follow-up from the HSCT team at Crumlin. Patients with IEI or haemoglobinopathies remain in the UK at this stage and are followed by the UK centres until approximately three months post-transplant.[9] ▪ The HSCT recipient and accompanying parent stay in commercial or hospital-affiliated family accommodation while visiting the hospital as an outpatient. The frequency of appointments will vary depending on clinical need, but will reduce over time to once weekly.[2, 3]
	Transport			▪ In a small number of cases, patients may travel from inpatient care to Ireland via chartered air ambulance. This may be for palliative treatment at home,[3] or in case of IEM, a hospital to hospital transfer via Air Ambulance from Manchester to Crumlin may be arranged by the HSCT transplant team if there no longer capacity in Manchester for the patient.[17]
Long-term care	Transport		✓	▪ HSCT recipient and parents normally travel home via commercial transport.[3]
	Long-term care	✓		▪ Patients with IEM, IEI and haemoglobinopathies are discharged from the UK service to the HSCT team in CHI at Crumlin, the Department of Immunology in CHI at Crumlin, and the Red Cell and Haemoglobinoapathy Service, respectively.[3] ▪ Patients with IEM are transferred from CHI at Crumlin to the care of the metabolic centre in Temple Street one year after transplant.[2, 3] ▪ Patients who received ECP abroad may travel over and back to the UK for further ECP treatment. This requires approval from the TAS section of the HSE and is assessed on a case-by-case basis.[50]

Key: CHI – Children's Health Ireland; ECP - extracorporeal photopheresis; GvHD – graft-versus-host disease; HSCT - haematopoietic stem cell transplantation; HSE - Health Service Executive; IEI – inborn errors of immunity; IEM –inborn errors of metabolism; TAS - Treatment Abroad Scheme.

2.13.2 The alternative pathway: HSCT in Ireland

Under the alternative treatment pathway, HSCT is provided to patients with these genetic conditions in Ireland. Compared to the current pathway, the most significant changes comprise all of the UK steps outlined above, taking place in Ireland rather than in the UK. There are a number of implications from a social and organisational perspective:

- Approval under the Treatment Abroad Scheme would no longer be required.
- At present, a proportion of donor and candidate tests performed in Ireland are duplicated in the UK for governance reasons. Repatriation would remove some of this duplication, albeit some tests would still have to be repeated depending on the length of time between evaluation and transplant.
- Chartered air ambulance flights to the UK for these patients would no longer be required.
- Transplant recipients, their parents and donors would no longer have to travel abroad for care. This would reduce both the financial and logistical burden associated with the transplant process, but also the burden on families associated with being separated for a lengthy period of time. Depending on the location of the family home (if located less than one hour from Dublin), some patients may be able to return home directly after discharge. The impact of the choice of treatment pathway on patients and families will be explored further as part of the social and ethical considerations chapters.
- Extracorporeal photopheresis (for GvHD) and gonadal tissue cryopreservation are interventions that may be offered as part of the standard HSCT package of care in the UK but which are not currently available as part of standard HSCT care in CHI at Crumlin and thus would not be available if care is repatriated. Further information regarding these treatments is provided in chapter 4.

2.14 Discussion

This chapter serves to provide a description of HSCT and relevant service standards. The current treatment pathway has been described and expected differences under a repatriated service have been outlined.

Information derived from the literature was combined with the results of consultation with stakeholders and validated with the Expert Advisory Group convened to support this assessment in order to describe the current HSCT treatment pathway and to understand how an alternative repatriated treatment pathway would differ from the current pathway.

In terms of accreditation, JACIE does not differentiate between transplants performed for different indications, and a JACIE accredited HSCT transplant centre already provides HSCT to patients with haematological malignancies and selected benign indications in Ireland. Therefore, the repatriation of these patients represents an expansion of the current HSCT service, rather than the establishment of a de novo service. This HTA assumes that both service delivery approaches (treatment abroad versus in Ireland) would result in equivalent clinical outcomes for people in a position to access either. The assumption of equivalent clinical outcomes is based on the existing model of HSCT care delivery in Ireland for malignant paediatric conditions; this involves an Irish multidisciplinary team with appropriate qualifications and expertise delivering a service that adheres to comparable service standards and best international practice. However, there is inevitably going to be a period at the beginning of the service where the level of experience and efficiency lags behind that of the UK service, which benefits from the accumulated experience of many years of providing care for patients with these genetic conditions. During the time it would take to develop this experience and build up the capacity of the service to meet the level of demand, it may be necessary to continue to source care for a proportion of patients with these genetic conditions through the Treatment Abroad Scheme.

Relative to the existing model of care provision, the potential impact of establishing a national service may include:

- reduced logistical and cost burden for families in relation to travel, accommodation and sustenance
- improved access to treatment for patients with haemoglobinopathies who are not in a position to travel overseas to access the treatment at present

- greater continuity of care, with management of all aspects of their care being performed within the same service
- reduced administrative burden for referrals abroad.

There are important differences between the current and alternative treatment pathway with regards to the availability of procedures which may preserve future fertility. As these procedures are ancillary to the provision of HSCT, the implications of this is described in later chapters. The impact of a national service on capacity, and the burden on families, will be described in greater detail in chapter four and six respectively.

3 Epidemiology and burden of disease

Key points

- Inborn errors of immunity (IEI), inborn errors of metabolism (IEM), and haemoglobinopathies represent broad groups of genetic disorders. While haematopoietic stem cell transplant (HSCT) is the standard of care for many patients with these conditions, it is not a treatment option for every patient. The decision regarding the provision of HSCT to treat these conditions is dependent on the form and severity of the disease, individual patient characteristics, and the availability of a suitable donor.

- The epidemiology and burden of disease varies for conditions within and between the three groups of disorders of interest to this HTA.
    - Between 2013 and 2021, severe combined immunodeficiency (SCID) and Hurler syndrome were the most common conditions referred for HSCT within the IEI and IEM cohorts, respectively.
        - Severe combined immunodeficiency (SCID) comprised 9 of 37 IEI cases referred, while Hurler syndrome made up 25 out of 27 IEM cases.
        - The burden of the disease associated with these conditions is considerable. In the absence of appropriate treatment, SCID is almost uniformly fatal in the first year of life. Hurler syndrome is a rapidly progressive disease resulting in neurocognitive impairment and death within the first decade of life without treatment. HSCT is considered the primary intervention for both.
        - Both SCID and Hurler syndrome display higher incidence in the Irish Traveller population.
    - Sickle cell disease represents the most common form of haemoglobinopathy internationally, with a rising prevalence in Europe owing to an increase in inward migration of people from high prevalence countries. The clinical presentation and overall outcomes are heterogeneous with HSCT typically reserved for more severe cases for whom the clinical benefit is considered to outweigh potential harm.

- HSCT is currently performed in the HSCT and Cellular Therapy Unit in CHI at Crumlin for patients with malignant and selected benign conditions. Between 2014 and 2021, a total of 93 allogeneic and 148 autologous HSCTs were performed at CHI, equivalent to an average of 12 allogeneic and 19 autologous HSCT procedures per year.
- While the number of HSCTs that would be repatriated is relatively low, repatriation would represent a large increase in the annual number of allogeneic transplants conducted at CHI's HSCT and Cellular Therapy Unit. It is estimated that repatriation would result in between 10 and 13 additional allogeneic transplants, on average, each year in CHI, potentially doubling the number of such procedures currently provided.
- The projected total demand for allogeneic HSCT under a scenario of repatriation at CHI was estimated using clinical opinion, historical data and projected national population estimates. The results suggest an average of 21 to 25 allogeneic transplants per year up to 2030. However, random variation associated with small patient numbers means this range would vary from year to year. These estimates do not incorporate a proposed increase in the upper age limit of patients with cancer treated in CHI from 16 to 20 years of age.
- CHI's HSCT and Cellular therapy Unit provides allogeneic HSCT, autologous HSCT and chimeric antigen receptor T-cell (CAR-T) therapy. A number of factors may impact future demand for these existing services, which may in turn impact the unit's ability to also meet the requirements for the repatriated services (that is, JACIE accreditation). These factors include:
    - changing epidemiology in Ireland (for example, increased inward migration)
    - potential for changes in clinical and age indications for HSCT and for CAR-T
    - availability of alternative treatment options to HSCT.

3.1 Introduction

The purpose of this chapter is to describe the epidemiology of paediatric conditions in Ireland for which allogeneic haematopoietic stem cell transplant (HSCT) is indicated, but which are currently most often referred abroad for treatment, typically to the UK. These conditions encompass three broad groups of genetic disorders:

- inborn errors of immunity (IEI)
- inborn errors of metabolism (IEM)
- haemoglobinopathies.

Each of these groups of genetic conditions are inherited disorders. The inheritance pattern for many of these conditions is autosomal recessive, whereby disease manifests when a child inherits one mutated copy of a gene from each parent. If both parents are carriers of the mutant gene, there is a one in four chance that one of their children will develop the disease.[51] Risk factors include a family history of the condition and consanguinity (that is, unions between related individuals). These risk factors can occur in higher frequency in subsets of a population for reasons including geographical isolation or factors relating to ethnicity.[52-54]

The British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) has listed indications for HSCT in children, as recommended by the UK Paediatric Bone Marrow Transplant (BMT) Group, which state that HSCT may be:[55]

- standard of care
- indicated subject to clinical opinion (requiring careful assessment of risks and benefits)
- developmental, that is, further trials are required to inform practice
- generally not recommended.

For the conditions relevant to this HTA, allogeneic HSCT is the standard of care for many patients. However, it is not a treatment option for every patient. The decision regarding the provision of HSCT is dependent on the form and severity of the disease, individual patient characteristics, and the availability of a suitable donor.[11, 20, 21, 56]

Estimates of historical demand for HSCT in Ireland were informed by data from Irish clinicians. To validate these estimates, anonymised claims data, provided by the

Health Service Executive's (HSE's) Treatment Abroad Scheme (TAS), describing paediatric HSCT episodes of care abroad from 2012 to 2021 were analysed. As the clinician estimates based on patient records were more complete, these were used in the estimates presented below. Further information on the analysis of the TAS data is described in chapter 5. Other data sources for this chapter include the BSBMTCT registry data from the UK and international data from peer-reviewed published literature.

The aetiology, incidence, natural history and treatment outcomes of IEI, IEM and haemoglobinopathies are discussed in sections 3.2 to 3.7, with a focus on the most common of the conditions within these groups. A summary of the HSCT procedures performed in the UK in recent years to treat patients referred with these conditions is provided in section 3.8. The current paediatric HSCT service in Ireland (which is typically restricted to the treatment of conditions of bone marrow failure and haematological malignancies) is briefly outlined in section 3.9, along with a description of the demand for same. Here, the relevant epidemiology for chimeric antigen receptor T-cell (CAR-T) therapy and both allogeneic and autologous HSCT performed in Ireland is described. CAR-T is a form of cancer immunotherapy whereby a patient's immune cells, specifically T-cells, are genetically altered in a laboratory to enable them to locate and destroy cancer cells more effectively. These T-cells are reintroduced to the patient by infusion as a form of cancer treatment.

While this health technology assessment (HTA) is concerned with the repatriation of allogeneic HSCT, the number of autologous HSCT and CAR-T procedures performed has implications for the capacity within the transplant unit and the degree to which repatriation may occur. Factors that may influence future demand for paediatric HSCT services in Ireland are discussed briefly in section 3.10. Projected demand for such services under current and proposed pathways, which were informed by estimates of historical demand, are presented in section 3.11.

3.2 Inborn errors of immunity

The term 'inborn errors of immunity' (IEI) describes a broad group of inherited disorders of varying severity, caused by variation in single genes, that, in turn, result in altered, depleted or an absent function in one or more components of the immune system.[57] The mechanisms of disease depend on the specific gene or genes affected, as well as the nature of the variation (that is, loss of function, altered function or increased function) leading to a wide range of clinical manifestations, such as conditions associated with absent immune function (for example, severe combined immunodeficiency (SCID)) or at the opposite end of the spectrum, autoimmune disorders (that is, immune cells attacking the body's own cells and

tissues).[58] According to the International Union of Immunological Societies' (IUIS) Expert Committee, there have been 498 variants of IEI reported; these are sub-categorised in turn according to the type of immune cells and genes affected and their associated phenotypes.[58]

Apart from a limited number of exceptions, to date, patients presenting with IEI in Ireland who require HSCT are referred to the UK for treatment, under the TAS. The procedures are undertaken in the Department of Paediatric Haematopoietic Stem Cell Therapy and Immunology at the Great North Children's Hospital in Newcastle upon Tyne. As noted, in the UK, decisions surrounding indications for HSCT are guided by the 2015 UK Paediatric BMT Group HSCT Indications document.[55] According to this guidance document, HSCT is considered standard of care for the treatment of selected immunodeficiencies and refractory autoimmune disease. These disorders vary in severity and are categorised into a number of subgroups as summarised in Table 3.1. For patients with selected autoimmune diseases, HSCT may be a treatment option subject to clinical opinion.

Table 3.1 Indications for HSCT in children with immunodeficiencies and refractory autoimmune disease

Disease type	Specific conditions indicated for HSCT
Immunodeficiencies	
Combined immunodeficiency	SCID: ADA, AK2, RAG1, RAG2, DCLRE1C, DNA Ligase 4, DNA PKcs, yc (X-linked), Jak 3 kinase, IL7 Ra, CD3γδε, CD45, ZAP70 kinase, Coronin 1A CID: CD40 ligand deficiency, CD4 lymphopenia, MHC class II, PNP, Omenn syndrome, leaky SCID, MALT1, LCK, MST1 (STK4), CTPS1, other/undefined
Combined immunodeficiency with associated features	WAS, DiGeorge syndrome, CHARGE, CID with skeletal dysplasia, CHH, Nijmegen breakage syndrome*, DOCK8, Tyk2, ICF, DKC, PI3Kδ activating mutant, LRBA, ORAI-1, STIM1, other/undefined
Antibody deficiencies	Severe CVID, MDS with hypogammaglobulinaemia
Immune dysregulation	Haemophagocytic disorders: Familial HLH with genetic diagnosis (PRF1, UNC13D, MUNC18-2, STX11), HLH without genetic diagnosis (but with recurrent/refractory disease, affected sibling, absent NK-cell function, CNS disease), Griscelli syndrome type 2 (RAB27A), Chediak-Higashi syndrome (LYST), other/undefined Lymphoproliferative disorders*: XLP1 and XLP2, chronic active EBV, ITK, CD27, MAGT1, other/undefined

Disease type	Specific conditions indicated for HSCT
	Autoimmune: ALPS (homozygotes), STAT3 gain of function, CTLA4, other/undefined Early onset inflammatory bowel disease: IPEX syndrome, IL10, IL10 receptor, immunodeficiency with multiple intestinal atresia (TTC7a), other/undefined
Phagocytic cell disorders	LAD1-3, X-linked CGD, AR-CGD, GATA2, other/undefined
Innate defects	NEMO, STAT1, STAT5, IFN-γ receptor, IL12 receptor, other/undefined
Refractory Autoimmune disease	
Autoimmune disease (Refractory)	includes refractory immune cytopaenias, Juvenile Inflammatory Arthritis, SLE, Systemic Sclerosis, other

*not all patients proceed to HSCT.

Key: ADA - adenosine deaminase deficiency, AK2 - adenylate kinase 2, ALPS - autoimmune lymphoproliferative syndrome, AR-CGD - autosomal recessive chronic granulomatous disease, CD - cluster of differentiation, CGD - chronic granulomatous disease, CHARGE - coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities, CHH - cartilage hair hypoplasia, CID - combined immunodeficiency, CNS - central nervous system, CTLA4 - cytotoxic T-lymphocyte-associated antigen 4, CTPS1 - cytidine triphosphate synthase 1, CVID - common variable immunodeficiency, DCLRE1C - DNA cross-link repair 1C, DNA PKcs -DNA-dependent protein kinase catalytic subunit, DKC - dyskeratosis congenita, DOCK8 - dedicator of cytokinesis 8, EBV - Epstein-Barr virus, Familial HLH - familial haemophagocytic lymphohistiocytosis, GATA2 - GATA2 deficiency, HLH - haemophagocytic lymphohistiocytosis, HSCT – haematopoietic stem cell transplant, ICF - immunodeficiency-centromeric instability-facial anomalies syndrome, IFN-γ- interferon-γ, IL – interleukin, IPEX - immunodysregulation polyendocrinopathy enteropathy X-linked syndrome, ITK - interleukin-2-inducible T-cell kinase, Jak - janus kinase, LAD - leukocyte adhesion deficiency, LCK - lymphocyte-specific protein tyrosine kinase, LRBA - lipopolysaccharide-responsive beige-like anchor, MAGT1 - magnesium transporter 1, MALT1 - mucosa-associated lymphoid tissue lymphoma translocation protein 1, MDS - myelodysplastic syndromes, MHC - major histocompatibility complex, MST1 - macrophage stimulating 1, NEMO - NFκB essential modulator, NK-cell - Natural Killer cell, ORAI-1 - calcium release-activated calcium modulator 1, PI3kδ - phosphoinositide 3-kinase δ, PNP - purine nucleoside phosphorylase, RAG - recombination-activating genes, SCID – severe combined immunodeficiency, SLE - systemic lupus erythematosus, STAT3 - signal transducer and activator of transcription 3, STIM1 - stromal interaction molecule 1, STK4 - serine/threonine kinase 4, TTC7a - tetratricopeptide repeat domain 7A, Tyk2 - tyrosine kinase 2, WAS - Wiskott-Aldrich syndrome, XLP1/2 - X-linked lymphoproliferative disease 1/2, ZAP70 - zeta chain of T-cell receptor associated protein kinase 70.

Source: UK Paediatric BMT Group 2015.[55]

In Ireland, between 2013 and 2021, there were 37 children with IEI recorded as having received a first HSCT abroad; eight distinct IEI were involved, as presented in Table 3.2 below. A small number of these patients (n = <5) required a second transplant abroad. A small number of procedures have been carried out at Children's Health Ireland (CHI) at Crumlin for patients with IEI during this time period in selected cases where patients were too clinically unstable to travel. Between 2013 and 2021, a mean of 4.6 (range: 1 – 8) allogeneic HSCTs were performed annually for this group.

Table 3.2 Patients with inborn errors of immunity in Ireland who received a first HSCT abroad between 2013 and 2021

Condition	Number of patients
SCID	9
Primary immunodysregulatory	7
Combined immunodeficiency	7
Wiskott Aldrich Syndrome	5
Treatment resistant JIA	< 5
Familial HLH	< 5
Leukocyte Adhesion Deficiency	< 5
Treatment resistant SLE	< 5

Key: HLH - haemophagocytic lymphohistiocytosis, JIA - juvenile inflammatory arthritis, SCID - severe combined immunodeficiency; SLE - systemic lupus erythematosus.
Source: Lead consultant in Inborn Errors of Immunity at Children's Health Ireland.[3]

SCID represents the IEI in Ireland for which HSCT has most commonly been provided (9 of the 37 patients between 2013 and 2021). The following sections discuss in detail its aetiology, incidence, clinical course, and treatment outcomes.

3.3 Severe Combined Immunodeficiency

3.3.1 Aetiology

SCID represents one of the most severe forms of primary immunodeficiency and results from mutations in at least 19 known genes. The specific gene affected will determine the immunophenotype observed.[59] While SCID is typically characterised by T-cell lymphopenia (TCL) (that is, lower than normal or absent number of T-cells), the absence of specific T-cell subsets, such as CD4+ helper T-cells, can directly impact B-cell and Natural Killer-cell numbers, due to disruption to, and loss of, immune signalling and activation pathways.[60] Thus, SCID is a disorder of both

cell-mediated and humoral immunity. In addition, a number of classification systems exist for SCID, including those published by the IUIS and European Society for Immunodeficiencies (ESID).[58, 61] Substantial genotypic, phenotypic and clinical heterogeneity exists within SCID, even between individuals with similar genetic mutations.[59] Broadly speaking, cases of SCID can be categorised as typical SCID resulting from amorphic mutations (that is, loss of gene function) or atypical SCID (also referred to as "leaky" SCID) or Omenn syndrome, both arising from hypomorphic mutations (that is, a reduced or diminished gene function).[58, 59] In the UK, the BSBMTCT differentiates between cases of typical SCID and leaky SCID. Cases of typical SCID, constituting the most severe form of the disease with absent gene function, are regarded as SCID cases. In contrast, cases of leaky SCID are grouped together with other combined immunodeficiency (CID) disorders, owing to the reduced severity compared to typical SCID cases.[55]

3.3.2 Epidemiology

The incidence of SCID is noted to vary widely across geographic locations and within certain populations. This is due to the wide range of genetic mutations associated with SCID.[60] In Ireland, between 2005 and 2020, there were 27 children diagnosed with SCID. Within this 15-year time period, there were 1,073,519 births registered, reflecting a birth prevalence of 1 in 39,760 births. ADA-SCID (that is one specific subtype) made up approximately 50% (n = 14) of these cases with the majority noted to be of Irish Traveller ethnicity (for whom a founder mutation has been previously documented).

Universal screening for ADA-SCID as part of the National Newborn Bloodspot Screening Programme (NNBSP) commenced in May 2022.[62] HIQA undertook a HTA of the addition of T-cell receptor excision circle (TREC)-based screening for all SCID subtypes to the NNBSP in Ireland to inform a recommendation by the National Screening Advisory Committee (NSAC).[63] In January 2023, the Minister for Health approved a recommendation from the NSAC to add these conditions to the NNBSP.[64] In addition to earlier detection of cases that currently present clinically, introduction of universal screening for all forms of SCID may lead to detection of previously undiagnosed cases (infants that experience early mortality), with consequences for the provision and demand for HSCT services. Early detection of SCID also has important relevance for childhood vaccination programmes; children with SCID should not receive live vaccines (for example, Bacillus Calmette–Guérin (BCG) and rotavirus), due to the potential for vaccine-related harms in these patients.[65, 66]

3.3.3 Natural history and treatment options

Typically, infants with SCID are asymptomatic at birth.[67] There are three routes through which SCID may be detected: risk based detection at birth (typically a sibling previously diagnosed); newborn bloodspot screening; or clinical presentation. Of the 27 cases of SCID diagnosed in Ireland from 2005 to 2020, eight infants were diagnosed at birth through risk-based detection and 19 were diagnosed on the basis of clinical presentation.[3] Typically, SCID presents clinically as recurrent, and often severe, infections, and non-infectious health complications such as failure to thrive (that is, arrested or abnormal physical growth and development).[60]

In the absence of appropriate treatment, SCID is almost uniformly fatal in the first year of life.[68] The gold standard for the treatment of SCID is HSCT;[55] gene therapy is an option for specific subtypes of SCID in instances where suitable matched family donors are unavailable.[60] In addition, for patients with ADA-SCID, enzyme replacement therapy may be used as a bridging therapy while awaiting HSCT or gene therapy; this is to mitigate metabolite build-up and subsequent damage arising from ADA-enzyme deficiency.[60, 68] Of the 25 documented SCID cases in Ireland from 2005 to 2020 who survived to treatment, 21 were treated with HSCT (four cases of ADA-SCID were treated with gene therapy under clinical trials at Great Ormond Street Hospital, London) with a small number (<5) receiving a second transplant. Amongst instances of HSCT, the donor types were matched family (n = 7), matched sibling (n = 5), umbilical cord blood (n < 5), matched unrelated (n < 5), and haplo-identical (n < 5).

3.3.4 Outcomes after HSCT

The aim of HSCT treatment is to achieve immune reconstitution in the patient (that is, the restoring of the immune system to protect against infection).[69] In some instances, treatment with HSCT may fail to achieve the desired outcome, resulting in graft failure.[33] There are several factors that can influence the outcome of HSCTs, including the degree of matching between donor and patient, the donor stem cell source, the use of a conditioning regimen, infection status before and at time of transplant and age at time of transplant.[33, 70] A systematic review of HSCT outcomes completed by HIQA noted that across 13 independent studies, survival estimates for children with SCID following treatment with HSCT ranged from 61% to 90%.[63] The majority of studies provided evidence to suggest that earlier diagnosis and or HSCT led to improved survival compared with later (for example, before or after 3.5 months of life), and further that the presence of infections prior to HSCT negatively impacted outcomes. It should be noted that given the rarity of the condition, studies tend to include clinical data from across several decades and

multiple locations, with a number of sub-cohort analyses indicating improved survival outcomes over time.

3.4 Inborn errors of metabolism

Inborn errors of metabolism (IEM) comprise a diverse and heterogeneous group of disorders resulting from mutations in genes that encode the proteins necessary for various metabolic pathways.[20, 71] These include lysosomal storage diseases, peroxisomal storage diseases and other rare diseases.[71]

The characteristic common to these diseases is that they involve a deficiency of enzymes that are central to proper metabolic pathways and functions, typically involved in the degradation of biological substrates within cells. This can result in the accumulation of toxic metabolites, cellular death and tissue dysfunction, and multisystem damage.[72] Mild disease phenotypes result from reduced enzyme activity, whereas patients with severe phenotypes have no enzyme activity and typically present during infancy.[71]

Newborns and infants presenting with a suspected IEM disorder are typically initially treated by discontinuing feeding and providing glucose infusions to stop the build-up of toxic metabolites while awaiting diagnosis.[73] For many IEM disorders, treatment by HSCT is a clinical option, while for some conditions, HSCT is considered standard of care, and can prevent disease progression in the long term.[20] The UK Paediatric BMT Group published a document in 2015 that describes indications for HSCT for a range of IEM disorders (Table 3.3). Patients with osteopetrosis who require a HSCT are treated in CHI at Crumlin. Patients with other IEM who require a HSCT receive treatment at the Royal Manchester Children's Hospital.

Table 3.3 Indications for HSCT in Inborn Errors of Metabolism

Disease grouping and specific condition	Suitability for HSCT*
Mucopolysaccharidoses	
Hurler (MPS IH)	Standard of care
Hurler / Scheie (MPS IH/S)	Clinical option
Scheie (MPS IS)	Clinical option
Hunter (MPS II)	Clinical option (only early and / or asymptomatic)
Maroteaux-Lamy (MPS VI)	Clinical option
Leukodystrophies	
X-ALD with cerebral involvement	Standard of care
Infantile MLD	Clinical option (only early and / or asymptomatic) Offer gene therapy if available as first option
Juvenile MLD	Clinical option (only early and / or asymptomatic) Offer gene therapy if available as first option
Late onset MLS	Clinical option (only early and / or asymptomatic)
Glycoprotein metabolic and miscellaneous disorders	
Alpha-mannosidosis	Standard of care
Aspartylglucosaminuria	Clinical option
Osteopetrosis+	
TCIRG1 mutation (47%)	Standard of care
CLCN7 mutation (15%)	Clinical option (if no neuropathic form)
OSTM1 mutation (5%)	Generally not recommended
RANK mutation (2%)	Standard of care*
RANK Ligand mutation (1%)	Generally not recommended
Genetically undefined	Clinical option (severe phenotype, no neuropathic form)

*'Standard of care' implies that HSCT is generally indicated in suitable patients and / or in the context of clinical trial; 'Clinical option' implies that treatment with HSCT requires careful assessment of the specific risks and benefits at the level of the individual.

Key: HSCT – haematopoietic stem cell transplantation, X-ALD - X-linked adrenoleukodystrophy, MLD - metachromatic leukodystrophy, MLS – McLeod syndrome; MPS - mucopolysaccharidoses.

Source: UK Paediatric BMT Group [55]

Of 27 patients who received a first transplant abroad for an IEM between 2013 and 2021, 25 (93%) had Hurler syndrome. A small number (<5) patients received a second transplant. During this time period, on average, 3.2 (range: 1 - 5) allogeneic HSCTs were performed for patients with IEM per annum.

As Hurler syndrome represents the IEM in Ireland most commonly indicated for HSCT, it is discussed in detail in the following sections in terms of aetiology, incidence, clinical course of the disease, and treatment outcomes.

3.5 Hurler syndrome

3.5.1 Aetiology

The mucopolysaccharidoses (MPS) are a set of rare, inherited lysosomal storage disorders caused by a deficiency of specific enzymes required for degrading glycosaminoglycans (GAGs) (complex carbohydrate molecules that are commonly expressed within and surrounding most cell types).[74] Mucopolysaccharidosis Type 1 (MPS-1) is an autosomal recessive lysosomal storage disease caused by deficiency in the enzyme α-L-iduronidase. Hurler syndrome is the most severe form of MPS-1, and patients with this condition have no α-L-iduronidase enzyme activity.[71] The absence of this enzyme leads to accumulation of GAGs, ultimately leading to multi-organ dysfunction, neurocognitive impairment, and severe cardiopulmonary complications, which can result in premature death.[71] In the absence of treatment, progressive organ damage and associated complications, such as cerebral atrophy, develop and patients who do not receive treatment present with irreversible neurocognitive regression and death within the first decade of life.[72]

3.5.2 Epidemiology

In 2008, the birth prevalence of Hurler syndrome in Ireland was estimated as 3.8 per 100,000 births.[53] This is considerably higher than that of the UK for the same period, estimated to be 0.76 per 100,000 births.[75] Of note, 73% of the cases of Hurler syndrome recorded in Ireland were among children of Irish Traveller ethnicity.[53] The presence of a founder mutation in the Irish Traveller population means that Ireland has one of the highest recorded incidences of Hurler syndrome internationally. The incidence of the disease in the Irish Traveller population is 27 per 100,000 births. This is equivalent to a carrier frequency of 1 in 10, which is the highest recorded carrier frequency worldwide.[53] Based on an annual birth rate of 58,443 in Ireland, this infers an average of 2.2 births per year with Hurler syndrome. Between 2012 and 2021, there were 28 children with Hurler syndrome referred for HSCT abroad under the TAS.

3.5.3 Natural history and treatment options

Children with Hurler syndrome present early in life with various clinical manifestations, including developmental delay, musculoskeletal abnormalities, cognitive impairment, auditory and visual problems, and severe cardiopulmonary complications.[71, 74, 76] In the absence of early intervention and treatment, this is a rapidly progressive disease resulting in neurocognitive impairment and death within the first decade of life.[72] Treatment options for Hurler syndrome include HSCT, gene therapy (currently clinical trial only) and enzyme replacement therapy, with the latter, used to treat milder phenotypes and as bridging therapy prior to definitive treatment with HSCT or gene therapy.[74, 76]

Due to the progressive nature of the disease, early treatment with HSCT is associated with better health outcomes as it can prevent neurocognitive decline and irreversible damage to the central nervous system.[74] For patients with minimal cognitive impairment, HSCT is considered the standard of care until 30 months of age; after this, HSCT is considered unlikely to impact the natural course of the disease.[55, 72, 77] Gene therapy, involving the use of a patient's own cells that have been genetically modified, presents a potential future treatment option for patients with Hurler syndrome. Clinical trials are ongoing to explore the efficacy of this therapy.[74] As noted, intravenous enzyme replacement therapy is routinely used to treat milder phenotypes of MPS-1 disease.[76] Administered in this way, the enzyme alpha-L-iduronidase circulates in the blood, but cannot cross the blood-brain barrier. It therefore cannot be used to prevent the cognitive decline associated with the severe Hurler syndrome MPS-1 phenotype, but may be administered while patients are waiting for transplant.[76]

3.5.4 Outcomes after HSCT

The therapeutic benefits from HSCT derive from donor stem cells that can circulate in the bloodstream and across the blood-brain barrier.[74] However, brain engraftment of donor myeloid cells is a slow process that may require up to one year, underscoring the importance of early intervention.[72]

A 2015 publication reported HSCT outcomes from two centres performing the highest number of HSCTs in patients with MPS in Europe: 90% of patients had MPS Type-1 Hurler syndrome (n = 56 / 62).[78] The median age at time of transplant was 13.5 (range: 3 to 44) months. Median follow-up was 36 months post HSCT (range: 1 to 93 months). The overall survival and event-free survival were 95.2% and 90.3%, respectively. Events included instances of graft-versus-host disease (GvHD) and graft failure of donor cells after HSCT. Three patient deaths were recorded, with the

causes of death noted to have been idiopathic pneumonia (n=2) and chronic GvHD (n=1).[78] A 2016 publication reported outcomes of treating MPS Type-1 with HSCT over a ten-year period in the UK.[76] Of 81 patients who underwent HSCT for Hurler syndrome, 88% (n = 71 / 81) survived and 81% (n = 66 / 81) were alive and achieved engraftment at a median follow up of 46 months (range: 3 to 124 months).[76] The incidence of acute GvHD (Grades II to IV) was 17% (n = 14 / 81), chronic GvHD occurred in 11% (n = 9 / 81) patients. The estimated five-year overall and event-free survival were 86% and 80%, respectively.[76]

3.6 Haemoglobinopathies

Haemoglobinopathies are inherited disorders arising from mutations in genes that code for globin, the protein component of haemoglobin.[79] Haemoglobinopathies are the most common monogenic diseases worldwide; carriers account for approximately 5.2% of the global population with over 300,000 affected infants born each year.[80] Mutations in the globin gene resulting in abnormal proteins cause haemoglobin variants, the most common of which HbS (sickle cell disease) accounts for about 83% of haemoglobinopathies. Mutations that alter protein output result in thalassaemia syndromes, which account for the remaining 17% of global haemoglobinopathies.[79, 80] While thalassaemia and sickle cell disease are both haemoglobinopathies, they have distinct pathophysiology and clinical features.[56]

Table 3.4 summarises the UK Paediatric Group indications for HSCT in paediatric patients with haemoglobinopathies. In addition, the American Society for Hematology published guidelines in 2021 for stem cell transplantation for patients with sickle cell disease[21] and the European Society for Blood and Marrow Transplantation (EBMT) published their guidelines for HSCT in patient with haemoglobinopathies in 2019.[77] Although a full consensus is lacking across the guidelines, they are in agreement that HSCT should be restricted to patients who have experienced specified health complications arising from the disease and careful consideration should be given to the benefit-harm balance of HSCT.[21, 47, 77]

Table 3.4 Indications for HSCT in haemoglobinopathies

Disease	HSCT indication
Sickle cell disease	Standard of care for allogeneic matched-related transplants after the occurrence of any of the conditions listed below. Clinical option for allogeneic unrelated or haplo-identical transplants after the occurrence of any of the conditions listed below, but requires careful assessment of the risks and benefits. ▪ Vaso-occlusive crisis despite hydroxycarbamide (≥ four episodes per year requiring hospitalization or impacting schooling) ▪ Recurrence of acute chest syndrome despite hydroxycarbamide ▪ CNS disease (stroke, TCD ultrasound and silent infarction or abnormal psychometric tests or poor school performance on formal assessment, silent infarctions with cognitive deficiency, significant abnormalities in MRA despite transfusions, abnormal TCD and generation of red cell alloantibodies, CNS disease requiring transfusions leading to significant iron overload despite optimum chelation treatment) ▪ Suboptimal medical care
Thalassaemia	Standard of care for allogeneic matched-related transplants. Clinical option for allogeneic unrelated or haplo-identical transplants, but requires careful assessment of the risks and benefits.

Key: CNS – central nervous system; MRA – magnetic resonance angiography; TCD – transcranial Doppler ultrasound.

Source: UK Paediatric BMT Group HSCT[55]

As described in chapter 2, patients with haemoglobinopathies have not routinely travelled for HSCT. In 2022, a memorandum of understanding (MOU) was established with St Mary's Hospital, London to provide access to HSCT for patients with haemoglobinopathies.

According to a 2021 report by the BSBMTCT in the UK, there were 80 HSCTs carried out for patients with thalassaemia and 99 for those with sickle cell disease, between 2014 and 2018.[47] As noted, historically, very few patients with haemoglobinopathies in Ireland have availed of HSCT. In the absence of historical data, projected demand for HSCT in this group was estimated using expert opinion.

Under the new St Mary's pathway, or under the scenario of the service being repatriated, and given current indications for HSCT, the Expert Advisory Group estimates that approximately five patients per year would require HSCT for sickle cell disease initially, but that this would fall to two patients per year once the initial back-log of referrals for HSCT is accommodated. Clinicians estimated that one patient with

thalassaemia major would present for transplant every second year. Data from the BSBMTCT registry indicates that 2.8% of patients require a second transplant.[47] Together these result in estimates of 5.7 transplants in year one of the new St Mary's pathway, falling to 2.6 HSCTs in year five.

As sickle cell disease represents the most common haemoglobinopathy in Ireland for which HSCT would be indicated, it is discussed in detail in the following sections in terms of aetiology, incidence, clinical course of the disease, and treatment outcomes.

3.7 Sickle cell disease

3.7.1 Aetiology

Sickle cell disease (SCD) is an inherited, autosomal recessive blood condition that results from a single point mutation of the haemoglobin (Hb) molecule gene.[81] These pathological Hb variants can aggregate, forming polymers, leading to the stretching of red blood cells into a defective, elongated rigid form (hence the term sickle cell). This can cause blockages in blood vessels, leading to vaso-occlusion and contributing to tissue and organ damage.[54, 82] The most common phenotype associated with these mutations is homozygous (that is, two copies of the same gene) HbSS. Heterozygous (that is, two different variants of a given gene) conditions also occur.[81]

3.7.2 Epidemiology

SCD is the most common inherited haemoglobinopathy in the world.[83] A 2018 systematic review, investigating the burden of SCD in paediatric populations, reported the birth prevalence of SCD in Europe to be 43.1 per 100,000 people (95% CI 30.3 to 55.9).[84] In the same publication, the estimate of birth prevalence for SCD in Africa was 1,125 per 100,000 (95% CI 680 to 1,570). As of 2022, there are 360 paediatric patients with SCD being managed by the National Red Cell and Haemoglobinopathy Service at CHI at Crumlin. During the last two decades, the prevalence of SCD has increased throughout Europe as a consequence of migration of people from countries of high SCD prevalence.[9, 54]

3.7.3 Natural history and treatment options

Children with SCD can experience a range of symptoms, including bacterial infection and sepsis, acute anaemia, acute pain episodes including painful swelling of the hands or feed, acute chest pain syndrome, and acute ischaemic stroke. Persistent complications can result in chronic multisystem organ damage.[54, 81, 82] According to

a 2017 review, children with heterozygous genotypes typically experience fewer clinically severe complications compared with those with the HbSS genotype.[82] SCD can result in early mortality. An evaluation of the newborn bloodspot screening programme for SCD in the UK found that the death rates from SCD in infants were 2.6 per 1,000 person-years for HbSS and 1.7 per 1,000 person-years for all sickle-cell conditions combined.[85]

A diagnosis of SCD is made on the basis of test results showing the presence of Hb variants.[86] Non-curative interventions for the treatment and management of SCD cases include hydroxycarbamide therapy, penicillin prophylaxis, and blood transfusions.[81] Currently, the only available curative treatment option for SCD is HSCT.[56] However, the decision to proceed with HSCT for the treatment of SCD is conditional and often based on clinical opinion.[55] HSCT is reserved for more severe cases of SCD where the potential benefit of the procedure outweighs the risks, such as conditioning regimen-associated toxicities, graft rejection, and mortality.[83] According to the EBMT guidelines, the recommendation of HSCT for SCD is conditional and typically is reserved for patients under 16 years of age with a human leukocyte antigen (HLA) identical sibling donor (matched sibling donor) and at least one clinical complication, such as lung disease, nephropathy, retinopathy, acute chest syndrome, or recurrent vaso-occlusive painful episodes.[83]

Gene therapy approaches provide potential future alternative curative treatment options for patients with SCD.[82] A recent review summarises the current research landscape of ongoing clinical trials involving gene transfer and gene editing approaches as potential curative treatment routes for SCD patients.[87]

3.7.4 Outcomes after HSCT

A 2016 review of HLA-identical sibling HSCT for the treatment of SCD reported on the outcomes of six different patient cohorts (N = 218).[88] The overall and event-free survival following matched sibling donor HSCT were approximately 95% and 92%, respectively. Transplant-related mortality was found to increase with increasing age with the report also noting that event-free survival following HSCT was significantly better in patients that underwent a transplant before developing SCD-related organ damage.[56] Similar findings were presented in a 2017 publication, including data collected from the Centre for International Blood and Marrow Transplant Research, EBMT, and Eurocard databases.[89] The five-year overall survival and event-free survival was 95% (95% CI: 93% to 97%) and 93% (95% CI: 92% to 95%), respectively for patients younger than 16 years with SCD who received HSCT between 1986 and 2013.[89]

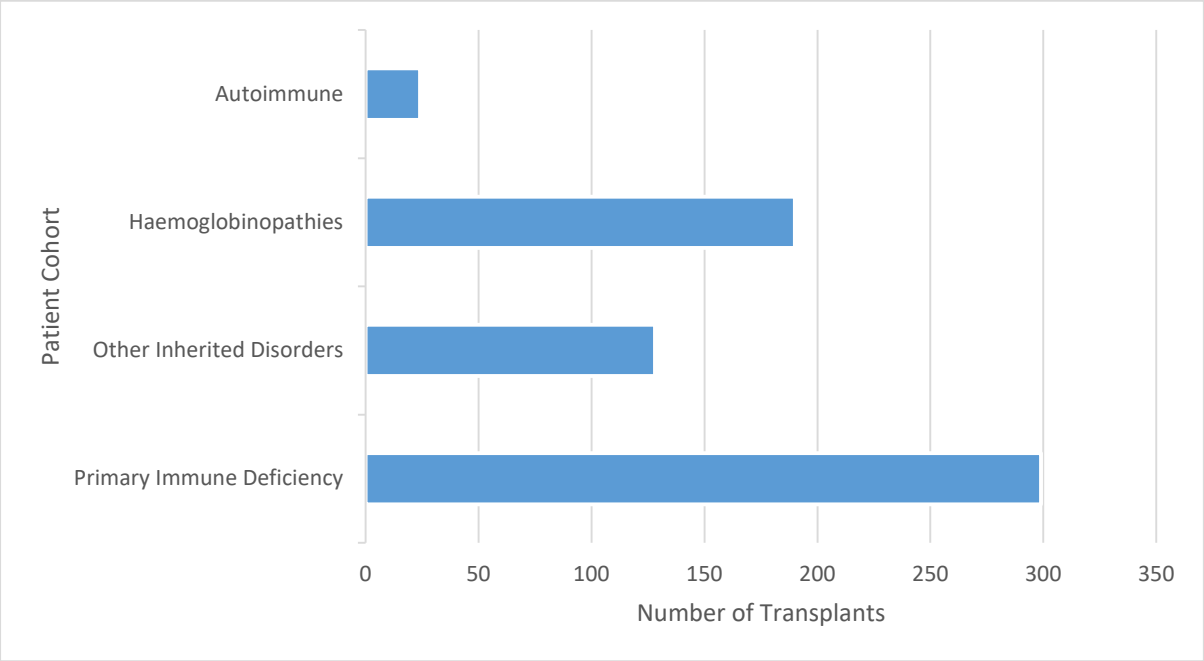
3.8 Transplant characteristics and patient outcomes

Understanding the characteristics of patients undergoing HSCT, the procedure types and outcomes is important to understanding the burden of disease and for informing the incremental budget impact associated with repatriation of HSCT (chapter 5). The British Society of Blood Marrow Transplant and Cellular Therapy (BSBMTCT) maintains the BSBMTCT registry which records this information for BSBMTCT member centres across the UK and Ireland. Member centres include CHI at Crumlin, and hospitals in the UK, that accept referrals for Irish paediatric HSCT recipients (that is, St Mary's London, the Royal Children's Manchester and the Royal Victoria Newcastle). Relevant information from BSBMTCT annual reports is presented below.[47] Where available, this is supplemented with data relating to Irish patients who went abroad for transplant, as collated by Irish clinicians.

The BSBMTCT registry categorises patients differently to the categorisation used in this HTA.[47] The BSBMTCT divides Inborn Errors of Immunity into two categories, primary immunodeficiencies and autoimmune conditions. The BSBMTCT include patients with IEM in the "Other inherited disorders cohort". Patients with Hurler syndrome made up 43% of this paediatric cohort (UK and Ireland data) in 2019.[47] The other inherited disorder cohort also includes conditions which are normally indications for transplant in CHI at Crumlin, such as osteopetrosis.

Figure 3.1 displays the total number of transplants in the UK and Ireland performed between 2014 and 2018 among paediatric patients with haemoglobinopathies (including thalassaemia), primary immunodeficiencies (or, primary immune deficiency) and autoimmune conditions.[47] Of the four disease categories, primary immunodeficiencies accounted for the largest number of transplants (n=299, 47%), followed by haemoglobinopathies (n=190, 30%), while autoimmune diseases accounted for the fewest transplants (n=24, 4%) over this time period. The median age at treatment was highest for those with haemoglobinopathies (nine years), followed by autoimmune (seven years), primary immunodeficiency (three years) and other inherited disorders (one year). The BSBMTCT analyses of UK and Irish data also include one patient with a primary immunodeficiency, and four patients with haemoglobinopathies who received forms of autologous transplant which are outside the scope of this HTA. Given they make up a small proportion of patients, it is not expected to materially influence the transferability of the result to our cohort.

Figure 3.1 Number of paediatric HSCT procedures performed in the UK and Ireland for selected cohorts between 2014 and 2018 and registered in the BSBMTCT



Source: BSBMTCT 12th Commissioner's Report.[47]

Information on donor type is presented specifically for Irish patients in Table 3.5 using data provided by Irish clinicians for the IEM and IEI cohorts that underwent HSCT in the period 2017 to 2021.[17, 90] No haemoglobinopathy patient underwent HSCT during this period, therefore, for illustration purposes, 2019 BSBMTCT data are presented for this cohort.[47] The distribution of donor types differs by cohort. The most common donor type for patients with IEI is matched unrelated donors at 61% (n = 11/18). For patients with IEM, cord donors were the most common (83%, n = 15/18). For patients with haemoglobinopathies, 85% were based on a familial donor with matched sibling donors the most common overall donor type (44%, n = 12/53). The proportion of related donors is important, as under the current care pathway, these donors must travel to the transplant centre in the UK to donate, which represents an additional logistical and social challenge for families. Related donors make up 33%, 17% and 85% of donors for the IEI, IEM and haemoglobinopathy cohorts, respectively.

Table 3.5 Paediatric HSCT donor type across cohorts

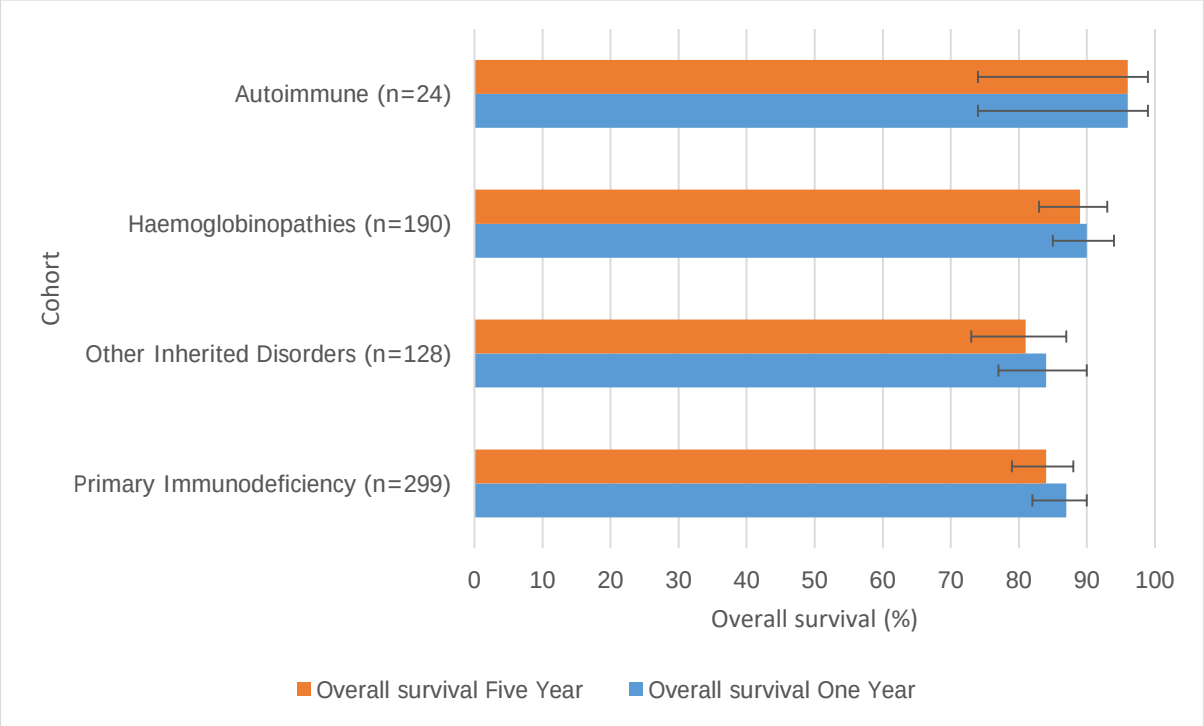
Donor type	IEM %	IEI %	Haemoglobinopathies %
Familial Donor	17	33.5	85
Matched unrelated donor	0	61	11
Cord	83	5.5	4

Key: IEI – inborn errors of immunity; IEM – inborn errors of metabolism.

*Data for IEI and IEM based on patients with Hurler syndrome referred from Ireland and who received a transplant abroad from 2017 to 2021, with available data; IEM: n=18; IEI: n=18.[17, 90] As no patient with a haemoglobinopathy was referred and underwent HSCT during this period, data are based on all paediatric patients with a haemoglobinopathy in the BSBMTCT that received a first transplant in the UK in 2019 (n=27).[47]

Figure 3.2 outlines overall survival at one and five years for patients who underwent HSCT, based on the total BSBMTCT registry.[47] Overall survival exceeds 80% in all cohorts with little difference in overall survival at year five compared with that observed at the first year post transplant. The five-year overall survival for each group was: 84% for primary immunodeficiencies, 81% for other inherited disorders, and 89% for haemoglobinopathies.

Figure 3.2 Overall Survival BSBMTCT Paediatric Transplant (UK and Ireland) 2014 to 2018



Note: These figures include one patient with a primary immunodeficiency, and four patients with haemoglobinopathies who received a form of autologous transplant instead of an allogeneic HSCT.

For the overall BSBMTCT cohort, data for the period 2014 to 2018 indicate that similar proportions of cases in all groups experienced grade 3 or 4 acute GvHD; 8% in those with diseases of primary immune deficiency; 7% among patients with other inherited disorders; 8% in patients with haemoglobinopathies and 4% for patients with autoimmune conditions. For Irish patients with IEI who underwent HSCT in the UK between 2017 and 2021, 22% experienced acute GvHD half of whom received extracorporeal photopheresis treatment (11.8% of the total cohort). Data are not available for the Irish IEM cohort who travelled abroad for treatment.

3.9 HSCT and cellular therapy performed in CHI at Crumlin

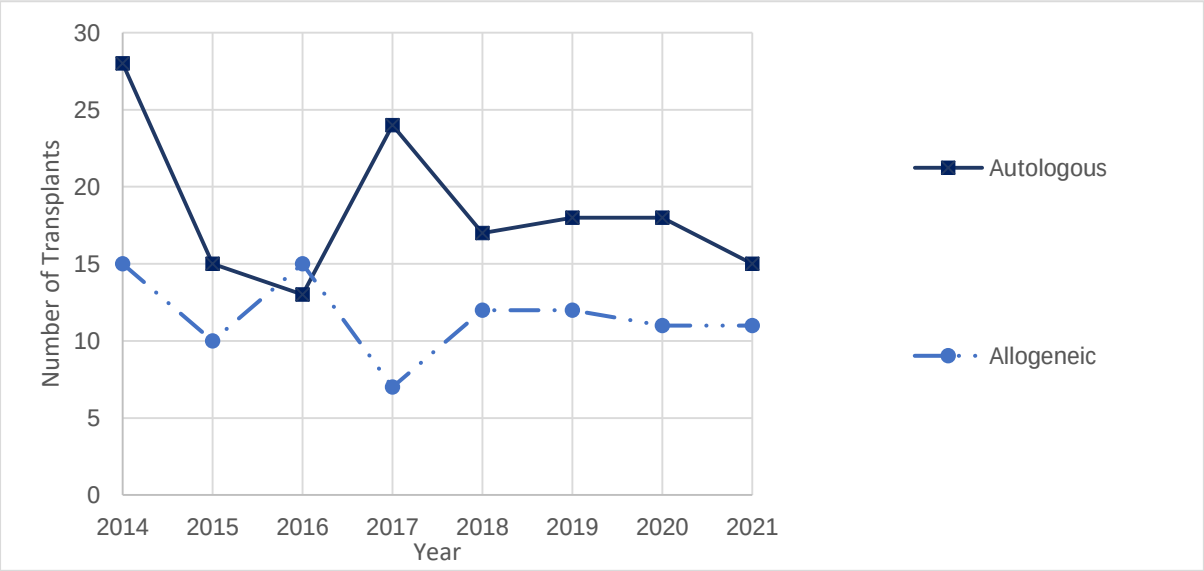
HSCT and cellular therapy services are available in Ireland to paediatric patients with haematological malignancies and select benign indications. In Ireland, these services are provided by a single paediatric HSCT and Cellular Therapy Unit, located in CHI at Crumlin, Dublin. CHI is accredited by the Joint Accreditation Committee of the International Society of Cellular Therapy (ISCT) and the EBMT (JAICE), reflecting adherence to international standards of HSCT.

The total number of transplants performed in the unit by year is presented in Figure 3.3. An understanding of the number of both allogeneic and autologous transplants conducted in the unit is important when considering the capacity of CHI to accommodate more allogeneic transplants. The number of chimeric antigen receptor T-cell (CAR-T) therapies provided to patients is also relevant for capacity considerations. The service was only established in Ireland in 2022, so historical data are unavailable.

Between the years 2014 and 2021 (inclusive), a total of 93 allogeneic and 148 autologous HSCTs were performed at CHI. This is equivalent to an average of 12 allogeneic and 19 autologous HSCT procedures per year. Almost all allogeneic HSCT were undertaken as first transplants, with a very small number of non-first transplants undertaken (n <5), all in 2016. JACIE accreditation requires an average of 10 allogeneic HSCT (first transplants) per year within each accreditation cycle. To date, this requirement has been met by the unit.

Between 2014 and 2018, 58% (n = 34) of allogeneic transplants were performed for malignant indications, with 42% (n = 25) performed for non-malignant indications, primarily bone marrow aplasias.[91] A small number of procedures were provided for patients with IEI during this time period for clinical reasons.

Figure 3.3 Total number of allogeneic and autologous transplants performed in CHI at Crumlin between 2014 and 2021



Source: Data from 2014 to 2019 is sourced from BSBMTCT Annual Reports.[40, 91] Data from 2020 and 2021 are from an analysis of patient records by the EAG.[92]

During the interval 2014 to 2021, there were also a limited number of instances where patients with benign conditions (for example, osteopetrosis), which are normally indications for HSCT in CHI at Crumlin, were referred for treatment in the UK through the TAS. This occurred due to capacity limitations in CHI at Crumlin meaning that timely HSCT was not available in Ireland, taking into account the patient's current health and the likely course of the patient's disease.

Between the years 2014 to 2021, a total of 93 allogeneic HSCT procedures were undertaken in CHI at Crumlin. Adjusting this figure to only consider the range of conditions which are normally transplanted in CHI at Crumlin (that is, excluding those for conditions ordinarily referred abroad and including those that would ordinarily be undertaken in CHI, but that were conducted abroad because of lack of capacity), a total of 95 procedures (primarily for malignancies and bone marrow failure syndromes) were conducted over this period. Considering the size of the population aged 0 to 16 years, this equated to an estimated current annual rate of allogeneic HSCT procedures for conditions normally transplanted in CHI at Crumlin (malignant and selected benign) of 1.1 per 100,000 people. The annual rate of autologous HSCT was 1.7 per 100,000 people.

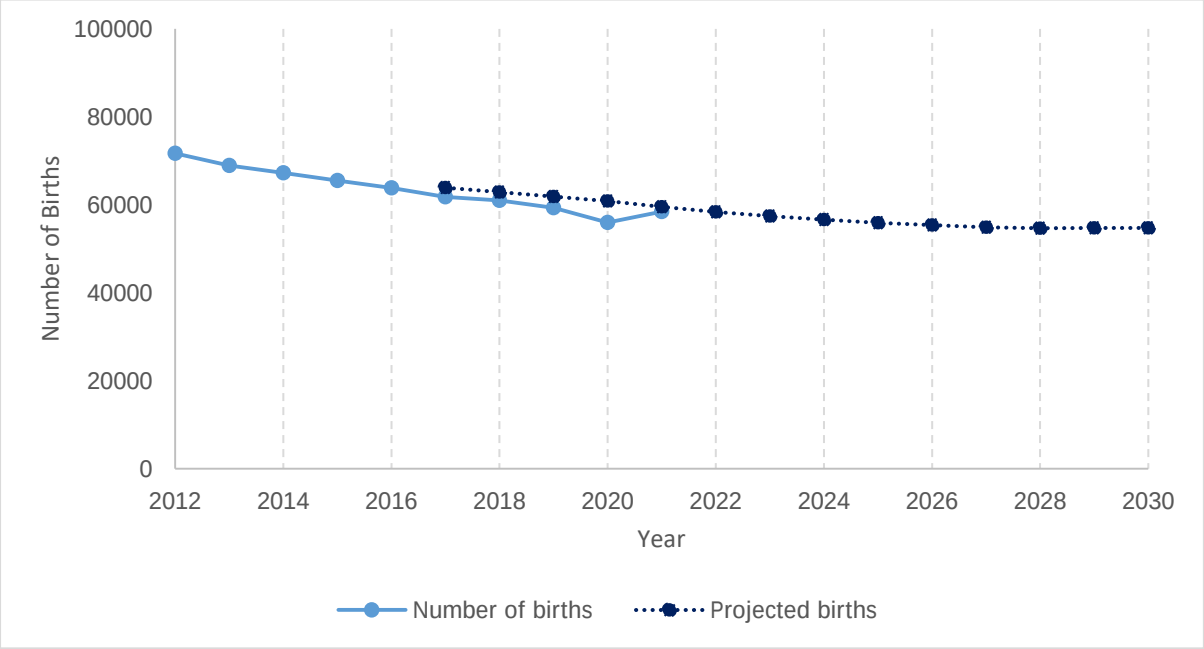
3.10 Factors that may influence future demand for HSCT

There are a number of factors that may influence future demand for HSCT including changes in population epidemiology and changes in indications either due to the availability of alternative therapies to HSCT (reducing demand) or an expansion of the range of indications based on new clinical evidence.

Population epidemiological trends

For most of the genetic conditions which are the subject of this HTA, HSCT is required in early life. Accordingly, the number of transplants required is expected to be related to the number of births per year. As shown in Figure 3.4, the number of births in Ireland has been falling over time. Over the nine-year period between 2012 and 2021, the number of births per year fell by 20%; 71,674 births were registered in 2012 compared with 58,443 in 2021. National projections estimate that the birth rate could continue to decrease each year, and by 2030, the projected birth rate is estimated to be around 55,000. A decreasing birth rate may impact the birth prevalence of inherited genetic conditions. These figures may however not fully account for population changes resulting from unpredictable migration patterns (for example, influxes of refugees and associated uncertainty regarding long-term residence).

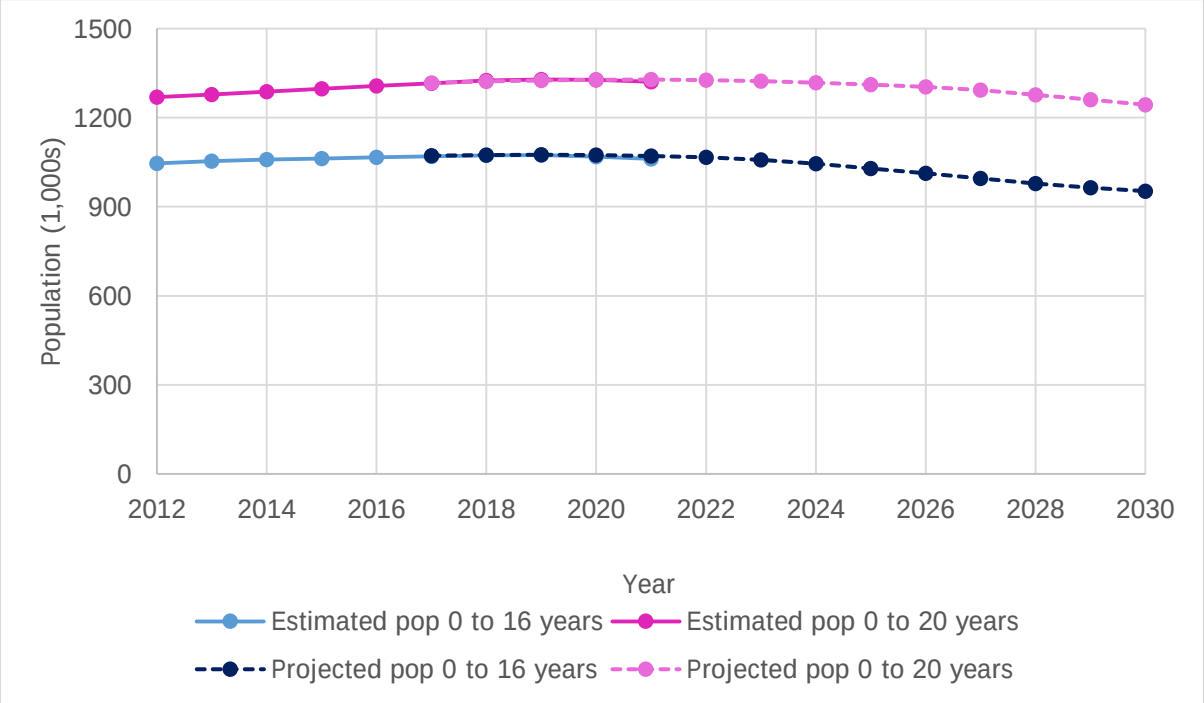
Figure 3.4 Number of births in Ireland (registered and projected from 2012 to 2030)



Source: CSO.[93]

Most of the HSCT procedures undertaken in CHI at Crumlin are for the treatment of malignancies and bone marrow failure syndromes. These conditions can develop at any time after birth. Therefore, the expected number of future transplants is expected to be proportional to the size of the prevalent Irish population. At present, patients aged 0 to 16 years are treated in paediatric services. National estimated and projected population estimates from this cohort are shown in Figure 3.5. Between 2012 and 2021, the estimated size of this cohort increased from 1.05 to 1.06 million people. In line with the projected fall in birth rate, the population aged 0 to 16 years is expected to fall to 0.95 million by 2030.

Figure 3.5 Current and projected Irish population estimates (thousands) between 2012 and 2030 by age group



Source: CSO.[93]

Impact of potential changes to age of eligibility for cancer care within the new children's hospital

The National Cancer Strategy 2017-2026 notes that child and young adolescent cancer services will be further developed in the new children's hospital and that the schedule of accommodation of the new haematology and oncology unit in the hospital will significantly increase the capacity to deliver more comprehensive cancer care; it is further noted that this could include treatment of specific clinically-driven conditions for adolescents and young adults (AYA) who have paediatric-centric tumours and who are aged between 16 and 20 years.[94, 95] As a proportion of these

patients would be likely to require HSCT, this would have implications for demand at the centre. Given this proposal, analyses presented within this HTA include consideration of an age extension scenario to provide a conservative estimate of the capacity available to meet demand.

Based on CSO data, there are 195,000 individuals aged between 16 and 20 years. Based on 2022 figures, this would increase the estimated size of the cohort potentially eligible for treatment in CHI from 1.07 million to 1.33 million (Figure 3.5). Accordingly, the demand for HSCT in CHI for malignant indications would be expected to increase if this cohort were treated in CHI. This is explored in section 3.11.

Differential epidemiological trends within population sub-groups

It should be noted that this trend in overall birth rates and prevalence may not be representative of trends among specific sub-groups within the overall population, such as particular ethnic groups. For example, data from the 2016 census estimate that 44.3% of Irish Traveller women aged 40 to 49 years had given birth to five or more children compared with only 4.2% of women overall in this age group.[(96)] This is a relevant consideration given the higher prevalence of a number of the conditions (SCID, Hurler syndrome) within the scope of this HTA in the Irish Traveller community. In addition, in recent decades, there has been an increase in migration of individuals from different countries into Ireland. This increased migration can also contribute to changing population epidemiology, such as in the case of sickle cell disease for individuals from Africa and the Middle East. These changing population dynamics may result in a shift in the proportions within the conditions indicated for HSCT in Ireland. Due to this uncertainty, changes in the number of births have been used to estimate the future demand for HSCT based on existing activity levels for the range of conditions typically undergoing HSCT in CHI.

Availability of alternative therapies and changes in the range of indications for HSCT

Other healthcare advances may reduce the demand for HSCT. New drug treatments for leukaemia may provide an alternative to HSCT thereby reducing future demand. Advancements in the field of gene editing have facilitated the recent development of gene therapies for the treatment of various genetic conditions, including IEI, IEM, and haemoglobinopathies, which may also reduce the demand for HSCT over time.[(77)] One such example is autologous gene therapy for the treatment of ADA-SCID, approved for use in Europe by the European Medicines Agency.[(97)]

In recent decades there have been improvements in patient safety and patient health outcomes following HSCT, due to improvements in treatments, conditioning

regimens, and adoption of consensus guidelines and standards.[77, 98, 99] Increases in patient safety and survival associated with HSCT may lead to an increased demand for such procedures. Moreover, as of July 2020, ADA-SCID was endorsed by NSAC for addition to the list of conditions screened for in the existing NNBSP and it was added to the programme in May 2022.[62] HIQA undertook a HTA of the addition of T-cell receptor excision circle (TREC)-based screening for all SCID subtypes to the NNBSP in Ireland to inform a recommendation by the National Screening Advisory Committee (NSAC).[63] In January 2023, the Minister for Health approved a recommendation from the NSAC to add these conditions to the NNBSP.[64]

It is unclear at present whether screening for these conditions as part of the NNBSP will result in an increase in cases requiring HSCT, given that SCID is a rare disease and there are no available data on missed cases of SCID-related infant death prior to diagnosis. Typically, cases of SCID that are missed at birth are detected later during the first year of life when they present clinically with symptoms.[60]

3.11 Demand for HSCT in Ireland under scenarios of repatriation versus no repatriation

The projected demand for allogeneic and autologous HSCT in Ireland was estimated for the current arrangement being extended (that is, no repatriation of allogeneic HSCT for IEM, IEI and haemoglobinopathies), and under the scenario of HSCT for these patients being repatriated. While all autologous transplants are currently provided in CHI at Crumlin, the future demand for autologous HSCT has implications for the capacity of the HSCT unit to repatriate allogeneic HSCT services for patients to Ireland.

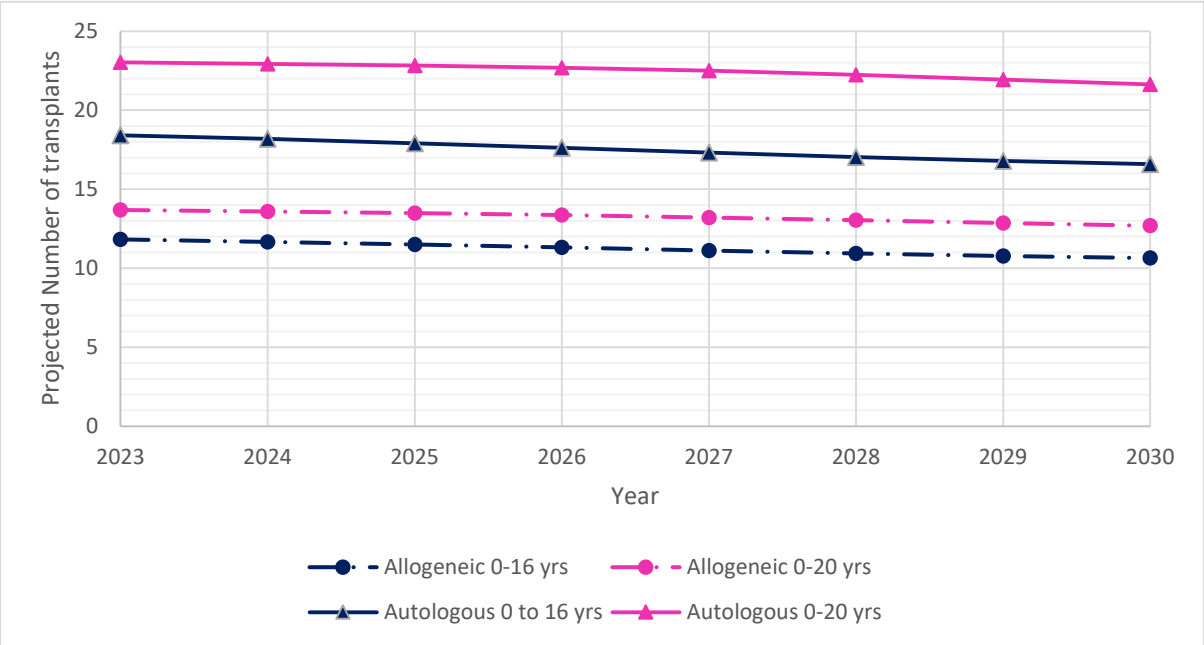
Under the current no-repatriation scenario, it was assumed that no transplants for patients with IEM, IEI and haemoglobinopathy would be conducted in Ireland. The projected demand for allogeneic and autologous HSCT for malignant and selected benign conditions for patients aged 0 to 16 years was estimated by applying the historical annual rate of allogeneic and autologous HSCT procedures derived in section 3.7 (1.1 and 1.7 per 100,000 people, respectively) to the Central Statistics Office (CSO) population projections for the relevant age cohorts. The results are illustrated in Figure 3.6. Under these assumptions, the projected annual number of allogeneic transplants for the cohort aged 0 to 16 years was 11.8 in 2023 falling to 10.6 by 2030. For the equivalent autologous HSCT estimates, the projected numbers were 18.4 in 2023 falling to 16.6 in 2030.

As discussed in section 3.10, there is a proposal to increase the upper age limit for treatment within CHI of AYA patients with malignant conditions, that is, for this age

limit to increase to include patients up to the age of 20 years. In considering this possibility, further assumptions are required to estimate demand. Between 2014 and 2018, 62.9% of allogeneic transplants performed in CHI were performed for malignant indications.[91] All autologous HSCT procedures were performed for malignant indications. These proportions were combined with the CSO population projections for those aged 16 to 20 years to estimate the total number of HSCT procedures that would be required if the age limit increases. It was estimated that the projected number of transplants for indications normally transplanted in Crumlin could increase by approximately 19% for allogeneic HSCT (from an average of 10.6 per annum to 12.7 per annum by 2030) and 29% for autologous HSCT (from 16.6 per annum to 21.6 per annum by 2030).

A limitation of this approach is that it assumes that the rate of allogeneic and autologous HSCT for malignant conditions is independent of age. If this assumption does not hold, the number of HSCT procedures for patients aged 16 to 20 could be over or under estimated.

Figure 3.6 Projected number of paediatric HSCT procedures for patients with indications normally transplanted in Ireland



For the allogeneic cohorts examined, the mean estimates remain above the average annual number of allogeneic HSCTs (average 10 allogeneic transplants per annum across each three-year accreditation cycle) required to maintain Foundation for the Accreditation of Cellular Therapy (FACT)-JACIE accreditation. These figures do not take into account the natural random variation in patient numbers observed in

clinical practice. A probabilistic analysis was conducted to take this into account. Assuming a normal distribution, the mean and standard deviation associated with the historical number of transplants conducted was used to vary the rate of paediatric allogeneic and autologous HSCT in 1,000 simulations. The simulated rates were applied to the CSO population estimates. For the population aged 0 to 16 years, the probability of meeting the three year rolling annual average of 10 allogeneic transplants in a non-repatriation scenario is 76.9% in 2025, falling to 66.6% in 2030. These estimates do not take into account uncertainty in the projected size of the Irish population or the possibility of the number of resourced transplant beds remaining at the current level (four beds). If the latter were to arise, this would decrease the probability of meeting the accreditation standard.

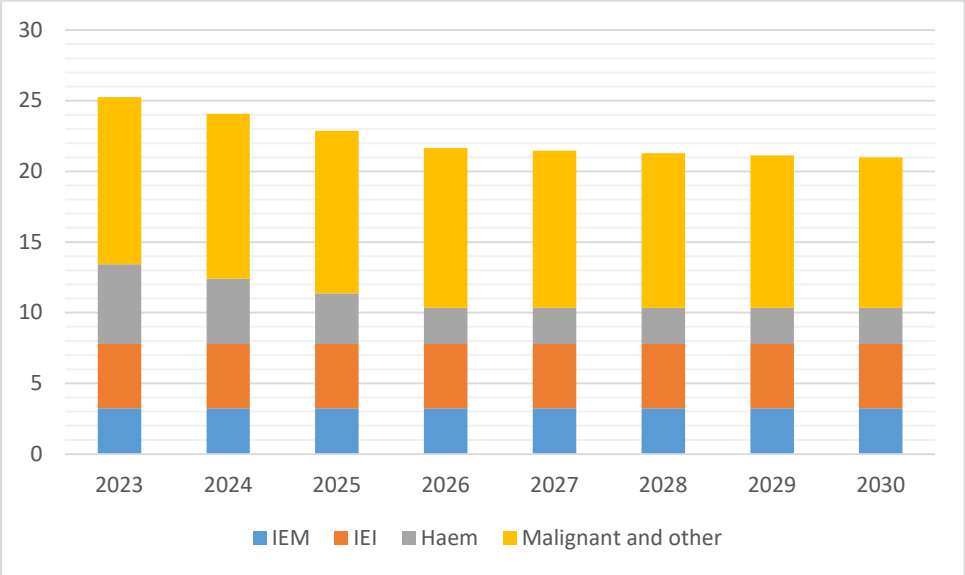
Under a scenario whereby the upper age limit for receipt of AYA cancer care in the new children's hospital is increased, the probability of the centre meeting the FACT-JACIE minimum numbers standard is increased. This probability is estimated at 90.3% in 2025, dropping to 86.5% in 2030, under the assumption that transplants in the 16 to 20 age group are considered by FACT-JACIE to fall under the paediatric setting. The implications of this analysis for the resilience of the service is discussed in chapter 4 – Organisational Considerations.

The demand for allogeneic HSCT in CHI at Crumlin under a repatriation scenario for the cohort aged 0 to 16 years, broken down by transplant indication, is presented in Figure 3.7 (a). This was estimated by projecting the number of transplants for IEM and IEI in line with historical demand (as outlined in sections 3.2 and 3.4, respectively), and by projecting the number of HSCT procedures required for haemoglobinopathies in line with expert opinion and with the expected rate of second transplants required (as outlined in section 3.7). These figures were not adjusted in line with changes in the birth rate due to the uncertainty associated with the applicability of changes in the national birth rate to the population in this assessment (section 3.7). Comparable estimates accounting for the scenario where the upper age limit for patients with cancer treated in CHI is increased to 20 years is presented in Figure 3.7 (b).

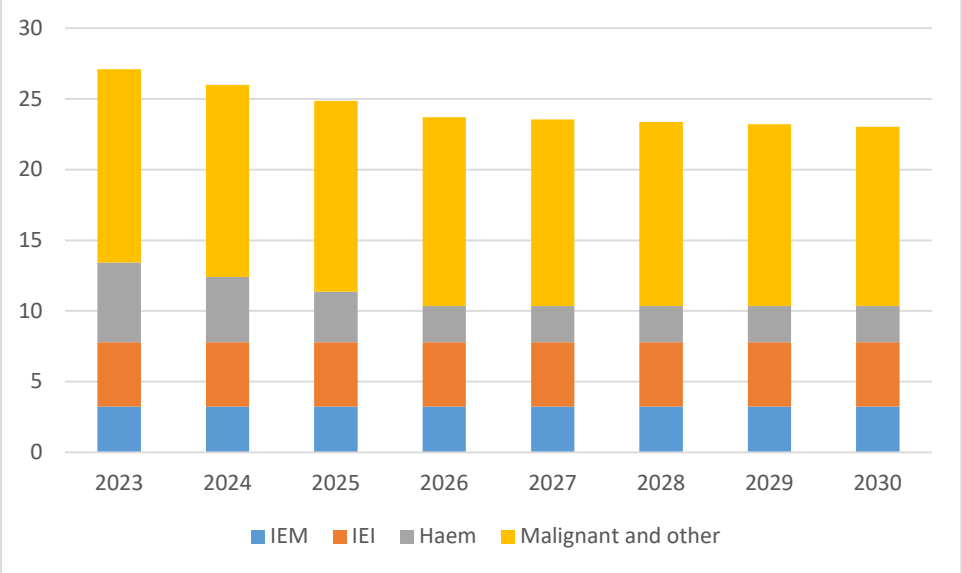
The 2023 and 2030 data presented in Figure 3.7 is presented in tabular form in Table 3.5.

Figure 3.7 Projected mean number of allogeneic transplants to take place at CHI if the service were to be repatriated

(A) Patients aged 0 to 16 years only



(B) Patients aged 0 to 20 years



Note: Osteopetrosis is included under the 'malignant and other' categorisation rather than under 'IEM' as transplants for this indication are accounted for within transplants in CHI at Crumlin.

Key: CHI – Children's Health Ireland; Haem – haemoglobinopathies; IEI – inborn errors of immunity; IEM – inborn errors of metabolism.

Table 3.5 The estimated mean annual number of allogeneic HSCT procedures at CHI by proposed and current indication groups

Proposed and current indication groups	Estimated number of procedures per annum
Proposed cohorts for repatriation	
IEM	3.2
IEI	4.6
Haemoglobinopathies: First year for which HSCT will be provided By year five of service	5.7 2.6
Malignancy and other indications already performed at CHI	
0 to 16 years age group: 2023 estimate 2030 estimate	 11.8 10.6
0 to 20 years age group: 2023 estimate 2030 estimate	 13.7 12.7
Total including proposed cohorts for repatriation and malignancy and other indications already performed at CHI	
0 to 16 years age group: 2023 estimate 2030 estimate	 25.3 21.0
0 to 20 years age group: 2023 estimate 2030 estimate	 27.1 23.0

Key: CHI – Children's Health Ireland; HSCT – haematopoietic stem cell transplant; IEI – inborn errors of immunity; IEM – inborn errors of metabolism.

These estimates are used to inform the resources required for repatriation in chapter 4 and the budget impact associated with repatriation presented in chapter 5. Using the same methods as described for the no repatriation scenario, probabilistic analysis was conducted to examine the effect of natural variation over time for IEM, IEI and the malignant and other indications currently treated at CHI at Crumlin. The expected number of transplants for haemoglobinopathies was not varied. If

repatriation were to occur, across the years 2025 to 2030, the probability of the three year rolling annual average of allogeneic transplants falling below 10 transplants was 0%, regardless of the upper age limit for transplant in CHI.

3.12 Discussion

The purpose of this chapter was to outline the epidemiology associated with the IEI, IEM, and haemoglobinopathies considered in a scenario of HSCT repatriation. The aetiology, incidence, clinical presentation and burden of disease, drawing on international and national data, for the most common conditions identified was outlined. A summary of the HSCT procedures performed in the UK in recent years to treat patients referred with such conditions was provided, alongside a summary of the current paediatric HSCT service in Ireland in terms of provision and demand (which is typically restricted to the treatment of conditions of bone marrow failure and haematological malignancies). The identified factors that may influence future demand for paediatric HSCT services in Ireland were presented, with estimates of the projected demand for such services under current and proposed pathways.

Defined indications for HSCT in each of the three groups of interest to this HTA have been published in the UK. Historical data indicates that the most common referral in Ireland for IEI has been SCID and for IEM has been Hurler syndrome. The burden of disease associated with each of these conditions was noted to be considerable, with both displaying higher incidence in the Irish Traveller population. Both conditions are associated with early morbidity and mortality in the absence of appropriate treatment.

HSCT is considered the primary intervention for both conditions with earlier treatment typically associated with improved outcomes. In terms of haemoglobinopathies, historically patients with these types of conditions have not availed of HSCT. However, as of 2022 the provision of HSCT for this cohort has been agreed with St Mary's Hospital London. Sickle cell disease represents the most common haemoglobinopathy internationally, with a rising prevalence in Europe owing to migration of people from countries of high prevalence (for example, Africa). The clinical presentation, and overall outcomes, of sickle cell disease is heterogeneous with HSCT typically reserved for more severe cases for whom the clinical benefit is considered to outweigh the potential harm.

To inform the budget impact analysis (chapter 5), the current and projected demands for HSCT in Ireland were explored. Currently, HSCT, with a limited number of exceptions, is provided at CHI at Crumlin for children with bone marrow failure syndromes and haematological malignancies. While the conditions under

consideration within this HTA are not typically treated in CHI at Crumlin, the projected demand for allogeneic HSCT under a scenario of repatriation to CHI is an important consideration in the capacity of the service as a whole to meet needs.

Collectively, the projected demands, which are based on historical data in Ireland and the UK (for those referred) alongside projected birth rates, infer an average of 25.3 allogeneic HSCT procedures per year in 2023 decreasing to 21.0 per year in 2030. This includes indications currently treated at CHI at Crumlin and the projected demand that would arise from repatriation of the remaining indications, and comprises an average of 3.2 HSCT procedures per year for IEM, 4.6 procedures per year for IEI, and 5.6 procedures per year for haemoglobinopathies, with the latter reducing to 2.6 per year once the initial demand for those not previously referred is addressed.

The impact of these estimates, and the required resources to accommodate the additional allogeneic HSCTs, will be explored in the remaining chapters of this HTA. It should be noted that these estimates may be influenced by a number of factors including a changing epidemiology in Ireland (for example, due to rising inward migration), the potential for changes in clinical and age indications for HSCT, and the availability of alternative treatment options.

Furthermore, CHI at Crumlin provides autologous HSCT for a number of indications which may further influence overall HSCT capacity. At present, adults from Northern Ireland who require a HSCT for malignant indications are accommodated in St James's Hospital. If similar arrangements were made for paediatric patients, the demand for HSCT in CHI would be higher than that estimated here.

Limitations

Future referrals for HSCT were estimated by applying historic transplant rates observed at CHI to CSO population projects. However, the approach does not consider uncertainties that may influence referrals for HSCT including migration patterns, the birth rate in subpopulations disproportionately affected by these genetic disorders, the availability of alternative treatments, changes in the indications for HSCT and random variation observed in clinical practice. Nevertheless, the data reported represent the best available estimates and would likely reflect demand in the short-term while the service is being expanded, if a decision is made to repatriate this service.

It should be noted that the disease classifications are rapidly evolving over time with changes in the understanding of the aetiology of disease and treatments. In the absence of a published list of indications for which HSCT is approved in Ireland, the

BSBMTCT indications table (2015 version) was described in this chapter. Of note, the UK NHS policy outlines the requirement for a biannual review of indications for HSCT reflecting the evolving situation.[42] For the conditions listed as indications for transplant in this report, without context it was difficult to understand whether all of the conditions listed under the immunology indication were true inborn errors of immunity or another form of immunological disease. In any case, for the individual circumstances, they were approved for transplant. While acknowledging that there is no formal list of indications that are approved for transplant in Ireland, it is not anticipated that practices would change under a scenario of repatriation.

4 Organisational considerations

Key points

- The current arrangements for receipt of HSCT are associated with considerable administrative and logistical burden for the system and for families availing of HSCT abroad. Challenges exist with respect to the scheduling of HSCT and the organisation of travel and family accommodation for the transplant episode. In addition, children who are medically unstable may need to travel by air ambulance, which is resource intensive.
- In terms of the resilience of the current service, there is a risk to access to HSCT for these cohorts should there be a change to the current agreements, or in a scenario in which demand in the host country exceeds available capacity. Additionally, while patients are travelling to centres of excellence for HSCT, this necessitates a concession of clinical oversight and management from the local treating team to an external team abroad, potentially interrupting the continuum of care.
- Prior to 2013, HSCT was provided to patients with Hurler syndrome (a form of IEM) in CHI at Crumlin. However, this service ceased on retirement of the consultant. In recent years, a dedicated transplant consultant has been appointed and additional consultants with expertise in inborn errors of immunity have been appointed.
- In considering repatriation of the HSCT service for cohorts of relevance to this HTA, a key consideration is the number of available dedicated 'transplant' beds (single ensuite rooms with antechambers and high efficiency particulate air (HEPA) filtration systems) to accommodate the additional allogeneic HSCT and the competing demand for these beds.
    - The HSCT and Cellular Therapy Unit at CHI at Crumlin has four dedicated transplant beds which accommodate patients receiving autologous HSCT, allogeneic HSCT and CAR–T cell therapy. On average, there would be additional capacity to repatriate four transplants annually in 2023 and 2024.
    - At the new children's hospital (expected to open in late 2024 at the earliest) the number of transplant beds will increase from four to six. If all six transplant beds are available, in a year of average demand,

there would be sufficient capacity to accommodate both existing patient groups and those for whom care is being repatriated.

- The estimates above do not account for the expected variation in demand every year. When this is taken into account, if all six beds were available, under model assumptions, the probability of meeting all demand is 90% in 2030. The potential expected shortfall would equate to an average of one patient over five years.
- In a scenario whereby HSCT for all patients aged up to 20 years with cancer is provided in the new children's hospital rather than at St James's Hospital, there would be a 57% probability of meeting all demand in 2030 (potentially, alternative arrangements would have to be made for the equivalent of nine patients over five years).
- Potential options to increase capacity to undertake the additional allogeneic HSCTs for the repatriated cohort include the use of non-dedicated transplant beds for those undergoing autologous HSCT. This option would be contingent on not displacing other necessary clinical care.
    - If autologous HSCTs were provided in a non-dedicated transplant bed, the probability of meeting demand across all years to 2030 is estimated to be 100% if six transplant beds are available.

- Additional skilled nursing staff would be required in the HSCT and Cellular Therapy Unit given the increased number of patients undergoing HSCT. Additional support staff across a range of disciplines would also be required. These staff will be required in CHI Crumlin if services are repatriated prior to the opening of the planned additional transplant beds in the new children's hospital.
    - Recruitment challenges have been identified for many disciplines. In particular, the limited and fluctuating number of trained HSCT nurses available to the unit has been identified by nursing management as a risk to the expansion of the service.
- Given that a proportion of patients undergoing HSCT require admission to the intensive care unit (ICU), repatriation would increase demand for ICU bed days. Repatriation would also increase demand for family accommodation at CHI. An inability to sufficiently increase any of these resources would adversely impact on the ability to successfully repatriate the service.

- Concerning a decision to repatriate care for these conditions, the following issues were identified:
    - A phased approach to repatriation may be required to support sustainable capacity to be built up within the service.
    - As the impact of time to transplant may differ between the indications for HSCT, and capacity for transplant will be finite, careful consideration would need to be given to the process and criteria applied for the prioritisation of patients for transplant.
    - Given the potential fluctuation in demand, there may be a requirement for contingencies at times when there are multiple high priority patients for transplant and demand exceeds available capacity. This could include continued agreements with centres abroad.
    - Consideration would need to be given to ensuring data management resources are sufficient to support the recording of patient outcome data and key performance indicators, and the engagement with international disease and transplant registries. The availability of such data supports quality management and ongoing accreditation.
- Special consideration is required in relation to the provision of extracorporeal photopheresis (ECP) and procedures aimed at preserving fertility, neither of which are currently provided in Ireland by the HSE for paediatric patients receiving HSCT:
    - ECP is used as second-line treatment for graft-versus-host disease and is currently available to those who receive HSCT in the UK. Among Irish patients with IEI who underwent HSCT in the UK between 2017 and 2021, 11.8% received ECP treatment. Some patients who have received treatment abroad return to the UK for additional ECP treatment after their initial return home; this has important cost and resource implications for both the patient and the HSE.
    - For an equivalent repatriated service, ECP would need to be available as a treatment option in Ireland.
    - Conditioning (for example, chemotherapy) is a common component of pre-transplant care. Patients receiving conditioning are at increased risk of subfertility or infertility. Procedures may be performed prior to the administration of conditioning with the aim of preserving future fertility. As part of HSCT provided in the UK, pre-

pubertal patients are given the option of this procedure with uptake reported to be high. The provision of these procedures should be evidence-based and take into account the benefit-harm balance for individual patients. Furthermore, any service providing procedures aimed at preserving fertility would need to comply with national legislation.

- Any decision to introduce ECP and procedures which aim to preserve fertility could also have implications beyond the HSCT repatriated cohort.

- If repatriation of HSCT services for the cohorts under consideration were deemed to be unfeasible, an alternative approach could involve attempting to alleviate some of the challenges posed by the existing model of care being delivered abroad. For example, initiatives could be taken to improve the model of subsistence, financial and logistical support for the patients and families who travel abroad for treatment.

4.1 Introduction

The purpose of this chapter is to describe the organisational considerations associated with the potential repatriation of HSCT services to Ireland. This chapter has been guided by the considerations outlined in the European Network of HTA (EUnetHTA) Core Model organisational aspects domain.[100]

This chapter first discusses arrangements for the provision of treatment abroad, including a description of the Health Service Executive's (HSE's) Treatment Abroad Scheme (TAS), and associated considerations relating to travel and accommodation. Resources necessary for repatriation are then described, including requirements relating to bed capacity, associated staffing, and other requirements such as the provision of family accommodation. Special consideration is given to requirements for the potential provision within the Irish setting of extracorporeal photopheresis (ECP). The resilience of the current service, and that of a repatriated service, is then discussed, followed by considerations relating to quality assurance. Finally, opportunities to improve the existing service have been outlined in the case that a decision is made not to repatriate the service. This chapter also provides a discussion of considerations relating to procedures aimed at preserving fertility.

Evidence included in this chapter is drawn from literature sources and, where suitable literature sources were unavailable, from correspondence and interviews with healthcare professionals involved in the care of patients who receive HSCT in Ireland and abroad. Furthermore, relatives of patients who have received HSCT abroad were consulted in order to understand the organisational considerations associated with their experience. Further information on these consultations is provided in chapter 6. Numerical estimates within this chapter are partly derived from analyses presented within chapter 3 (epidemiology) and chapter 5 (budget impact analysis); these analyses have been cross-referenced within this chapter, where applicable.

4.2 Provision of treatment abroad

4.2.1 Treatment Abroad Scheme (TAS)

As described in chapter 2, the TAS is operated by the HSE for individuals entitled to treatment in another EU/EEA member state, the UK or Switzerland. The TAS is underpinned by EU Regulation 883/2004.[101] The scheme is operated in accordance with procedures set out in EU Regulation 883/2004 and under the direction of guidelines from the Department of Health. The treatments must be within Irish law and either not available in Ireland, or not available in the time normally necessary to

receive them in Ireland, taking into account the health of the patient and the likely course of their condition or disease.(101)

The provisions of EU Regulation 883/2004 were mirrored in the Trade & Co-Operation Agreement concluded by the UK and the EU on 24 December 2020. Therefore, access to TAS for patients post the UK exit from the EU (Brexit) remains unchanged.(102)

Patients require prior authorisation from the HSE before travelling abroad for treatment. An application for treatment along with a referral letter must be submitted by an Irish-based public consultant detailing: the patient's condition, the proposed treatment that is being applied for and the planned treatment facility. The consultant must certify that the proposed treatment is:

- a proven form of medical treatment, not an experimental or test treatment
- medically necessary and will meet the patient's needs
- among the benefits provided for by Irish legislation.

The proposed treatment facility (located in an EU/EEA state) must accept the EU/EEA form E112 (IE) and be a recognised public hospital or other location under the control of a registered medical practitioner. Since 2010, applications for the TAS have been centralised within the HSE. The HSE notes that it endeavours to give a decision on applications within 15 to 20 working days of receipt of completed application forms and supporting documents.(45) However, applications requiring the advice of a medical expert may take longer to process. This may be required for some transplants in this cohort depending on the indication for transplant. Separate E112 forms are issued in respect of each specific episode of care. Approval may be granted for multiple visits when these are recommended by the referring consultant, however, the local TAS office must be contacted confirming each appointment and providing proof of each appointment date, so that an E112 may be issued in advance with an estimated cost of treatment. Patients may be liable for the cost of care if authorisation is not obtained prior to travel; post-dated forms are only considered in the case of extreme emergencies. After treatment, a form E125 is issued to the HSE by the hospital who provided treatment for the patient for the purposes of claiming reimbursement.

As noted in chapter 2, where the patient is under the age of 18, the air or sea fares of the patient and two accompanying adults will also be provided by the HSE, subject to available funding.(12) The fares covered are restricted to the cost of the airline or ferry ticket charge and the government and airport/sea port charges only.

Other costs, for example, luggage charges, travel agent fees, and seat reservations, are excluded. Fares must be purchased before travel by the families themselves. Families may only apply for reimbursement from the HSE after the travel has occurred; this is accomplished by submitting boarding passes and itinerary details.

There are several additional costs that fall outside the remit of the TAS and therefore are an additional financial burden on the families of children receiving treatment. For example, the TAS will cover the air or sea fare from Ireland to the relevant EU/EEA country or Switzerland only. This excludes the cost of transport within the country where the HSCT is being provided (for example, the train, bus, or mileage from the port or airport to the transplant centre). This means that additional travel costs are currently paid by families.

Also, patients and healthcare professionals may not be fully aware of entitlements to funding for families travelling to receive HSCT. For example, it is common for patients to receive their transplant from a donor relative, necessitating the donor (and an accompanying adult if a minor) to travel to the transplant centre; in interviews with HIQA, patients were not always aware that they were entitled to claim travel costs on behalf of the donor.[50] Similarly, the TAS travel policy was changed in December 2020 to allow for the travel of two accompanying adults rather than one. While the national TAS travel policy is issued to all patients who are approved for treatment, it is possible that some families who were not in a position to fully access the documentation may not have received the associated funding.

Additionally, an analysis of TAS claims by the review team found that most patients do not claim back their travel costs.[103] The exact reasoning for this is unclear; it is possible that the administration burden, at a time of stress, may have been prohibitive, or patients may be unaware of their entitlement for a refund or may have claimed the cost back from charitable sources.

In the tragic occurrence of death abroad of a patient receiving treatment under the TAS, the TAS covers the cost of repatriation of remains.[10] Such a tragic event, and the associated repatriation, is an extremely difficult situation for all involved. This is discussed further in the chapter on patient and social considerations (chapter 6).

4.2.2 Travel and accommodation under TAS

The existing service, whereby treatment for HSCT is provided abroad, poses various challenges, often with negative consequences, with respect to arrangements for travel and accommodation.

General travel arrangements

While HSCT is an elective procedure, as outlined in chapter 2, a diagnosis of a condition such as SCID is considered a paediatric emergency with evidence of improved patient outcomes with early diagnosis and or treatment. Pending availability of a suitable donor, standard care is therefore to expedite HSCT, where possible. Patients, therefore, may be travelling at short notice either in the case of emergencies or due to the limited notice provided by centres abroad, which can create a significant burden for those involved.

Health system staff including medical social workers, nurses and clinicians may be required to prepare the patient for travel and there may be an administrative requirement to obtain a passport at short notice when travelling by air. To ensure the patient receives a passport in the short window of time, the Department of Foreign Affairs may be contacted and, as An Garda Síochána are required to sign off on passport applications, a member of the Gardaí has in the past been required to be present at the hospital.[104] While patients who travel by ferry are not required to have a passport, some form of personal identification will be required, and medical social workers who were consulted within this HTA, reported that families were more confident travelling by ferry if they had a passport with them, particularly after Brexit.[104] Additional challenges may arise in the case of patients and or family members who are non-nationals, particularly for those whose visa status in Ireland has not been regularised, for example, undocumented migrants.

In addition to the administrative requirements, the short confirmation time and the possibility of a transplant being cancelled mean that patients and their families are not in a position to book their flights or ferry far in advance. Therefore, families will often have to pay premium prices, and while the cost of the flight and ferry is reimbursable by TAS following travel, this may represent a large upfront cost. As noted, the cost of transfers from the port or airport to the transplant site are not covered by TAS and must be paid by the family.

Irish Air Corps

Some patients with inborn errors of immunity (IEI) and, less commonly, patients with inborn errors of metabolism (IEM) who are too unwell to travel to the UK by commercial transport may require air ambulance transfer. The Irish Air Corps is the air component of the Permanent Defence Forces, based at Casement Airbase, Baldonnel, County Dublin. Through a service level agreement (SLA) between the Department of Health and the Department of Defence, the Air Corps provides air ambulance patient transport. This agreement includes the provision of transport for patients requiring specialised emergency treatment in the UK, particularly when the child is too ill to travel by a commercial airline. Air ambulance services are provided

using the most appropriate aircraft on an "as available" basis; that is, there are no dedicated aircraft. Each child and adult travelling by Air Corps is required to have a passport.

The use of the Air Corps service is resource intensive. Hospital staff members are required to travel with the patient to provide medical assistance. Such staff members must also have a passport and visa clearance for the UK; these visa requirements may pose barriers for non-Irish healthcare staff. Between 2017 and 2021, 39% of patients (n = 7) with an IEI travelling to the UK required an Air Corps transfer.[3] For patients with an IEM, clinicians estimated that approximately one to two patients every five years required an Air Corps transfer.

Travelling during the COVID-19 pandemic

It is noteworthy that the COVID-19 pandemic affected transport arrangements for many HSCT patients. The restrictions meant that the Air Corps ambulance was required more often and there was additional hardship for families as travel arrangements were often cancelled. Also, the isolation periods that were required on both sides of the Irish Sea meant that patients had to spend more time away from their family, sometimes at an additional financial cost, particularly with respect to lost wages. This experience highlights risks regarding the resilience of the service, as discussed in later sections of this chapter.

Accommodation arrangements

Accommodation must be arranged for the family member(s) or carer accompanying the child undergoing transplant. Where available, this may entail obtaining access to family accommodation set up by charitable organisations at a location on or near the hospital site, for example, at a Ronald McDonald house. The responsibility for coordinating this accommodation generally falls on the medical social worker.

Environmental considerations

In the context of considering the various impacts of the existing service arrangements, the environmental consequences of air travel may also be noted as a consideration, particularly when the Air Corps service is regularly required.

4.3 Resources required for repatriation of HSCT services

The National Paediatric HSCT and Cellular Therapy Unit is currently located at Children's Health Ireland (CHI) at Crumlin. This unit is led by the HSCT and Cellular Therapy Director with the support of additional haematologists, radiation oncologists

and the clinical nurse management and specialist team. The unit is an annex to St. John's Ward, which is the primary haematological/oncological ward for paediatric malignant and bone marrow failure syndromes in Ireland, and many resources are shared between this ward and the unit. The unit also shares resources across the hospital system, including ICU, theatre and laboratory services.

The impact that repatriation of the HSCT service would have for bed capacity, staffing requirements, shared resources (theatre and laboratory capacity) and parent accommodation is described in turn below. Special consideration is given to the implications of repatriation for the provision of ECP, as this therapy is not routinely available to patients receiving allogeneic HSCT in Ireland.

4.3.1 Funding arrangements

The TAS is a demand-led scheme that provides funding for treatments undertaken abroad when criteria are met. The provision of transplant services is resource intensive. Therefore, should repatriation occur, resources may need to be allocated to CHI ahead of the activity-based funding allocation to ensure the timely availability of the required resources.

4.3.2 Transplant bed capacity

This section presents an analysis of the bed capacity to enable repatriation of HSCT services for the IEM, IEI and haemoglobinopathy cohorts. Firstly, a description is provided of the current bed availability at CHI at Crumlin and at the new children's hospital, alongside an explanation of sources of demand (as discussed in greater detail in section 3.10). Secondly, an analysis is presented of the degree to which bed capacity is likely to meet transplant needs under repatriation including consideration of a scenario whereby the upper limit of the age of eligibility for cancer care at CHI is increased.

4.3.2.1 Bed availability and sources of demand

The inpatient transplant unit at CHI at Crumlin includes four dedicated transplant beds comprising individual cubicles with antechambers, ensuite facilities, and high efficiency particulate air filtered (HEPA) air filtration systems. These rooms allow for the adjustment of positive pressure to reduce the risk of infection entering the room. This is important for the care of immunocompromised children receiving allogeneic HSCT in the peri-transplant period.[105] The ward is an annex to the primary haematology/oncology ward. The latter has 15 additional single patient rooms and

two additional HEPA-filtered rooms; these are used for patients admitted for haematology and oncology-related care.[17, 18]

The new children's hospital at St James's Hospital campus is expected to open in late 2024, at the earliest.[106] This will have six dedicated transplant beds and a further 22 single patient rooms in the primary haematology/oncology ward. This represents an increase of seven additional inpatient beds compared to the unit in CHI at Crumlin.[107] Expert opinion of the EAG convened to support this HTA was that, while strict infection control prevention measures are always required, rooms with HEPA filtration systems are not mandatory for patients receiving autologous transplants.[3] Many centres, including Great North Children's Hospital, Newcastle, and Great Ormond Street Hospital, London, routinely perform these transplants in a non-HEPA-filtered room.[108] Notably, in the new children's hospital, a HEPA-filtration system will be in operation for the entire ward area including all 28 rooms. In total, 12 rooms (including the six dedicated transplant rooms) will additionally have antechambers.

At present, there are demands from multiple indications for the currently and prospectively available transplant beds. These beds are currently designated for patients receiving autologous and allogeneic HSCT for a range of malignant and benign indications. Since April 2022, CHI at Crumlin has been resourced to provide chimeric antigen receptor T-cell (CAR-T) therapy to five patients annually. To date, these have been accommodated in the transplant beds which represents an additional demand.[109]

Furthermore, as highlighted in chapter 3, children currently attend CHI up to the age of 16, but there is the possibility of expansion to the age of eligibility for those with cancer. The National Cancer Strategy 2017-2026 notes that care in the new children's hospital could include treatment of specific clinically-driven conditions for adolescents and young adults (AYA) who have paediatric-centric tumours and who are aged up to 20 years.[94] As a proportion of these patients would be likely to require HSCT, this may further increase demand for HSCT services within the paediatric setting.[17]

4.3.2.2 Analysis of bed capacity under repatriation scenario

As outlined in chapter 3, repatriation of HSCT services for the IEM, IEI and haemoglobinopathy cohorts is estimated to require an average of 10 to 13 additional allogeneic HSCT procedures to be performed per annum.

Approach to analysis

An analysis was conducted to determine if there would be sufficient bed capacity to accommodate the additional HSCT procedures that would occur under repatriation. It was assumed that transplant beds are available over the full calendar year with 100% occupancy of these beds. This is equivalent to an annual capacity of 1,460 and 2,190 bed days for four transplant beds (current availability) and six beds (future availability), respectively. To estimate the annual overall demand for these beds, the mean projected total number of future transplants was used (that is, for transplants currently conducted in Ireland as well as those that would occur under repatriation), as derived in section 3.11. This was combined with assumptions regarding the average length of stay (varied according to the patient cohort), which are presented in table 4.1.

Table 4.1 Transplant bed length of stay assumptions by patient cohort

Cohort	Length of stay (days)
Autologous patients (malignant and selected benign)	24*[110]
Allogeneic patients (malignant and selected benign)	57[111]
CAR-T therapy	28[17]
Allogeneic, IEM, IEI and Haemoglobinopathies	57**[111]

Key: CAR-T - chimeric antigens receptor T-cell, IEI – inborn errors of immunity, IEM – inborn errors of metabolism.

*Clinical opinion confirmed that the diagnostic-related group (DRG) A08A (corresponding to an autologous bone marrow transplant with complications) was most appropriate in identifying length of stay.[17]

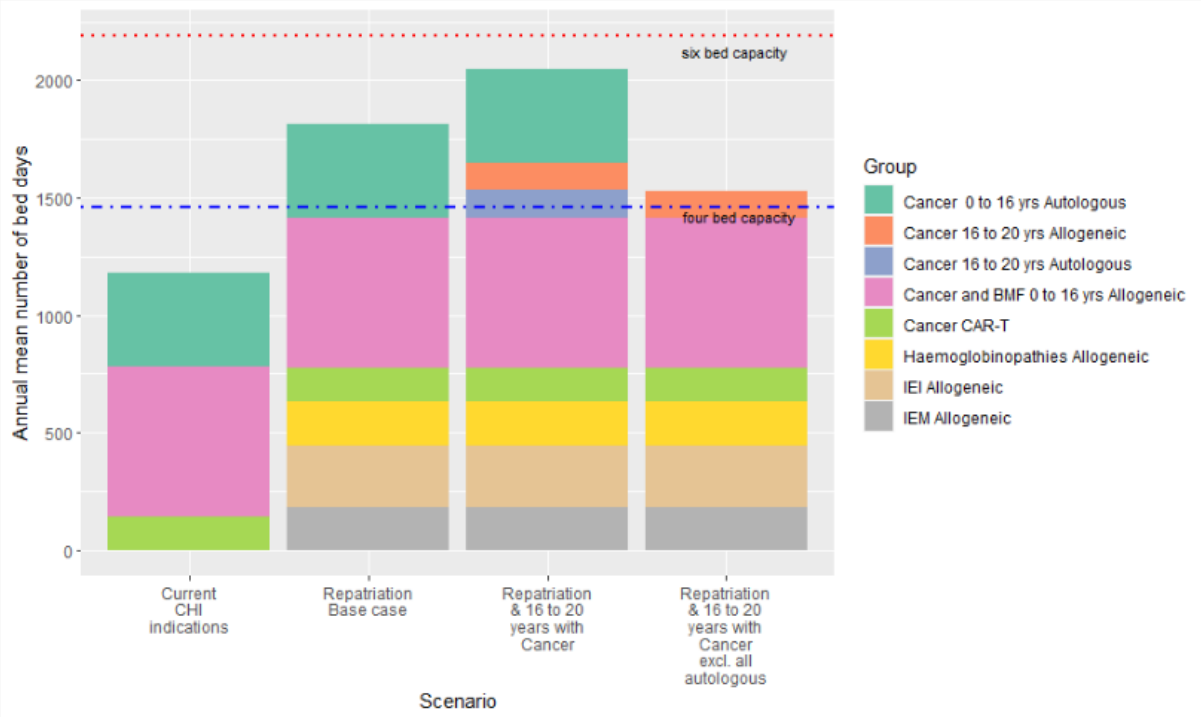
**Based on the mean length of stay corresponding to all paediatric HSCT conducted in the UK.

The projected mean annual numbers of HSCT and CAR-T therapy procedures assume no change in the range of indications for these procedures. To account for random variation in the number of patients presenting for HSCT every year, a probabilistic analysis was conducted whereby the number of patients presenting for autologous or allogeneic HSCT was varied using a normal distribution over 1,000 simulations. The estimated average lengths of stay were applied to the projected number of procedures. Due to a lack of data, no variation was made to the length of stay or the number of patients with haemoglobinopathies undergoing HSCT. The number of patients presenting for CAR-T therapy was also not varied as the unit is currently only funded for a maximum of five procedures per annum and it was assumed that all five procedures would occur. The probability of having sufficient capacity was based on the percentage of simulations within the capacity of 1,460 and 2,190 bed days for a four-bedded and six-bedded transplant unit, respectively.

Results

The results of the above-described analysis, which considers annual mean estimates of demand, are depicted in Figure 4.1. For simplicity in this figure and due to minimal change over time, the average of the results from 2023 to 2030 is presented. This figure shows the annual mean number of bed days required firstly in the case of current levels of demand continuing, secondly with the added impact of repatriation (bar two), in the scenario where cancer patients up to the age of 20 are treated in the unit (third bar) (see section 3.10), and finally in the scenario where cancer patients up to the age of 20 are treated in the unit but where dedicated transplant beds are not used in the case of autologous HSCT patients (fourth bar).

Figure 4.1 Mean projected transplant bed days required by scenario (average of 2023 to 2030 projections)



Key: BMF – bone marrow failure; CAR-T - chimeric antigen receptor T-cell, IEI – inborn errors of immunity, IEM – inborn errors of metabolism.

Note: The blue dashed line represents the current capacity of four transplant beds. The red dotted line indicates a capacity of six transplant beds.

Capacity based on average demand

This analysis found that, in an average year, 81% of the capacity that is currently available at CHI at Crumlin (1,182 / 1,460 transplant bed days from four beds) would be accounted for by patients aged up to 16 years with malignant or selected

benign indications who are already expected to receive HSCT or CAR-T at this hospital.

In the current unit, where four transplant beds are available, it is expected that there would not be sufficient capacity to accommodate all HSCT procedures for the repatriated cohort. In an average year, there would only be additional capacity for four transplants from this cohort to take place.

In late 2024 or early 2025, the HSCT unit is expected to be established in the new children's hospital; this will increase the transplant bed capacity to six beds. From 2025, in a year of average demand, there would be sufficient transplant bed capacity to accommodate all of the repatriated cohort if all six dedicated transplant beds are available.

As discussed in section 3.10, the National Cancer Strategy 2017-2026 has outlined the potential for treatment at CHI of AYA cancer patients up to the age of 20 years. Should this occur, there would still be sufficient capacity, in a year of average demand, for all HSCT procedures both in the repatriated cohort and in the cohort aged 16 to 20 years with cancer.

Accounting for known variation in demand

The estimates above do not account for random variation in the number of patients presenting for treatment every year or for variation in the length of stay. Results of the probabilistic analysis of demand for transplant beds are presented in Appendix 1; this analysis aims to account for this random variation.

The probabilistic analysis identified that, after accounting for the expected variation in demand, there is a potential risk of insufficient transplant bed capacity for all patients in a given year. The analysis predicts that expected transplant bed demand, when including the repatriated cohort, will exceed capacity at CHI at Crumlin if only four dedicated transplant beds are available. This supports the findings of the deterministic analysis that in an average year, there would only be capacity to undertake four (of the additional 10 to 13) HSCT required for the repatriated cohort.

When the service moves to the new children's hospital, and if all six transplant beds are available, the probability of meeting all demand is estimated to be 78% in 2023, increasing to 90% in 2030. This means that, while all demand is expected to be met in most years, in some years alternative arrangements would have to be made to accommodate all patients. The potential expected shortfall equates to an average of one patient over five years.

Scenario where HSCT for cancer patients aged up to 20 years is provided in CHI.

In a scenario whereby, in addition to repatriation of care, HSCT for all patients aged up to 20 years with cancer is provided in the new children's hospital rather than at St James's Hospital, there would be a 57% probability of meeting all demand in 2030 (alternative arrangements would potentially have to be made for the equivalent of nine patients over a five-year period).

For this scenario, there are, however, other potential options that may be available to meet demand. In the new children's hospital, a HEPA-filtration system will be in operation for the entire ward area. Assuming that autologous HSCT could be provided outside of the dedicated transplant beds when necessary, and where the six dedicated transplant beds are also available, there is a 100% probability of meeting the additional transplant bed demand associated with both the repatriated cohort and the potential increase in the upper age limit for patients with cancer.

This option of other bed capacity within the main oncology and haematology ward for autologous HSCT would be contingent on this not displacing other necessary clinical care. Other potential arrangements that may ensure sufficient capacity in years where demand is higher than expected include continuing arrangements with centres abroad or with St James's Hospital for patients aged 16 to 20 years.

It is important to note that, apart from changes in population size, these probabilities assume no other change in the future demand for HSCT or cellular therapies. As the urgency of transplant varies by indication, careful scheduling is important to ensure HSCTs are conducted in a timely manner. To maximise the number of HSCT procedures that are undertaken, patients may be required to relocate to lower intensity beds as soon as it is clinically appropriate.

Intensive care unit (ICU) beds

Most patients do not require an intensive care unit (ICU) admission during their transplant episode. However, for those patients that develop complications requiring admission to ICU, their stay there can be protracted. Information was provided by consultant clinicians at CHI regarding the expected number of ICU bed days for a patient undergoing HSCT.[3, 17] These data indicated that, in 2021, the mean number of ICU days per allogeneic transplant in Crumlin was 4.2 days (12 allogeneic HSCT procedures, 50 ICU bed days in total).[17] For patients with IEI who went abroad for transplant, between 2017 and 2021, the mean number of ICU days per allogeneic transplant was similar at 4.3 days (19 allogeneic HSCT procedures, 78 ICU bed days in total).[3] Assuming an increase in the mean number of allogeneic transplants by between 10 and 13 allogeneic transplants following repatriation (chapter 3), on

average, an additional 49 ICU bed days would be required per annum for these patients.

4.3.3 Staffing requirements

Prior to 2019, the transplant unit at CHI at Crumlin was supported by four to five consultants who also held other responsibilities. In 2019, funding was provided for a new consultant haematologist post as a dedicated HSCT director, two advanced nurse practitioner posts for transplant services, and four allied health care professionals who are deployed across all of the primary haematology/oncology ward. However, due to difficulties in filling the advanced nurse practitioner posts, these were converted to alternative posts. Funding was also provided to CHI at Crumlin from the National Cancer Control Programme (NCCP) to develop a CAR-T service.

Currently, the HSCT and Cellular Therapy director is supported by three consultant haematologists and two radiation oncologists, and non-consultant hospital doctors including a specialist registrar, registrar and a senior house officer, all of whom have responsibilities for the provision of inpatient, day ward and outpatient care for patients with haematological conditions. In 2022, a new permanent immunology consultant with a special interest in transplant joined the CHI team, further increasing the HSCT expertise available to the unit.

The dedicated transplant day ward has three beds with a dedicated clinical nurse manager at grade 3 level (CNM3), who acts as the HSCT and CAR-T coordinator, a clinical nurse specialist, and a staff nurse.

Nurses caring for inpatients are shared between the transplant unit and the rest of the primary haematology/oncology ward. There are 15 senior nursing staff members comprising advanced nurse practitioners, clinical nurse specialists, shift leaders and CNM3 grades. Approximately 40 staff nurses are shared between the transplant unit and the rest of the primary haematology/oncology ward (19 beds in total). However, only nurses who are trained in HSCT can work in this unit. Nursing management personnel estimate that 40 to 45% of nurses have the required training which consists of on-the-job training over two years. It has further been reported that it can be difficult to retain trained HSCT nurses due to the demanding nature of the role.[112] The limited and fluctuating number of trained HSCT nurses available to the unit has been identified by nursing management as a risk to the expansion of the service.

The recommended patient-to-nurse ratio on the primary haematology/oncology ward is 3:1, but lower ratios of 2:1 are recommended for the transplant unit given the

greater nursing demands in this setting.[105] With respect to repatriation of HSCT for IEM, IEI and haemoglobinopathies, the projected additional nursing capacity required equates to 5.1 full time equivalents (FTE). This estimate takes into account the mean length of stay for the HSCT episode based on TAS data (56 days for IEM, 71 days for IEI) or UK registry data (56 days for haemoglobinopathies), the mean number of transplants (11.6 per annum for the entire cohort over the next five years; chapter 3), and a 2:1 nursing ratio. Assuming that the required beds are already staffed on a 3:1 basis and the only additional requirement is a reduction in the staff ratio to 2:1, an additional 1.7 FTE nurses would be required to support the additional transplant activity.

These figures take into account annual leave and public holidays, but do not take account of any additional capacity that may be required due to the known variation in numbers of patients undergoing HSCT from year to year. However, these figures relate to the additional staffing requirement compared to the current arrangements in CHI at Crumlin. These do not account for any spare nursing capacity at CHI at Crumlin (if any) or additional resources already budgeted for the new children's hospital given the planned increase in transplant beds at that site, resources for which may already have been allocated.

Prior to 2013, HSCT for patients with Hurler syndrome was provided at CHI at Crumlin, but the service ceased on retirement of the consultant. Currently, the HSCT unit at CHI at Crumlin manages these patients directly after their discharge from the HSCT unit in the UK. Therefore, staff in the unit have some experience of this patient cohort.[112] There is more limited experience among the staff in the transplant unit of patients with IEI or haemoglobinopathies post-transplant. If the service were repatriated, close cooperation with clinical staff with specialist clinical knowledge in these disease areas would be required for shared learning.

Allied health and social care professionals care for all patients on St John's Ward. They also have responsibility for patients in the haematology/oncology day ward, outpatient department and the survivorship/late effects clinic, which provides an outpatient-based service monitoring children's health after HSCT and CAR-T therapy.[107] Such professionals include dietitians, physiotherapists, psychologists, occupational therapists, speech and language therapists, play therapists, medical social workers and pharmacists.

If HSCT services are repatriated for patients with IEI, IEM and haemoglobinopathies, additional staff may be required to cope with the additional number of HSCT procedures. At present, some staff are allocated to the provision of care for cancer patients rather than to all patients on St. John's Ward.[9] This means that patients

with non-malignant conditions on the ward receive care from professionals assigned to general beds in CHI at Crumlin who may not have expertise with this cohort. If the service were repatriated, careful consideration should be given to the staff allocation model to ensure fair and optimal allocation and expertise.

4.3.4 Theatre capacity

The HSCT unit in CHI at Crumlin is part of the Haematology and Oncology department, which has a dedicated half day (morning) theatre list (Monday to Friday), with dedicated times for specific procedures including bone marrow biopsies, insertions of central lines and other procedures performed by the haematologist.[105, 112] For procedures that require a surgeon, a request is made for surgery and patients are put on the elective surgical list. Most HSCT patients will need two theatre episodes per transplant procedure to insert and remove a Hickman line. A subset of patients will require an additional theatre episode to manage a transplant-related complication.

Depending on the cohort, between 17% and 85% of HSCT recipients have a related donor which necessitates a procedure in theatre to harvest the graft (chapter 3). However, as some of these will be adult donors, these procedures would take in place in a local adult hospital rather than at CHI at Crumlin. While repatriation of HSCT will increase requirements for theatre time, is not expected to place significant additional demand when considering overall theatre capacity.

4.3.5 Laboratory capacity

The HSCT laboratory in CHI at Crumlin is a purpose built clean room facility for the processing, preservation and storage of haematopoietic stem cells prior to transplantation.[113] The facility was completed in 2009 in conformance with the requirements of S.I. 158 of 2006 and 2006/86/EC. The laboratory is licensed by the Health Products Regulatory Authority (HPRA) to carry out a prescribed list of cell processing techniques. The service is currently provided to patients receiving allogeneic and autologous HSCT and CAR-T therapy. The laboratory personnel reported that the expertise is available in house to support cell selections or depletions, which are used for patients with IEI, and cord blood transplants, which are most commonly used for patients with IEM.

The laboratory personnel reported that additional resources would be required to support the additional demand before the service could be repatriated. A business case prepared in 2018 estimated that one additional medical scientist would be required for repatriation of the service.[105] In the context of the planned move to

the new children's hospital, planning and resources for this may already have been budgeted for, given the additional transplant beds that will be available at that location.

4.3.6 Parent accommodation

The provision of parent and family accommodation close to the hospital means that families can stay close to their child during their treatment at an affordable rate and remove some of the logistical stresses associated with caring for a sick child. Under the current service provision, parents travelling to the UK for treatment have access to hospital-affiliated accommodation for parents, although this may not be available at all times due to capacity constraints. If the service were repatriated to Ireland, these patients would require access to accommodation in Dublin instead.

CHI at Crumlin currently has 44 onsite bedrooms comprising twin, double and single rooms.[114] The Ronald McDonald House Charity provides an additional 20 rooms.[115] The co-pay varies from €9 to €30 per night, depending on the accommodation provider, room type, and the family's medical card status. Reduced rates or supports from community welfare officers may be available to those who need it.

Under a repatriated service, if every patient's family availed of the family accommodation, on average, 720 bed nights of family accommodation would be required annually to accommodate an average of 12 additional transplants per year (details of underpinning assumptions are presented in chapter 5); this is equivalent to an additional two rooms over a full year. However, some families may not require family accommodation if they live close to the hospital. An analysis of data by the TAS estimated that, among patients with IEI and IEM who were referred for HSCT treatment abroad under the TAS between 2012 and 2021, 27% were from Dublin, 41% were from Leinster (excluding Dublin) and 32% were from outside Leinster. If accommodation were only required by those living outside Dublin, 526 bed nights would be required to accommodate these families, equivalent to an additional 1.4 rooms over a full year.

The new children's hospital will include a bed for a parent or guardian in each individual, en-suite inpatient bedroom. However, the long length of stay and strict infection control measures mean that the provision of family accommodation beyond the child's room is also important. There are plans to build a new Ronald McDonald House on the grounds of the new children's hospital. It is proposed that the new accommodation unit will have 53 family bedrooms across four floors.[116] The charity aims to have the building ready in time for the opening of the new children's hospital with efforts ongoing to raise sufficient funds to build the centre. If a decision is

made to repatriate the service, there is a risk that there will be insufficient family accommodation available in the short to medium term if the new accommodation is not built on time.

4.3.7 Extracorporeal photopheresis

Extracorporeal photopheresis (ECP) has been used for over 20 years to treat GvHD. In recent years, technological advancements in the devices available mean it can now be used to treat patients of lower body weight, including paediatric patients.[49] ECP is not currently available in CHI for children who experience GvHD post-transplant. However, as outlined in chapter 2, patients with IEM, IEI or haemoglobinopathies who travel abroad to receive a HSCT have access to ECP in the transplant centre abroad. Some patients return to the UK for additional ECP treatment after their initial return home, which has important cost and resource implications for both the patient and the HSE. Other patients, however, are too unwell to travel to UK centres or cannot access further treatment in the UK due to a lack of capacity. For an equivalent service under the repatriation scenario, consideration would need to be given to how access to ECP would be provided. Of note, ECP is not available in every centre internationally. A 2018 survey on behalf of the European Society for Blood and Marrow Transplantation (EBMT) Paediatric Diseases Working Group found that ECP was a second-line treatment for acute GvHD for 30% of centres surveyed (response rate was 74 out of 193 centres).[117]

Since 2017, ECP is commissioned by NHS England as a second-line treatment for acute and chronic graft-versus-host disease.[118] This decision was based on a review of the clinical evidence. In the context of high patient morbidity and challenges associated with the conduct of studies in small patient populations, it was acknowledged that the favourable clinical response rates observed in the available literature at the time of the analysis were sufficient to inform clinical practice. Guidelines recommend continuation of ECP therapy in the event of a partial response.[49] The long-term duration and intensity of treatment required to maintain these response rates is unclear.

There are important resource considerations associated with the provision of ECP. As outlined in chapter 5, costs associated with ECP include the capital cost associated with the purchase of the device and the consumables required with each procedure. Also, additional senior skilled nurses would be required to administer and supervise the treatment. The duration and intensity of treatment is variable and depends on the treatment response. Therefore, it is very difficult to project the resources that would be required to provide the service in Ireland.

The resources required would increase if ECP were provided as an option to treat all patients with chronic GvHD and or all allogeneic HSCT recipients who experience GvHD in CHI. Furthermore, indications for ECP may expand in the future; studies are ongoing into its use as first-line treatment in graft-versus-host disease and as preventative treatment.[119] Also, ECP has other potential indications, for example, cutaneous T-cell lymphoma and organ transplant rejection. If the service were introduced, defined protocols for its appropriate use should be considered.

4.4 Resilience of the existing service and of a repatriated service

The resilience of current HSCT services, alongside elements required to safeguard the resilience of prospective HSCT services, are important factors for consideration and are outlined in the following sections.

4.4.1 Current service

As HSCT is currently provided abroad under the TAS, there is a reliance on external capacity and prioritisation which is outside the control of those referring patients from Ireland. The established agreements and processes for the provision of the service at each location in the UK have been associated with extensive cooperation and relationships built up over many years.[3, 17] If there were to be a change to the current agreements in place, or a scenario in which demand in the host country exceeded available capacity, there would be a risk to the provision of HSCT to those travelling from Ireland. A termination of the agreement by one location or an inability of that location to meet requirements would reduce access for the particular clinical indication until agreements are arranged for an alternative service provider. Additionally, while patients are travelling to centres of excellence for HSCT this still necessitates a concession of clinical oversight and management from the local treating team to an external team abroad.[3, 17] Transfers between centres has the potential to disrupt the clinical care continuum whereby the patient and their families engage with one treating centre before HSCT and for long-term follow-up, while the treatment and recovery stage is deferred to another centre.

The Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and European Society for Blood and Marrow Transplantation (EBMT), is known as 'JACIE'. JACIE stipulates a number of criteria for the accreditation of a transplant centre.[39] JACIE accreditation standards require a minimum annual average of 10 allogeneic transplants in each three-year accreditation cycle. The analysis in chapter 3 estimated that the probability of meeting this requirement in Children's Health Ireland in a non-repatriation scenario is 76% in the 2023-2025

accreditation cycle and falling to 64% in the 2028-2030 accreditation cycle. These estimates however do not account for increases in the upper age limit undergoing HSCT in CHI or changes to the range of indications for HSCT, which would increase the probability of meeting the JACIE requirements. A decision not to repatriate therefore has implications for the resilience of the service for patients with indications currently transplanted in Ireland.

4.4.2 Repatriated service

Before 2013, HSCT was provided to patients with Hurler syndrome (a form of IEM) in CHI at Crumlin, but the service ceased on the retirement of the consultant. The resilience of a prospective national service will be reliant on the clinical expertise and infrastructure available to support it. There would be a need to ensure there are a sufficient number of trained clinicians to provide the service required by each clinical indication, accounting for requirements around cross-cover and contingency in the event that a key clinician leaves a service. In recent years, a dedicated transplant consultant and additional consultants with expertise in inborn errors of immunity have been appointed.

Furthermore, the prerequisites for accreditation in HSCT will also need to be fulfilled. JACIE stipulates the minimum number of autologous and allogeneic transplants performed at a centre during each three-year accreditation cycle, which is set at an average of five and 10 per annum, respectively. Given the historical data outlined in chapter 3, and the reducing birth cohort annually,[(93)] should the clinical indications remain the same, there is a risk that these thresholds may not be reached. Repatriation would represent a substantial increase in the number of transplants performed in CHI annually.

To increase the resilience of the service, a phased approach to repatriation, where the number of transplants performed annually is increased in a stepwise manner, may represent a pragmatic approach to building capacity. Patients whose transplants are expected to be straightforward could be selected for repatriation first. This would mean that in the short term, some patients would still be required to travel to the UK and agreements with treatment providers in the UK would need to be maintained. In light of the annual variability in case numbers, there may also be a need to maintain these agreements in the longer term to incorporate surge capacity to meet sudden changes in demand if demand outweighs capacity in urgent cases. Similarly, with respect to reciprocity, capacity may be warranted to facilitate transplants for patients travelling from abroad or Northern Ireland whose national services are unable to meet demand.

4.5 Quality assurance of a repatriated service

Under current processes, clinical responsibility for HSCT is transferred to the treating centre abroad for the duration of care, with such centres conforming to their own national quality assurance standards. Should the service be repatriated, there will need to be consideration given to establishing and completing quality assurance processes in Ireland.

As outlined in chapter 2, the NHS minimum service specifications for the provision of HSCT in England stipulate that all transplant units are required to register transplants in the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) registry and to participate in a national retrospective audit of outcomes.[29] The minimum data collection requirements include the indication, donor stem cell source, stem cell manipulations, conditioning therapy, and outcomes and complications, with detailed descriptions of serious morbidities and mortality. In the case of inborn errors of immunity, specifically, there are further requirements for data to be submitted to the EBMT and the Stem Cell Transplant for Immunodeficiencies in Europe (SCETIDE) registries.

While such registries provide an infrastructure for reporting, the context of a relatively small population size in Ireland, and heterogeneity in terms of complexity, may give rise to challenges in having sufficient case numbers to enable appropriate quality assurance and audit. The HSCT unit in CHI at Crumlin already submits data to the BSBMTCT registry. Given the increased importance of audit with the expansion of a service, consideration should be given to ensuring data management resources are sufficient to support engagement with international registries and oversight of same.

In terms of case presentation and shared expertise, the NHS policy further outlines that all centres nationally should aspire to contribute to a weekly teleconference to discuss patient selection, transplantation approach, management of complications, and waiting lists, alongside an annual confidential audit meeting where the outcomes of all transplanted patients are discussed. In the scenario of a centralised service for HSCT, this may be facilitated through regular and structured communication between the directors of care for individual groups of conditions and collaboration with centres abroad. If services are repatriated to Ireland, consideration could be given to continued collaboration with the UK sites to support ongoing shared learning in the context of managing rare diseases.

4.6 Patient selection and prioritisation

Should a decision be taken to repatriate HSCT services to Ireland, consideration will need to be given to criteria for the selection and prioritisation of patients for transplant. As capacity for transplant will be finite, such criteria will need to take account of factors such as clinical indication and urgency.

Time to transplant

As outlined in Table 4.2, historical data indicate that time to transplant for urgent cases of inborn errors of immunity under the current treatment pathway is numerically higher for the years 2017 to 2021 compared with 2012 to 2016. While the specific reason for this increase is not clear (for example, random variation, differences in the types of presenting conditions, reduced capacity abroad, or consequences of the COVID-19 pandemic), it is noteworthy that such conditions typically have improved clinical outcomes with earlier transplant and hence it is preferable that this period is as short as possible.[120, 121] Time to transplant is also an important consideration for patients with Hurler syndrome. Under the current arrangements, the time to transplant is between two to three months. If the service is repatriated, the time to transplant should continue to be monitored to ensure optimal patient outcomes are achieved.

Table 4.2 Interval from referral to date of definitive treatment - inborn errors of immunity 2012-2021

	2012-2016	2017-2021
Cases	Total (n = 7) • SCID (n = 6) • HLH (n = 1)	Total (n = 6) • SCID (n = 3) • HLH (n = 3)
Median (days)	48	79
Mean (days)	50	79
Range (minimum, maximum) (days)	(23,90)	(44,97)

Key: HLH - haemophagocytic lymphohistiocytosis; SCID - severe combined immunodeficiency.

Criteria exist for clinical indications for which HSCT is provided through the current TAS process. However, in the context of a prospective national service, such indications may change with decisions regarding care made at the local level and influenced by the treating clinicians. Clearly defined criteria for the clinical indications for which HSCT is provided will be required to ensure equitable access to this form of treatment. As a case example, in the UK, HSCT is automatically commissioned for indications outlined by the UK Paediatric BMT Group[41] (see chapter 3), with clinicians also able to apply for individual patient funding for other indications.

Associated policy from the NHS highlights that these indications are scheduled for review by the group on a biannual basis, given the evolving evidence base.[41]

Beyond the clinical indications considered for HSCT, the prioritisation of treatment between and within patient groups are important considerations. The impact of time to transplant on clinical outcomes depends on the patient's underlying condition, clinical condition at the time of HSCT (for example, if they are acutely unwell) and the availability of alternative treatment options in the interim period from diagnosis to definitive treatment. In the current service, patients are prioritised by a multidisciplinary team led by the HSCT and Cellular Therapy Director. With the expansion of the HSCT service, criteria to assist in prioritisation may be required as a transparent system will support equity and fairness of access. Such criteria may become particularly important during periods of spikes in demand. Should demand exceed capacity, it may be necessary for some patients to travel abroad to access care. In these cases, factors beyond indication and urgency, for example, social and economic elements, may require consideration. One option may be to assign designated transplant beds for the care of certain cohorts; however, considering the rarity of the conditions for whom this service will be required, such designation would require flexibility.

4.7 Procedures aimed at preserving fertility

An important part of the HSCT treatment is conditioning. This involves the administration of a combination of chemotherapy, radiotherapy and or serotherapy to the transplant recipient for up to 10 days prior to transplant.[26] Patients receiving these treatments are at increased risk of subfertility or infertility. The risk of infertility varies and depends on the underlying disease, type and dosage of chemotherapy, conditioning regimens and the age at the time of transplantation. Some patients, depending on their individual condition and the degree of human leukocyte antigen (HLA) match with the donor, require only reduced conditioning or may not require any conditioning. In these cases, the risk of subfertility or infertility associated with HSCT is reduced or removed.[27] Guidelines recommend that paediatric patients receiving an HSCT, and their families, should receive appropriate counselling regarding the risk of infertility specific to their individual circumstances.[122]

Procedures may be performed prior to the administration of conditioning with the aim of preserving future fertility.[122] Each procedure can be divided into two stages:

- stage 1 involves the preservation of the genetic tissue prior to conditioning therapy

- stage 2 involves the use of that genetic material to conceive a child. The types of procedures aimed at preserving fertility depend on the gender of the child and whether the child has entered puberty.

Within this section, firstly, a description of procedures aimed at preserving fertility is provided. Secondly, the availability of these procedures to different groups of patients in Ireland is outlined. Finally, the potential impact that repatriation of HSCT services would have in relation to these procedures is described. As conditioning regimens are most commonly indicated in patients with cancer, much of the evidence about the effectiveness of these procedures is derived from this setting.

4.7.1 Types of procedure

Semen and egg cryopreservation

Semen and egg cryopreservation, (collectively known as gametes) are established methods of fertility preservation in post-pubertal patients. Egg cryopreservation involves multiple stages. Over a number of weeks, the post-pubertal girl is given medications to suppress the natural menstrual cycle, to help the ovaries produce multiple eggs and to help the eggs mature. Following collection of eggs by a fertility specialist, they are cryopreserved until needed.[123] Post-pubertal boys may produce a semen sample in a healthcare setting, which is immediately cryopreserved. Cryopreserving more than one sample collected at an interval of a few days increases the chance of future conception. Surgical sperm retrieval is an option for some peri- and post-pubertal boys who are not in a position to produce a semen sample for cryopreservation.[124]

In the future, if the transplant recipients wish to conceive a child, the samples may be thawed and used as part of in vitro fertilisation (IVF) or intrauterine insemination (IUI) treatment.[122] In an evidence review informing recent clinical guidelines for fertility preservation in childhood, adolescent and young adult cancer patients, no studies of live births in post-pubertal male or female patients were identified as using these techniques.[125, 126] However, live births in patients without cancer, and in patients older than 25 years with cancer, were considered transferable to this patient cohort by the guideline development group.

Strong recommendations were made for the use of these techniques in patients with cancer who need a HSCT. Egg and sperm cryopreservation are recommended for paediatric HSCT recipients in clinical guidelines published by EBMT in 2017.[122]

Gonadal Tissue cryopreservation

In pre-pubertal patients, sperm or egg cryopreservation is not possible as the body does not produce mature gamete cells.[125, 126] Ovarian and testicular tissue cryopreservation (collectively known as gonadal tissue cryopreservation) is, however, a potential option. For post-pubertal patients with malignant conditions, ovarian tissue cryopreservation may be performed instead of egg cryopreservation; this is because it may be too risky to delay cytotoxic treatment for the time (weeks) required by the protocol for egg stimulation and maturation as part of egg cryopreservation.[126]

Another reason for conducting ovarian tissue cryopreservation is that ovarian tissue transplantation following this procedure can be used instead of hormone replacement therapy to restore endocrine function if a patient experiences primary ovarian insufficiency as a side effect of the conditioning treatment.[127] This is where the ovaries do not produce typical amounts of the hormone oestrogen. Depending on the degree of insufficiency and the age at treatment, this can mean either that they do not enter puberty or that they can experience symptoms similar to menopause, such as, irregular periods, hot flashes, night sweats and vaginal dryness.[128, 129]

Ovarian and testicular tissue collection procedures are performed under general anaesthetic. The operation may be performed at the time of insertion of the child's central line for HSCT to reduce the additional risk of anaesthesia. Ovarian tissue is collected during a keyhole surgery procedure (laparoscopic oophorectomy), where, provided both ovaries are confirmed as normal, one is removed.[130, 131] If the patient subsequently develops primary ovarian insufficiency and/or is unable to conceive, the ovarian tissue can be thawed and re-transplanted with the aim of restoring ovarian function.[128]

Testicular tissue is collected during a short surgical procedure whereby the surgeon collects a section from one of the testes. This is subsequently prepared by laboratory staff for freezing and storage in a tissue bank until required.[131] Analysis of data from the Oxford Future Fertility programme, which provides a service of cryopreservation of reproductive tissue to young patients at risk of infertility (including patients from Ireland who receive HSCT in the UK), found no serious adverse events were reported with this procedure. The overall morbidity was 0.8% with one umbilical wound infection, one umbilical hernia, and three scrotal haematomas.[128, 131]

A review published in 2021 reported outcomes of the transplantation of cryopreserved ovarian tissue in 285 women from five European centres who presented with failure of IVF treatment.[128] Following ovarian tissue transplantation,

26% of women gave birth through a mixture of natural conception and IVF. With regards to restoration of ovarian function, it was noted that, of 204 patients with primary ovarian insufficiency who underwent ovarian tissue transplantation, 181 (89%) had resumption of endocrine function. In the subgroup of patients who had complete five-year follow-up data, the five-year ovarian graft survival rate was 55%.[128]

There is an extremely limited evidence base with respect to the effectiveness of ovarian tissue cryopreservation for the treatment of infertility using tissue harvested in pre-pubertal patients.

In a review by the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group, only two potentially relevant case reports of live births were identified.[126] One described a live birth from a patient with sickle cell disease who was nine years of age at the time of cryopreservation before HSCT. Pubertal status was not confirmed at the time of cryopreservation. Further, it was not possible to completely exclude that the egg leading to the pregnancy was not derived from her non-cryopreserved ovary. The second case report was also from a patient with sickle cell disease. This patient was almost 14 years old at the time of cryopreservation and was post-pubertal, but pre-menarchal. However, the applicability of these case reports to the pre-pubertal cohort is not clear; most of the patients in this cohort are under the age of two at the time of cryopreservation. Recommendations from this group emphasise that for pre-pubertal girls, the provision of treatment is considered ethically complex given the scarcity of evidence for this group and the inevitable long lag time between collection of ovarian tissue and its use for fertility treatment. The risk of the procedure was considered small in the context that it can be performed concurrently with other surgical procedures. Therefore, they made a moderate recommendation to offer ovarian-tissue harvesting for cryopreservation and storage to pre-pubertal and post-pubertal patients as standard care (very low quality evidence).[126] The panel agreed that transplantation of post-pubertal cryopreserved ovarian tissue can be offered as clinical care, but advised careful research into the clinical outcomes. They recommended that transplantation of pre-pubertal cryopreserved ovarian tissue should be offered only in the context of a research protocol, due to the experimental nature of this procedure.[126]

The PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group have also issued recommendations with respect to fertility preservation in male patients with child, adolescent and young adult cancer. Clear distinctions are again made between recommendations for pre- and post-pubertal patients and between cryopreservation and auto-transplantation of

tissue.[125] The guideline group noted that while mature sperm has been generated using cryopreserved testicular tissue in animal models, the technique has not been successful in humans. They also noted that no studies have been identified that describe a human live birth as a result of using cryopreserved testicular tissue as a source of sperm.[125] The guidelines note that the procedure is experimental, but could be offered as part of a specific research protocol.[125] This is consistent with the recommendations in 2017 consensus EBMT guidelines for paediatric HSCT recipients.[122]

4.7.2 Availability of procedures under the current service

As part of the current HSCT package of care provided within the UK, pre-pubertal patients with an IEM, IEI or haemoglobinopathy who travel abroad to receive a HSCT may be given the option of undergoing gonadal tissue cryopreservation with uptake reported to be high.[1-3] As the service was only introduced in 2018 in the UK, Irish patients whose tissue was cryopreserved have not yet reached an age where transplantation of the tissue can be considered. It is expected that patients would have to travel to England for this procedure; the financial and organisational implications associated with this are unknown. The current status of provision of sperm and egg cryopreservation to Irish post-pubertal patients who travel to the UK is also unclear.

At present, the HSE does not provide funding for procedures aimed at preserving fertility for patients receiving a HSCT in CHI at Crumlin.[9] However, through partnership between the Irish Cancer Society and the not-for-profit organisation Merrion Fertility (the 'Childhood Cancer Fertility Project'), patients receiving a HSCT for a malignant indication receive support for these procedures. Pre-pubertal patients receive a grant towards the £6,500 cost of undergoing gonadal tissue cryopreservation in the UK. Post-pubertal patients receive counselling and egg/sperm cryopreservation procedures and storage with Merrion Fertility.

For adult patients with cancer, the HSE funds egg and sperm cryopreservation through a private healthcare facility.[132] Patients are referred to the service by their treating physician. After an initial counselling session, a person can choose to freeze their sperm, eggs, or embryos and they are stored for ten years at no charge to the patient. Each week, two to four males and two to three females are referred to this service. At present, there is no state funding for the IVF procedures required to conceive a child from the cryopreserved eggs and sperm.

4.7.3 Organisational considerations for a prospective service

If the service were to be repatriated, the appropriate provision of fertility-related procedures would need to be considered for an equivalent service. Criteria could include the risk of infertility, the expected benefits of treatment, ethical and legal considerations, and the availability of resources.

International practice with regards to the funding of these procedures varies. While NICE recommends cryopreservation of gametes to those undergoing gonadotoxic therapy for malignant and benign indications, implementation of the policy across the NHS varies and many trusts deviate from NICE recommendations.

In England, cryopreservation of gametes is funded for all those undergoing treatment for cancer, but eligibility criteria and duration of storage vary across trusts. In Scotland, a national policy is in place which covers cryopreservation of gametes, ovarian and testicular tissue for benign and malignant conditions. In Wales and Northern Ireland, cryopreservation of gametes is funded, but cryopreservation of ovarian tissue is not.[133] In many centres in the UK, gamete and tissue cryopreservation is funded through charities rather than NHS funding.[134]

The establishment of a gonadal tissue preservation service as part of a programme of research could be considered as part of the potential repatriation of the HSCT service for patients with IEM, IEI and haemoglobinopathies. Considering existing work in this area in Ireland, Merrion Fertility have, as part of the Childhood Cancer Fertility Project, preliminarily assessed the clinical and organisational requirements of establishing a gonadal tissue cryopreservation service for cancer patients in Ireland.[135]

Generally, given the experimental nature of the procedure, guidelines recommend that testes tissue preservation is conducted as part of clinical trials or approved protocols.[122] Development of the service in Oxford has been described.[131] This service is led by a multidisciplinary team including a paediatric oncologist, paediatric surgeon, gynaecologist with expertise in teenagers and young adults, gynaecology-fertility experts, paediatric anaesthetist, the Human Tissue Authority license holders and research leads, with a consultant ethicist contacted when required.

For a service to be established in Ireland, any development of a service providing procedures aimed at preserving fertility would need to comply with legislation. As of December 2022, the proposed Health (Assisted Human Reproduction) Bill (29 of 2022) has been presented to the Oireachtas and is at the third stage.[136] The aim of the bill is to provide regulations surrounding the provision of assisted human reproduction in Ireland. Under the current draft, the bill permits a treatment provider

to provide treatment for a child for the purposes of obtaining the child's gametes for a relevant storage period, where a treatment is likely to cause a significant impairment to the child's fertility and such storage is in the child's best interests. Assisted human reproduction treatment is defined as:

"*...any treatment or procedure that involves the handling of gametes or embryos (including the storage thereof), or any combination thereof, for the purposes of establishing a pregnancy or enabling a pregnancy to be established".*[(136)]

'Gametes' is a collective term for sperm or egg. Therefore, the bill in its current form does not provide any regulation or provision for gonadal tissue cryopreservation. If the service were provided, the only legislation that would apply is the general regulation that applies to the storage of all tissue and cells.

Separate to the legal framework for such a service in Ireland, HPRA approval for cryopreservation and storage of collected tissue would be required. In terms of the repatriated cohort, most of the children for which these procedures would apply are infants so robust agreements, and infrastructure would be required to facilitate storage over a number of decades. From the point of view of infrastructure, the main consideration would be the establishment or identification of a laboratory to process the samples and to provide ongoing storage; there may be potential efficiencies if the service were to be established as an add-on to an existing facility, rather than as a separate facility. Considering laboratory standards, it is important to note that environmental standards mandated by the HPRA are higher for areas where gonadal tissue is processed than for egg and sperm processing.

With respect to the procedure for obtaining tissue, logistically, the surgical procedure to be conducted is relatively simple. However, any introduction of the service would have potential implications for the theatre waiting list at CHI, particularly if the service were to be offered to all patients with malignant and non-malignant indications at risk of infertility and not just the patients being considered for repatriation in this HTA.

4.8 Opportunities to improve the existing pathway: patient support

If repatriation of HSCT services for the cohorts under consideration were deemed to be unfeasible, an alternative approach could involve attempting to alleviate some of the challenges posed by the existing treatment pathway. For example, the existing pathway could be improved by developing a formal model of subsistence, financial

and logistical support for the transport, accommodation and living expenses of patients and families who travel abroad for treatment.

The role of a TAS Liaison Officer could additionally be considered by the HSE to provide a more holistic approach to the management of the patients required to access care in the UK. This officer could co-ordinate the navigation of the pathway for families in what is a stressful context. There may be possibilities to achieve economies of scale through direct bookings of flights and accommodation for families by the TAS Liaison Officer, using a HSE corporate account. This would eliminate the need for families to fund flights and accommodation upfront and would reduce the financial and administrative burden associated with retrospective reimbursement.

4.9 Discussion

The purpose of this chapter was to describe the organisational considerations associated with the potential repatriation of HSCT services to Ireland. Firstly, the organisational challenges posed by the existing service arrangements were presented, followed by a discussion of the likely impact of the provision of HSCT in Ireland on resources, as well as the likely impact on the resilience, governance, and continuity of care of the service.

Treatment abroad is available to patients under the TAS scheme. Under TAS there is considerable administrative and logistical burden for the system and families availing of the service. Challenges exist with respect to the scheduling of HSCT, and the organisation of travel and accommodation for the transplant episode. Travel poses various challenges; for children who are medically unstable, and during times of restricted flights for example during the COVID-19 pandemic, transport to the UK has been provided by the Irish Air Corps, which is resource intensive.

Under a no-repatriation scenario, patients with genetic conditions would continue to travel abroad for treatment. This continued reliance on external capacity makes it difficult to identify and mitigate risks. If established referral pathways were to fail, it may be difficult to re-establish new ones. As observed for patients with haemoglobinopathies, it can take many years to establish new treatment pathways.

In the context of a falling birth rate, a scenario of no repatriation could also put JACIE accreditation of existing allogeneic transplant services at risk as there may be insufficient transplant numbers to meet the minimum numbers required to maintain accreditation.

As shown in chapter 3, on average, between 10 and 13 transplants per year would be required for this cohort. While the numbers are small, each allogeneic transplant requires significant healthcare resources. Therefore, small variations from year to year in the number of patients who require a transplant, variation in the length of stay, or variation in the number requiring ICU admission can have a significant impact on the demand for health care resources. Transplant numbers will vary each year and it is important to take this known variation into account when planning services.

The analysis presented within this chapter estimated that, across indications, a capacity of four transplant beds (as is currently the case at CHI at Crumlin) would be insufficient to meet demand for all groups every year. If six transplant beds were available (as is planned for the new children's hospital), the probability of meeting demand was estimated to be 78% in 2023 increasing to 90% in 2030. The potential expected shortfall equates to an average of one patient over five years. These estimates do not incorporate a proposed increase in the upper age limit of patients with cancer treated in CHI from 16 to 20 years of age or outliers in patient length of stay, which may represent challenges in managing bed capacity from year to year. The estimate also does not consider the potential for new technologies, which may increase or decrease the number of patients that require HSCT.

There are a number of options to enhance capacity for allogeneic HSCT. Use of non-dedicated transplant beds for autologous HSCT and CAR-T therapies may be an option, but is contingent on this not displacing other necessary clinical care. Care of these patients is resource intensive, so if such an approach were taken, the non-transplant beds used for these patients would need to be adequately staffed by trained nurses and comprehensive infection control protocols would still be required.

A repatriated service will result in additional demand for ICU bed days. While the additional requirements (on average 49 bed days per annum) are relatively small in the context of over 7,500 staffed ICU bed days in CHI at Crumlin, it is noted that existing ICU occupancy at the site exceeds 95%, so accommodating any additional demand could be challenging.[137] The new children's hospital will have 60 paediatric and neonatal critical care beds, representing a significant increase in capacity if fully staffed. A repatriated service will also result in additional demand for family accommodation during the transplant period. Again, while additional capacity is planned to support the new children's hospital, challenges may arise in meeting demand if this is not completed on time.[138]

The resilience of the national service is reliant on the clinical expertise and infrastructure available to support it. Should a decision be made to repatriate care

for the indications currently undergoing HSCT abroad, a sufficient number of trained staff will be required to manage the additional HSCT procedures that must be undertaken, accounting for requirements around cross-cover and contingency. These include clinical and nursing staff, medical scientists, and allied health professionals. While acknowledging the additional staffing that will be required to cater for the increase in HSCT procedures, it is noted that the allocation of such resources to CHI may have already been budgeted from 2025 onwards given the planned additional transplant beds in the new children's hospital. As with every service, allocation of funding does not necessarily mean that positions will be filled. Recruitment challenges have been identified for many disciplines. In particular, the limited and fluctuating number of trained HSCT nurses available to the unit has been identified by nursing management as a risk to the expansion of the service.

In light of the potential variability in case numbers annually, there may be a need to incorporate surge capacity to allow for expedited access to HSCT for urgent cases, so that agreements with treatment providers in the UK may need to be maintained. Furthermore, should indications for autologous HSCT (for example, autoimmune conditions) or CAR-T (for example, solid tumours) expand, this will place additional demands on the service here. However, this expansion in indications would likely also apply to services abroad, which may impact their capacity to receive Irish patients.

As the capacity for transplant will be finite if services are repatriated to Ireland, criteria will be needed for the selection and prioritisation of patients for transplant, such as clinical indication and urgency, as the impact of time to transplant on outcomes is likely to differ across patient groups.

The context of a relatively small birth cohort in Ireland, and heterogeneity in terms of complexity, may give rise to challenges in having sufficient case numbers to enable appropriate quality assurance and audit. The HSCT unit at Crumlin already has quality assurance processes in place. The HSCT unit at Children's Health Ireland is FACT-JACIE accredited and clinicians at CHI at Crumlin submit data to the BSBMTCT registry. Should the service be repatriated, there will need to be consideration given to the strengthening of data management within the BSBMTCT framework to account for the increased patient numbers and the increased risk associated with the extension of the service.

Special consideration is required in relation to the provision of ECP to treat graft-versus-host disease and procedures aimed at preserving fertility. Currently, these treatments are not available in CHI for children undergoing HSCT but are available to those who undergo HSCT in the UK. Some patients who have received ECP

treatment abroad return to the UK for additional ECP treatment; this has important cost and resource implications for both the patient and the HSE. If the repatriated HSCT service were to be equivalent to current care, ECP and procedures aimed at preserving future fertility would be required as treatment options in Ireland. However, this would have implications beyond the cohort of genetic conditions considered in this HTA. Any decision to provide these procedures to one group may have implications for their provision to other groups. Assessment of the effectiveness, cost effectiveness and feasibility of providing ECP and procedures aimed at preserving future fertility to other groups and the resources required to provide these treatments was beyond the scope of this HTA.

If repatriation of HSCT services were deemed to be unfeasible, an alternative approach could involve attempting to alleviate some of the challenges posed by the existing model of care being delivered abroad. For example, if it were possible for the TAS to be altered to alleviate some of the out-of-pocket expenses for families undergoing treatment abroad, particularly the need for upfront payments, this might ease the financial burden on parents who are already in a stressful situation.

5 Budget impact analysis

Key points

- A budget impact analysis was carried out to assess the financial consequences of providing HSCT in Ireland for the additional indications of IEM, IEI and haemoglobinopathies for which treatment is currently provided abroad. The budget impact of repatriation of HSCT was examined from several different perspectives, including the HSE, the Department of Defence, and the provider of accommodation to families of patients undergoing HSCT in Ireland.
- The BIA only considers aspects of the service that are expected to change in a repatriated service, that is, none of the services that are already provided to the patient in Ireland before they leave or when they return to Ireland are included. Therefore, the figures presented here should not be taken to represent the full cost of care.
- From the perspective of the HSE, while subject to substantial uncertainty, the estimated five-year incremental budget impact is expected to result in cost reductions. Over a five-year time horizon, depending on whether costs arising from ECP and procedures aimed at preserving fertility are excluded or included, the reduction is estimated as €2.3 million (95% CI -€5.8m to +€1.1m) or €1.5 million (95% CI -€5.0m to +€1.9m), respectively. From the perspective of the Department of Defence, the estimated cost saving is €100,000 over a five-year time horizon. From the perspective of the Irish family accommodation provider, the estimated five-year budget impact is an increase of €370,000.
- All budget impact analyses are sensitive to changes in the number of patients receiving treatment. Given the small patient population, and historical variation in patient numbers, small fluctuations would have a significant impact.
- The budget impact associated with repatriation under the patient perspective is especially complex. The extent of the financial burden depends on family circumstances. Significant accommodation, travel and sustenance costs may be incurred by families regardless of treatment location. It is difficult to quantify how treatment abroad affects all of these costs
    - The patient perspective in the formal budget impact analysis only considers the costs associated with the minimum level of transport and accommodation required. In this analysis, the estimated additional cost per family associated with repatriation is €120. Supports are available that may alter the budget impact associated with repatriation.

- The costs associated with going abroad for treatment were considered in two vignettes representing hypothetical families. While the families are fictional, the types of financial challenges documented have been described to the review team as lived experiences by families who have travelled abroad for treatment and by medical social workers who assist such families. Under these assumptions, repatriation would reduce the financial burden on families.

- A decision to provide ECP and procedures aimed at preserving fertility to the repatriated cohort would have further implications for resource use if they were also to be made available to other patient groups. The costs associated with such expanded use are not accounted for in this analysis.

5.1 Introduction

The purpose of this analysis is to assess the financial consequences of providing haematopoietic stem cell transplant (HSCT) services in Ireland for the additional indications (inborn errors of metabolism (IEM), inborn errors of immunity (IEI), and haemoglobinopathies) within the scope of this HTA for which treatment is currently provided abroad. If the service were repatriated to Ireland, it is expected that the cost of providing treatment would change but also that the burden of some costs would shift between different stakeholders. Therefore, this budget impact analysis (BIA) is considered from the perspective of multiple stakeholders (including the HSE, Department of Defence, relevant charities and the patient and their family). The BIA considers the time from pre-transplant assessment until the point at which the transplant recipient and family would return to Ireland and require no further visits abroad. Only aspects of the service that are expected to change in a repatriated service are included. Therefore, the figures presented here should not be taken to represent the full cost of care.

5.2 Methodology

The BIA was conducted in accordance with the Health Information and Quality Authority (HIQA) guidelines for BIA in Ireland,[139] using the Excel 2013 and R Studio (version 4.1.2) software packages. The following sections describe the target population, intervention and comparators under consideration, perspective and time horizon, approach to sensitivity and scenario analysis, input parameters used for the BIA, and the quality assurance approach.

5.2.1 Target population

The target population for this model is paediatric patients with IEM, IEI, or haemoglobinopathies for whom a HSCT has been indicated, as described in chapter 3.

5.2.2 Intervention and comparators

The HSCT treatment pathway is the technology under assessment in this HTA. Repatriation of paediatric haematopoietic stem cell services to Ireland (HSCT repatriation scenario) is compared with the current treatment pathway (HSCT abroad scenario) where patients are offered treatment abroad under the TAS.

A detailed description of the alternatives is provided in chapter 2. To note, in the protocol for this HTA it was stated that an additional scenario analysis would be conducted examining the incremental cost of a repatriated service versus no HSCT treatment specifically for patients with haemoglobinopathies; this was to be conducted given that patients in Ireland with haemoglobinopathies have, to date, not routinely accessed HSCT. However, limited data were available to enable this analysis to be performed. As this scenario analysis would therefore not have been sufficiently robust, a decision was made not to proceed with this aspect of the BIA.

5.2.3 Perspective and time horizon

The BIA estimated the incremental cost, over a five-year time horizon, associated with the repatriation of paediatric HSCT to Ireland.

Repatriation of the HSCT service would involve a change in the cost of providing HSCT to the HSE but also a shift in some of the financial burden between different stakeholders. Therefore, the budget impact is considered under multiple perspectives:

- Health Service Executive (HSE)
- Department of Defence
- charities providing family accommodation in Dublin
- patient perspective.

The budget impact associated with repatriation from the patient perspective is especially complex. Costs incurred by parents, the transplant recipient and donors include travel, accommodation, sustenance, and additional childcare costs. There

may further be losses to income, including changes in social welfare entitlements and changes in hours worked.

The extent of the financial burden depends on many factors including the employment situation of the child's primary carer(s), the social care needs of other family members, a family's social welfare entitlements, the distance between a family's home and Dublin (the location of Children's Health Ireland, and, consequently, where HSCT services would be provided under the scenario of repatriation), the availability of family accommodation near the transplant centre, and the child's length of hospital stay. Significant accommodation, travel and sustenance costs will be incurred by families regardless of treatment location. It is difficult to quantify how treatment abroad affects all of these costs.

Therefore, two types of analyses were considered under the patient perspective, as follows:

- Firstly, an analysis was conducted of the minimum travel and accommodation costs that would directly change under repatriation, and which are independent of a family's personal financial and social circumstances.

- Secondly, two vignettes have been provided which illustrate the potential impact of repatriation on the financial circumstances of hypothetical families. These descriptions, while hypothetical, were based on information provided by healthcare professionals involved in the care of patients who travelled abroad for treatment, and from patients' family members.

5.2.4 Input parameters

As specified in the HTA protocol, input parameters were obtained from multiple sources including the TAS, the Healthcare Pricing Office (HPO), analyses of patient records performed by the associated service clinical leads ('clinician analyses'), and international literature. A detailed description of the input parameters is provided below under individual topic headings.

All costs presented are valued in 2021 Irish Euro. Where appropriate, healthcare costs were adjusted using consumer price indices (CPI) for health, and purchasing power parities (PPP), to the last cost year for which complete data are available (2021), in line with national Health Technology Assessment (HTA) guidelines for the conduct of BIA.[139] Goods and services were inclusive of value added tax (VAT), at the standard or reduced rate, as appropriate, in line with current VAT rates.[140]

For estimation of staff unit costs, salary scales were identified from consolidated salary scales available from the HSE in Ireland.[141] Salary costs were based on the mid-point of the scale and adjusted for pension, pay-related social insurance (PRSI) and overheads (such as office space, lighting and heating), in line with national HTA guidelines.[139]

To estimate the number of HSCT procedures, and the associated costs, analysis was conducted of anonymised claims data provided by the TAS section of the HSE, describing paediatric HSCT episodes of care abroad from 2012 to 2021. For some treatments, the invoiced cost of treatment may differ from the estimated cost of treatment at the time of application. To ensure the data were representative and to reduce the administrative burden on the HSE, more detailed cost data were systematically provided for the years 2018 to 2020 only. As invoices are received in arrears, treatment costs were not available for every patient at the time of analysis. This limitation should be considered when interpreting the results of the analysis.

5.2.4.1 Annual number of patients

Methods used to project the expected number of patients in each of the three cohorts are described in chapter 3. In brief, the estimated number of patients for the IEM and IEI cohorts was based on historical demand; this was derived from analysis of patient records as conducted by the relevant leading clinicians in Ireland for these conditions. The estimated number of transplants for patients with haemoglobinopathies was derived from expert opinion as patients have not accessed this treatment in the past.

Using standard methods for probabilistic analysis (see section 5.2.5), uncertainty in the mean number of patients per year is projected in the model. Given the small number of patients and the implications of random variation in patient numbers over time for bed capacity, this analysis took the approach of modelling uncertainty in the number of patients per year rather than uncertainty in the mean number of patients, that is, the standard deviation of the number of patients was used rather than the standard error of the mean.

Due to the small number of patients, year on year variability in the number of patients can have important consequences for capacity. Patient number parameters for the model are outlined in Table 5.1 below.

For the purposes of the BIA, it was assumed that 100% of patients would be repatriated from Year 1. In practice it may be necessary to repatriate patients on a phased basis.

Table 5.1 Patient number parameter assumptions

Parameter	Mean	95% CI	Distribution	Source
Annual number of patients				
IEM	3.22	(1 to 5.44)	Normal	Clinician analysis of patient records[17]
IEI	4.56	(0.75 to 8.37)	Normal	Clinician analysis of patient records[3]
Haemoglobinopathies				
Year 1	5.65	(4.52 to 6.78) *	Normal	Clinical Opinion[1] and BSBMT[47]
Year 2	4.62	(3.70 to 5.55) *	Normal	Clinical Opinion[1] and BSBMT[47]
Year 3	3.60	(2.88 to 4.32) *	Normal	Clinical Opinion[1] and BSBMT[47]
Year 4	2.57	(2.06 to 3.08) *	Normal	Clinical Opinion[1] and BSBMT[47]
Year 5	2.57	(2.06 to 3.08) *	Normal	Clinical Opinion[1] and BSBMT[47]
Proportion Repatriated				
Years 1 to 5	100%	Not varied.	Not varied.	Assumption

Key: BSBMT - British Society of Blood and Marrow Transplantation and Cellular Therapy; CI – confidence interval; IEI - inborn errors of immunity; IEM - inborn errors of metabolism.

*For the purposes of the analysis upper and lower bounds of ±20% were assumed.

5.2.4.2 Patient characteristics

The characteristics of the three cohorts (IEM, IEI, and haemoglobinopathies) have been described in chapter 3. For the purposes of the budget impact model, gender and pre-pubertal status are the only patient characteristics which affect the budget impact model as they inform the options available with respect to procedures aimed at preserving fertility.

Data from the international literature were used to inform the gender proportion in each group. Data regarding pre-pubertal status were not identified. Therefore, the proportion of pre-pubertal patients was estimated by HIQA based on the median age of transplant for the cohort in the BSBMTCT and on the natural history of the individual conditions in each group. The assumptions used are presented in Table 5.2.

Table 5.2 Patient characteristic parameter assumptions

Parameter	Mean	95% CI	Distribution
Male			
IEM + (76)	53%	(0.42 to 0.64)	Not included in PSA
IEI # (142)	62%	(0.43 to 0.79)	Not included in PSA
Haemoglobinopathies ~(89)	49%	(0.46 to 0.53)	Not included in PSA
Pre-pubertal			
IEM	100%		Not included in PSA
IEI*	80%		Not included in PSA
Haemoglobinopathies*	60%		Not included in PSA

Key: CI – confidence interval; IEI - inborn errors of immunity; IEM - inborn errors of metabolism; PSA - probabilistic sensitivity analysis.
*For the purposes of the analysis, upper and lower bounds of ±20% were assumed in the one way sensitivity analysis.
#Derived from patients with SCID only
+Derived from patients with Hurler syndrome only
~Derived from patients with sickle cell disease only.

5.2.4.3 Healthcare resource use

Pre-transplant visits

As described in chapter 2, the proportion of patients who require a pre-transplant work-up visit differs across the three cohorts and whether transplant takes places abroad (HSCT abroad scenario) or in CHI (HSCT repatriation scenario).

IEM

Under the current arrangements (TAS), clinical opinion stated that no work-up visit abroad takes place.(2) If the service was repatriated, no additional pre-transplant work-up would be required as evaluations are already conducted in CHI under the current arrangements.

IEI

Most patients, who receive a transplant, travel to Great North Children's Hospital in Newcastle upon Tyne for a pre-work-up visit. Patients who need an urgent transplant do not undergo this step. The proportion of patients who require a pre-transplant work-up abroad is currently 66%. Considering the HSCT repatriation scenario, no additional resource use would be required beyond the current standard of care according to expert clinical opinion.(3)

Haemoglobinopathies

The St Mary's pathway for patients with haemoglobinopathies includes a pre-transplant visit to London.[1] Therefore, for the HSCT abroad scenario in the model it was assumed that this is required by 100% of patients. For the HSCT repatriation scenario, it was assumed that three day case visits (equivalent to the length of a pre-treatment visit abroad) would be required to evaluate patients before transplant, additional to the current standard of care.

The assumptions and data used for the BIA are outlined in Table 5.3 below. It is assumed that all patients who undergo a pre-transplant visit proceed to transplant.

Table 5.3 Transplant visit parameter assumptions

Parameter	Estimate	95% CI	Distribution	Source
Proportion who require pre-transplant assessment				
IEM	0.00		None	Clinical Opinion[17]
IEI	0.66	(0.49 to 0.80)	Beta	HIQA analysis of TAS data[103]
Haemoglobinopathies	1.00		None	Assumption
Proportion related Donor				
IEM	0.17	(0.04 to 0.36)	Beta	Clinician analysis of patient records[17]
IEI	0.33	(0.14 to 0.56)	Beta	Clinician analysis of patient records[3]
Haemoglobinopathies	0.85	(0.70 to 0.96)	Beta	BSBMTCT[47]
Mortality abroad (proportion)				
IEM	0.13	(0.05 to 0.23)	Beta	BSBMTCT[47]
IEI	0.095	(0.03 to 0.18)	Beta	BSBMTCT[47]
Haemoglobinopathies	0.08	(0.03 to 0.15)	Beta	BSBMTCT[47]
Length of inpatient phase (TAS and repatriation)				
IEM	57 days	(46 to 69)	Gamma	Anthony Nolan stem cell charity[111]
IEI	71 days	(58 to 86)	Gamma	Clinician analysis of patient records[3]
Haemoglobinopathies	57 days	(46 to 69)	Gamma	Anthony Nolan stem cell charity[111]
Length of outpatient phase (TAS and repatriation)				
IEM	0		None	
IEI	46 days	(37 to 56)	Gamma	Clinician analysis of patient records[3]
Haemoglobinopathies	46 days	(37 to 56)	Gamma	Assumed equal to length for patients with IEI.

Table 5.3 continued.

Parameter	Estimate	95% CI	Distribution	Source
Outpatient Phase				
Rate of day case visits per day spent in the outpatient phase				
IEM	0			Clinical opinion[17]
IEI	0.36	(0.29 to 0.43)*		Clinical opinion[3]
Haemoglobinopathies	0.36	(0.29 to 0.43)*		Clinical opinion[1]
Complication rate per day during outpatient phase				
Inpatient readmission	0.018	(0.014 to 0.022)	Normal	Anthony Nolan stem cell charity[111]
A&E Visit	0.004	(0.003 to 0.005)	Normal	Anthony Nolan stem cell charity[111]

Key: A&E – accident and emergency; BSBMTCT - British Society of Blood and Marrow Transplantation and Cellular Therapy; CI – confidence interval; IEI - inborn errors of immunity; IEM - inborn errors of metabolism; TAS – treatment abroad scheme.

*For the purposes of the analysis, upper and lower bounds of ±20% were assumed in the one way sensitivity analysis.

Transplant phase

All patients in the model proceed to transplant. For patients with IEI, the mean length of the inpatient phase was estimated at 71 days. This was derived from a clinician analysis of patient records of those who went abroad for transplants between 2017 and 2021. For patients with IEM or haemoglobinopathies, the mean length of stay was assumed to be equal to 57 days, which was derived from a UK analysis of all paediatric allogeneic transplants in 2015 and 2016.

For patients who require an extended stay, the length of that stay is also a relevant parameter as patients with a length of stay greater than 69 days attract a higher payment from the HSE to CHI under the Activity-Based Funding model. Information on the distribution of the length of stay parameter was not available. Therefore, the uncertainty associated with this was assessed by conducting a threshold analysis whereby the increase in the mean cost that would be required to make repatriation cost neutral was assessed.

Post-transplant phase

IEM

After discharge as an inpatient, patients require continued monitoring. Under the current arrangements (that is, treatment abroad), this monitoring takes place in Ireland. Therefore, if the service is repatriated, there will be no change in resource requirements for this cohort, and such monitoring requirements were not included as an additional resource requirement in the model.

IEI and Haemoglobinopathies

For patients with an IEI, the mean duration of the post-transplant outpatient phase abroad was estimated as 46 days. This was derived from a clinician analysis of patient records of Irish patients with an IEI who went abroad for a transplant between 2017 and 2021. In the absence of alternative data, the same duration was assumed for patients with haemoglobinopathies.

Incorporation of post-transplant phase resource use within the model

As all healthcare costs in this phase are accounted for in the TAS price for patients with IEM and IEI, healthcare resource use for patients in this phase was not estimated separately when costing the current arrangements.

Clinical opinion stated that if the service were repatriated, patients in Ireland would be discharged home and would return to CHI at Crumlin for routine day case follow-

up appointments one to three times weekly. Therefore, the model assumes that, under repatriation, patients attend twice weekly for the duration of the outpatient time normally experienced abroad.

Patients may also experience complications during the outpatient phase. A report commissioned by 'Anthony Nolan', a UK charity working in stem cell transplantation, reported on the rate of Emergency Department visits and the rate of inpatient readmission for adult and paediatric patients combined in the 100 days post discharge.[111] These estimates were applied pro-rata to the outpatient length of stay derived above.

5.2.4.4 Travel costs

Current arrangements – Treatment Abroad Scheme

Some patients with severe disease require an Air Corps transfer to the treatment centre in the UK when travelling for their transplant. This is discussed further as an organisational consideration within chapter 4.

For patients with an IEI travelling to the UK, the proportion who transfer and return by Air Corps was derived from a clinician analysis of patient records between 2017 and 2021.[17] During this time period, use of Air Corps transfer was more common because of disruptions to travel due to the COVID-19 pandemic, and therefore represents a limitation of the present analysis. For patients with an IEM, the proportion who transfer by Air Corps was estimated from expert opinion.[3] It was assumed that no patient with a haemoglobinopathy would transfer by Air Corps due to differences in the characteristics of these patients and indications for transplant.

Since December 2020, the TAS travel policy allows for the reimbursement of travel expenses of the patient and two travelling companions for patients under 18 years. Prior to this time, only one travelling companion was allowed. Although families are entitled to claim for the cost of air or sea travel, as discussed in chapter 4, many families do not claim back these costs.

Claims data provided by TAS were analysed by HIQA. The probability of making a TAS travel claim, and the cost of each claim for each healthcare visit type for both the IEM and IEI cohorts, was estimated. Cost data were adjusted using the CPI for transport. Data from 2021 were excluded to allow adequate time for patients to make a claim. The probability of making a claim was adjusted to account for the proportion travelling by Air Corps transfer. For patients with haemoglobinopathies, the mean probability of claiming for travel for IEM and IEI was assumed.

Data and assumptions regarding transport costs are given in Table 5.4.

Table 5.4 Transport cost parameter assumptions

Parameter	Estimate	95% CI	Distribution	Source
Proportion who claim transport cost for pre-transplant visit abroad				
IEM	N/A			
IEI	0.35	(0.17 to 0.55)	Beta	HIQA analysis of TAS records[103]
Haemoglobinopathy	0.35	(0.17 to 0.55)	Beta	Assumed equal to IEI value
Proportion who claim transport cost for transplant of those who went via commercial provider				
IEM	0.21	(0.06 to 0.38)	Beta	HIQA analysis of TAS data[103] (adjusted for proportion who went by air-corps)
IEI	0.18	(0.02 to 0.25)	Beta	HIQA analysis of TAS data (adjusted for proportion who went by Air Corps)
Haemoglobinopathy	0.20	(0.04 to 0.32)	Beta	Assumed as average of IEI and IEM.
Proportion travelling by Air Corps to UK for transplant				
IEM	0.09	(0.08 to 0.11)	Beta	Clinical opinion[17]
IEI	0.39	(0.18 to 0.62)	Beta	Clinician analysis of patient records (2017 to 2021)[3]
Haemoglobinopathy	0.00		None	Assumption
Proportion travelling by Air Corps to Ireland following transplant				
IEM and Haem	0.00			Assumption
IEI	0.17	(0.04 to 0.36)	Beta	Clinician analysis of patient records (2017 to 2021)[3]
Air Corps flight costs				
IEM	€6,157*	(€4,987 to €7,447)	Gamma	Department of Defence[143]
IEI	€6,942*	(€5,624 to €8,398)	Gamma	Department of Defence[143]
Pre-transplant visit travel costs				
IEM	N/A			
IEI	€147	(€95 to €211)		HIQA analysis of TAS records[103]
Haemoglobinopathy	€147	(€95 to €211)		Assumed equal to IEI cost.
Transplant episode travel cost (commercial)				
IEM	€414	(€212 to €683)	Gamma	HIQA analysis of TAS records[103]

Parameter	Estimate	95% CI	Distribution	Source
IEI	€387	(€186 to €661)	Gamma	HIQA analysis of TAS records[103]
Haemoglobinopathy	€401		Varied with IEM and IEI.	Assumed equal to average value for IEM and IE.
Travel Cost Donor				
Proportion who claim travel costs for donor	0%			No donor costs reimbursed in TAS dataset.
Cost of travel for donor	Assumed equal to cost of travel for transplant recipient.			Assumption.

Key: CI – confidence interval; IEI - inborn errors of immunity; IEM - inborn errors of metabolism; N/A – not applicable; TAS – Treatment Abroad Scheme.

*Differences in Air Corps flight costs due to differences in the distance from Dublin to the treating centres (Manchester for IEM, Newcastle for IEI).

5.2.4.5 Healthcare costs

Currencies

Healthcare costs under the TAS scheme were derived from analysis of the TAS database, with all costs converted from pound sterling (GBP) to 2021 Euro. As prices are set and invoiced in GBP, future fluctuations in the exchange rate will change the amount payable by the HSE. In 2021, the Purchasing Power Parity between the Euro and GBP was the strongest for the Euro since 2002. A stronger Euro reduces the cost of transplant for the HSE. Since the purchasing power parity in 2021 may not represent the future relationship of GBP and Euro, variations in the future purchasing power parity were examined in a scenario analysis.

HSCT Abroad Scenario

Pre-transplant phase

- For patients with IEM, there is no difference in the pre-transplant resource use between scenarios, therefore there are no costs associated with this in the model.
- For patients with an IEI, the TAS price of a pre-transplant visit is set at £16,000 (€18,187). Clinical opinion stated that no additional resource use would be required as the investigations required are already conducted for these patients in Ireland.
- For patients with haemoglobinopathies, the price of a pre-transplant visit was set at the IEI price in the absence of cohort-specific data.

Post-transplant phase

The extent of the treatment provided differs between the cost of IEM and IEI transplants. Therefore, transplant costs across indications should not be compared.

The cost of the transplant phase in the TAS dataset includes the cost of the donor graft, the cost of procedures aimed at preserving fertility, and extracorporeal photopheresis (ECP). For patients with IEI, it also includes the cost of follow-up in Great North Children's Hospital in Newcastle upon Tyne in the days following inpatient discharge, including both accommodation and transport from the accommodation to the hospital for the transplant recipient and carer. As patients with IEM return to Ireland post inpatient discharge, the cost of follow-up is not included.

For patients with IEM, the cost varies depending on the complications arising and the final invoiced cost can be substantially lower or higher than the initial estimated cost of treatment. Invoiced costs were provided for all patients for the application years 2018 to 2020. However, as invoices are issued in arrears, final invoiced costs were not available for all patients. In the absence of further information, or patient characteristics on which to adjust the data, it is assumed that data are missing at random.

The mean cost of transplant was £89,146 (2021) which is equivalent to €101,330. All patients in this time period had similar costs (standard deviation: €11,100). Where unusual values were identified, invoiced costs were provided by TAS for selected other patients outside the 2018 to 2020 time period.

Due to the low numbers of cases and sometimes substantial differences in case complexity, there can be large variation in the invoiced costs for patients with the same condition, and the invoiced cost for a single patient can potentially skew the average cost quite substantially. When one of these patients was included in the average estimates, the mean cost was estimated at £133,987 (€152,298, adjusted to 2021) for HSCT for patients with IEM. This value was chosen for the budget impact analysis as the mean cost of £89,146 derived above is a known underestimate. However, as the chosen analysis incorporates a potential outlier, the estimate may represent an overestimate of the true average cost of treatment.

The cost of transplant for patients with haemoglobinopathies was not available for this analysis. Therefore, in the absence of cohort-specific data, the transplant price was set at the IEI price of £256,000 (2021) equivalent to €295,534, which includes the price of post-discharge follow-up.

HSCT Repatriation Scenario

Under the Activity Based Funding (ABF) Model, the routine cost of a paediatric allogeneic transplant in Ireland is captured in the code 'DRG A07A – Allogeneic BMT age<=16 years or major complications'. The price paid by the HSE is €215,162 where the inpatient stay is between 35 and 69 days. However, some patients will require stays greater than this. For stays longer than 69 days, an additional price of €4,435 per day is payable. Therefore, the mean cost is expected to be greater than €215,162. Information on the distribution of the length of stay was not available to HIQA. Therefore, a threshold analysis was conducted to examine the increase in the mean cost of HSCT required for repatriation to remain cost neutral.

This cost does not include post-discharge follow-up. The cost of routine day case follow-up and readmission for complications were obtained from the HSE ABF price

list.[110] The cost of an Emergency Department admission was estimated based on data from St. Vincent's Hospital, Dublin.[144]

Table 5.5 Parameter estimates for healthcare costs

Variable	Mean	95% CI	Distribution	Source
Pre-transplant visit - TAS				
IEM	0			No change to current practice
IEI	€18,187	None		HIQA analysis of TAS[103]
Haemoglobinopathy	€18,187	(€14,732 to €22,000)	Gamma	Assumed equal to IEI
Pre-transplant costs - Repatriation				
IEM	0			Clinical opinion. No change to current practice
IEI	0			Clinical opinion. No additional tests required over current practice.
Haemoglobinopathy	€3,591	(€2,909 to €4,344)	Gamma	Assumed equal to the cost of three day case visits (Q61A Red Blood cell disorders, Major Complexity[110]
Transplant costs - TAS				
IEM	€152,298	(€69,197 to €267,621)	Gamma	HIQA analysis of TAS data[103]
IEI	€295,534		None	HIQA analysis of TAS data[103]
Haemoglobinopathy	€295,534	(€239,395 to €357,498)	Gamma	Assumption equal to IEI cost.
Transplant cost - Ireland				
All cohorts	€215,162	(€174,290 to €260,275)	Gamma	HSE ABF Price list[110]
Follow-up and complications costs - Repatriation				
Day case	€1,203	(€975 to €1,455)	Gamma	ABF Price list 2022. Average day case Q60 A and B[110] Reticuloendothelial and Immunity Disorders, Major Complexity and Minor
ED visit	€300	(€243 to €363)	Gamma	St Vincent's Hospital international patient charges.[144]
Re-admission	€9,474	(€684 to €1,021)	Gamma	ABF Price list 2022. Q60A[110] Reticuloendothelial and Immunity Disorders, Major Complexity

Key: ABF – activity based funding; CI – confidence interval; ED – Emergency Department; HSE – Health Service Executive; IEI - inborn errors of immunity; IEM - inborn errors of metabolism; TAS – treatment abroad scheme.

5.2.4.6 Family accommodation costs

Under the TAS scenario, there is no additional cost to the HSE or families for family accommodation provided by the NHS. Under the repatriation scenario, families would stay in the Ronald McDonald house or other family accommodation provided by the CHI. The cost parameters are outlined in Table 5.6 below.

Providing accommodation to the family of the transplant recipient has an opportunity cost given that if the service is not repatriated, the room will be occupied by another family. The cost per room in Ronald McDonald house was estimated by dividing the 2021 annual expenditure by the number of rooms (20) and nights per year.[145] This gave an estimated cost per night of €156. Families may pay a €10 co-pay per night, although this may be waived by the centre if required. Therefore, the cost per night to the family accommodation provider is €146.

Table 5.6 Accommodation cost parameters

Variable	Estimate	95% CI	Distribution	Source
Cost per room per night (after removal of co-pay)	€146	(€118 to €176)*	Gamma	Ronald McDonald[145]
Room co-pay	€10	-	None	Ronald McDonald[145]

Key: CI – confidence interval.

*assumed ±20%

5.2.4.7 Procedures aimed at preserving fertility

In the case of procedures aimed at preserving fertility (described further in chapter 4), the cost of these can be divided into (i) the cost of the treatment procedure and the initial cryopreservation of the sample, and (ii) the ongoing storage of the sample. The cost associated with the use of the sample to conceive a child is beyond the scope of this analysis.

It was assumed that all patients undergo procedures aimed at preserving fertility under both scenarios.

HSCT Abroad Scenario

Under the TAS, the cost of gonadal cryopreservation and storage is included in the transplant price. There is a lack of clarity about the length of the storage period included in that price.

HSCT Repatriation Scenario

For post-pubertal girls and boys, established methods of fertility preservation are available in the private healthcare system. The costs of oocyte and surgical sperm retrieval, egg and sperm cryopreservation, and annual storage were estimated as the mean published cost obtained from a sample of three healthcare facilities. In the absence of data, it was assumed that 50% of cases require surgical sperm retrieval.

For pre-pubertal girls and boys, the cost of ovarian and testicular tissue procedures were estimated as the mean inpatient and day case cost from the respective diagnosis-related group (DRG). In clinical practice, costs could potentially be lower as the procedure can be conducted while the child is in theatre under general anaesthetic for insertion of their central line, as part of the HSCT procedure.

In the base case model, the costs of tissue storage are applied annually to surviving patients. Storage costs may be substantial as many patients are infants at the time of procedure, potentially necessitating storage of the samples for a number of decades. In scenario analysis, the cost of storage upfront for a period of 30 years for each patient is estimated.

It is also possible for patients to travel to the UK to have the procedure conducted privately. This currently costs £6,500 and requires patients to undergo a second general anaesthetic as the procedure would not be conducted at the time of transplant.[9] This was not examined in scenario analysis. Depending on the pubertal status and gender of the transplant recipient, different options are available. The evidence surrounding each procedure is outlined in chapter 4.

Table 5.7 Cost parameters for procedures aimed at preserving fertility: Repatriation Scenario

Variable	Cost	95% CI	Distribution	Source
Ovarian tissue harvesting, cryopreservation and one year of storage	€7,046	(€5,707 to €8,523)	Gamma	HSE ABF Price list Average day case and inpatient prices : N05 Oophorectomy and Complex Fallopian Tube Procedures for Non-Malignancy[110] Mean cost of cryopreservation and storage from sample of three private fertility clinics. [146-148]
Testicular harvesting, cryopreservation and one year of storage	€4,597	(€3,724 to €5,561)	Gamma	HSE ABF Price list Average day case and inpatient prices : Testes Procedure M04 (all complexities)[110] Mean cost of cryopreservation and storage from sample of three private fertility clinics. [146-148]
Sample cryopreservation	€550	(€456 to €652)	Gamma	Mean cost of cryopreservation and storage from sample of three private fertility clinics.[146-148]
Annual storage of tissue samples	€261	(€215 to €311)	Gamma	Mean cost of cryopreservation and storage from sample of three private fertility clinics. [146-148]
Oocyte retrieval cryopreservation	€2,994	(€2,674 to €3,332)	Gamma	Mean cost of cryopreservation and storage from sample of three private fertility clinics. [146-148]
Surgical sperm retrieval, cryopreservation and storage.	€1,663	(€1,133 to €2,294)	Gamma	Mean cost of cryopreservation and storage from sample of three private fertility clinics. [146-148]
Scenario Analysis				
30-year storage upfront: private healthcare system	€7,381	-	-	Mean cost of storage from sample of three private fertility clinics.[146-148]

Key: ABF – activity-based funding; CI – confidence interval; HSE – Health Service Executive.

5.2.4.8 Extracorporeal photopheresis

Extracorporeal photopheresis is a second-line treatment for both acute and chronic graft-versus-host disease (GvHD). Acute GvHD (aGvHD) is of relevance for this assessment as it presents within the first 100 days of transplant at a time when transplant recipients would still be abroad following their transplant procedure.

In the UK, ECP is indicated as a second-line treatment option for Grade II to IV aGVHD following failure or dependency on corticosteroid treatment; this equates to up to 60% of patients potentially requiring second-line treatment.[118]

There is no established treatment regimen for ECP. UK photopheresis guidelines recommend two or three cycles weekly for weeks one to four followed by twice weekly treatments for weeks four to eight.[49] After this point, treatment may be stopped if there is a complete response or lack of response. For patients with a partial response, or in those dependent on corticosteroids, treatment may be tapered slowly to one treatment cycle a month until cessation of treatment. Given the small patient numbers, and heterogeneity in treatment response and clinical practice, and the indefinite treatment duration, it is difficult to define the average number of cycles in clinical practice. In a recent phase III clinical trial in the UK sponsored by the device manufacturers, patients received ECP three times per week of treatment for weeks one to four followed by twice weekly treatment for weeks 5 to 12. Patients received an average of 21 cycles over the 12 weeks.[149]

Clinical opinion stated that between 2017 and 2021, two out of 17 (11.7%) patients with an IEI received ECP during the transplant abroad. In the absence of alternative data, this value was used for the proportion of patients who receive ECP for the other cohorts.

Data supplied from TAS indicated that at least two patients who received a HSCT abroad were later approved to return to England for additional ECP treatment. The approved treatment duration for these cases was 10 months and 4.5 months. Decisions to approve a patient for a treatment abroad are assessed on a case-by-case basis. The cost of this subsequent ECP in England for patients who return home is not included in the transplant price. During this period, patients would have resided in Ireland and travelled to the UK for each appointment. The frequency of appointments is not presented in the TAS and would not have been known at the time of analysis given its dependency on treatment response. The estimated cost of ECP treatment submitted to TAS for each of the two patients was very similar, at an average of £104,346 (€118,607). At the time of analysis, a claim had only been

received for one patient. The invoiced cost (£20,719, or €23,551) was substantially less than the estimated cost.

HSCT Abroad Scenario

In the TAS scenario, it is assumed that 11.7% of patients require ECP. The costs associated with ECP in the inpatient and outpatient phase are included in the cost of transplant. Therefore, no costs are included for this part of the model. It is assumed that 11.7% of patients in all cohorts return to UK for ECP treatment at a further cost of €23,550. In scenario analysis, the cost is increased to €118,607.

HSCT Repatriation Scenario.

As ECP is not included in the transplant price for patients receiving treatment in Ireland at any stage of the patient journey, the number of cycles must be calculated for the total duration of therapy. The mean number of cycles per patient (21.6) observed in the 12 week trial by Kitko et al. is assumed to be equivalent to the number of cycles received abroad.[149]

ECP is not provided in CHI at Crumlin at present. The cost per cycle in the UK has been previously estimated as £3,170 (2016 GBP) or £3,542 in 2021 GBP.[150] Therefore, it is assumed that the invoiced TAS data represented 5.85 cycles and the estimated TAS data for actual costs represented 29.4 cycles. These cycles are also included in the repatriation scenario.

The costs associated with ECP can be considered in terms of four components:

- capital costs associated with the purchase of the machine
- fixed costs associated with the maintenance of the machine
- costs associated with the consumables for each procedure
- healthcare and staff cost associated with each procedure.

The cost of the device and consumables for ECP was obtained from the list price of a 2019 quote obtained from CHI at Crumlin.[17] The cost of the device was recorded as an upfront investment. If a decision were made to repatriate the service, procurement and tendering may result in acquisition of the device at a lower cost. For patients receiving ECP as a day case, the healthcare cost was assumed to be equal to the cost of a day case in the unit.[110]

For patients receiving ECP treatment as an inpatient, the staff cost was assumed to be already included in the transplant cost. Based on the ECP treatment regimen and the average length of stay, 43% of cycles in the initial regimen 21.6 cycles were

assumed to be administered in the inpatient setting. The additional 5.85 cycles (29.4 in scenario analysis) were all assumed to take place in the outpatient setting.

The costs associated with ECP are uncertain given the numerous assumptions used to derive them and that the parameters are derived from very small patient numbers. As such, costs were not varied.

Table 5.8 Cost parameters for ECP

Variable	Cost	Distribution	Source
Repatriation Scenario: Fixed Costs			
Cost of ECP device	€102,813	Not varied	Personal Communication[17]
ECP Warranty Year 1	€12,852	Not varied	Personal Communication[17]
ECP Maintenance (applied annual Year 2 to 5)	€10,281	Not varied	Assumption. 10% of device
Repatriation Scenario: Variable Costs			
Cost of ECP kit (per cycle)	€1,349	Not varied	Personal Communication[17]
Cost of ECP administration (per cycle)	€1,238	Not varied	ABF Price list 2022. A day case Q60 B[110] Reticuloendothelial and Immunity Disorders, Major Complexity Not applied to 53% of initial treatment cycles as it is assumed to be captured in transplant inpatient price.
Cost of initial treatment (assume 21.5 cycles)	€44,428	Not varied	No. of cycles based on Kitko et al.[149]
Cost of additional treatment (assume 5.85 cycles)	€15,136	Not varied	Assumption based on TAS data and UK cost of ECP cycle.[150]
Proportion of patients who require ECP	11.7%	Not varied	Clinician analysis of IEI patient data. Assumed to apply to all cohorts.
TAS scenario			
Cost for initial cycles	Included in transplant price		
Cost of additional cycles	€23,551	Not varied	Assumption based on TAS invoice data and UK cost of ECP cycle.[150]
Scenario Analysis - Higher estimate scenario for additional ECP treatment			
Repatriation	€76,228	Not varied	No. of cycles based on estimated TAS cost and cost of UK treatment with Irish ECP cycle costs.
TAS	€118,607	Not varied	Estimated cost provided to TAS pre-treatment.

Key: ABF – activity based funding; CI – confidence interval; ECP – extracorporeal photopheresis; IEI - inborn errors of immunity; TAS – treatment abroad scheme.

5.2.5 Sensitivity and scenario analysis

One-way sensitivity analyses were performed whereby input parameters were varied and ranked in order of increasing influence on the budget impact. The result is presented as a 'tornado plot' which provides a visual representation of the sensitivity of the model to the uncertainty associated with individual parameters. Although all parameters with probability distributions assigned were varied in the analysis, only the five most influential parameters are presented.

Parameter uncertainty, relating to the imprecision of the model inputs, was assessed using probabilistic sensitivity analysis (PSA). PSA involves assigning statistical distributions to each of the input parameters and simultaneously drawing a random sample from the plausible range for each parameter. These random samples are drawn repeatedly in a Monte Carlo simulation (where the model was run 10,000 times) with different sets of inputs simulated.

Scenario analyses were conducted to further explore uncertainty in the model as it relates to specific scenarios. In each scenario, model assumptions were changed or a base case parameter was replaced with an alternative estimate.

5.2.6 Quality assurance

This BIA was developed in accordance with national HTA guidelines,[139] and was quality assured in accordance with the HTA quality assurance framework.

All model inputs and outputs were reviewed by a second member of the evaluation team. Input parameters and assumptions underpinning this BIA were reviewed and endorsed by the EAG.

5.3 Results

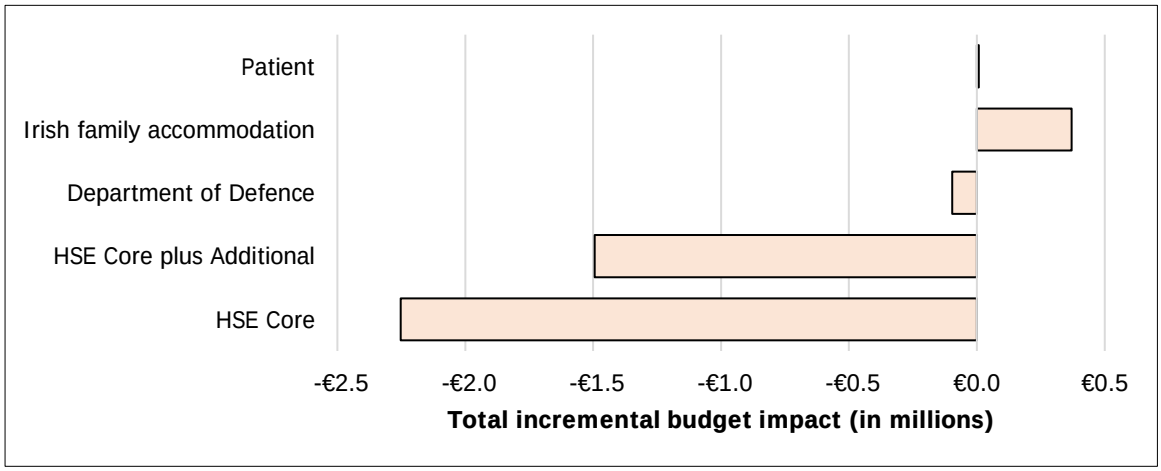
5.3.1 Total five-year incremental budget impact

Base case analysis

The incremental budget impact associated with repatriation was found to reduce costs from the perspectives of the HSE and the Department of Defence. From the perspective of the HSE, while subject to substantial uncertainty, the estimated five-year incremental budget impact is expected to result in cost reductions. These are expected to range between a reduction of €1.5 million (95% CI -€5.0m to +€1.9m) and a reduction of €2.3 million (95% CI -€5.8m to +€1.1m) over a five-year time horizon, depending on whether costs arising from ECP and procedures which aim to preserve fertility are included. From the perspective of the Department of Defence,

the reduction in cost was approximately €100,000 over a five-year time horizon. From the perspective of the Irish family accommodation provider, the five-year budget impact was approximately €370,000, while this figure was approximately €7,200 from the patient perspective. This is equivalent to an increased cost per family per transplant of approximately €120. The analysis does not take into account all patient costs due to patient heterogeneity. Further analysis on the patient perspective is provided in section 5.3.2. The five-year incremental budget impact by perspective is presented in Figure 5.1.

Figure 5.1 Five-year incremental budget impact, by analysis perspective



Note: 'HSE Core' reflects the incremental budget impact to the HSE excluding the cost of ECP and fertility-sparing treatments. 'HSE Core plus Additional' reflects the incremental budget impact to the HSE including these costs.

Disaggregated costs according to each perspective

Table 5.9 summarises the five-year incremental budget impact according to the main cost items under each perspective. Table 5.9 also presents the 95% confidence intervals of the incremental budget impact, as estimated in the probabilistic analysis.

From the perspective of the HSE, the majority of the reductions in costs were due to reduced transplant costs. However, these savings would be offset by additional costs relating to the potential adoption of ECP and procedures aimed at preserving fertility.

The costs of Air Corps travel and accommodation were the only costs included in the Department of Defence and Irish family accommodation provider perspectives. If HSCTs were to be repatriated to Ireland, the costs of Air Corps travel would be removed and therefore represent a saving for the Department of Defence.

From the patient perspective, the estimated costs included those of travel and family accommodation. If HSCTs were to be repatriated to Ireland, the travel costs would no longer be borne by patients and their families and would therefore represent a cost offset.

Table 5.9 Five-year incremental budget impact, by analysis perspective and cost items

Perspective	Cost items	Budget impact (95% CI)
HSE core	Pre-transplant	-€596,879 (-€906,296 to -€332,656)
	Transplant	-€2,351,324 (-€5,922,443 to €1,069,642)
	Post discharge	€711,618 (€350,911 to €1,161,521)
	Travel	-€30,826 (-€51,645 to -€15,484)
	Total (Excluding ECP and fertility-related procedures)	**-€2,267,411 (-€5,796,879 to €1,129,105)**
HSE core plus ECP and fertility-related procedures	ECP (current)	€299,899 (€84,228 to €736,650)
	ECP capital	€102,962 (€83,237 to €124,762)
	Fertility-related procedures	€355,392 (€224,191 to €497,615)
	Total additional costs	€758,254 (€460,861 to €1,251,158)
	Total HSE (core plus ECP and fertility-related procedures)	**-€1,509,157 (-€4,967,651 to €1,946,360)**
Department of Defence	Air Corps travel	-€96,890 (-€202,614 to -€20,975)
Irish Family Accommodation Provider	Accommodation	€369,087 (€146,355 to €617,867)
Patient	Travel	-€29,079 (-€47,972 to -€15,426)
	Family accommodation	€36,240 (€20,758 to €52,799)
	Total (patient)	**€7,161 (-€8,144 to €22,103)**

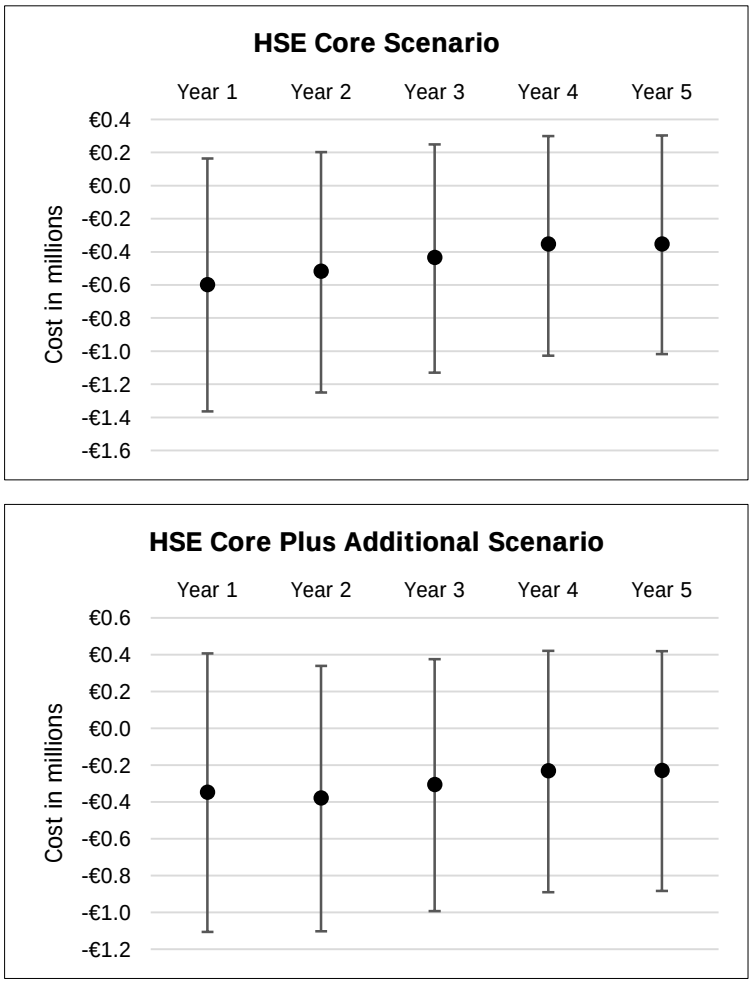
Key: CI – confidence interval; ECP extracorporeal photopheresis; HSE – Health Service Executive**.**

Annual budget impact by perspective

HSE perspective

From the HSE core perspective, the annual reduction in costs ranged between €355,000 and €600,000. When including potential costs in relation to the adoption of ECP and procedures aimed at preserving fertility, the annual reduction in costs ranged between €230,000 and €382,000. The annual estimates are presented in Figure 5.2.

Figure 5.2 Annual incremental budget impact from HSE perspective



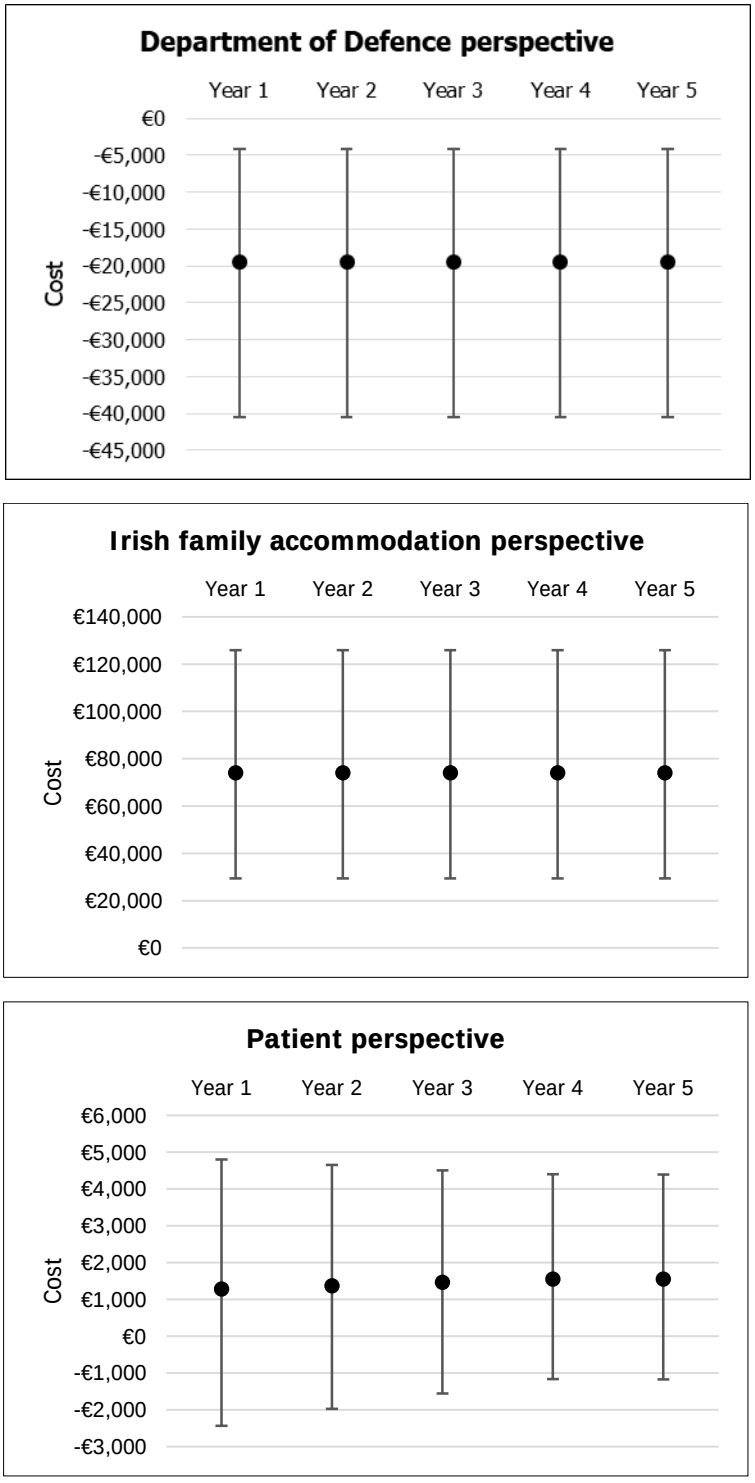
Note: The error bars represent the 95% confidence intervals estimated in the probabilistic analysis.

Note: 'HSE Core' reflects the incremental budget impact to the HSE excluding the cost of ECP and fertility-sparing treatments. 'HSE Core plus Additional' reflects the incremental budget impact to the HSE including these costs.

Department of Defence, Irish family accommodation provider and patient perspectives

From the perspective of the Department of Defence, the annual reduction in costs was consistently €19,000 year on year. From the Irish family accommodation provider perspective, the annual incremental budget impact was consistently €74,000 year on year. From the patient perspective, the annual incremental budget impact was between €1200 and €1550 each year. This is equivalent to a cost per family of around €120. The annual estimates for each of these perspectives are presented in Figure 5.3.

Figure 5.3 Annual incremental budget impact from Department of Defence, Irish family accommodation provider and patient perspectives



Note: Error bars represent the 95% confidence intervals estimated in the probabilistic analysis.

One-way sensitivity analysis

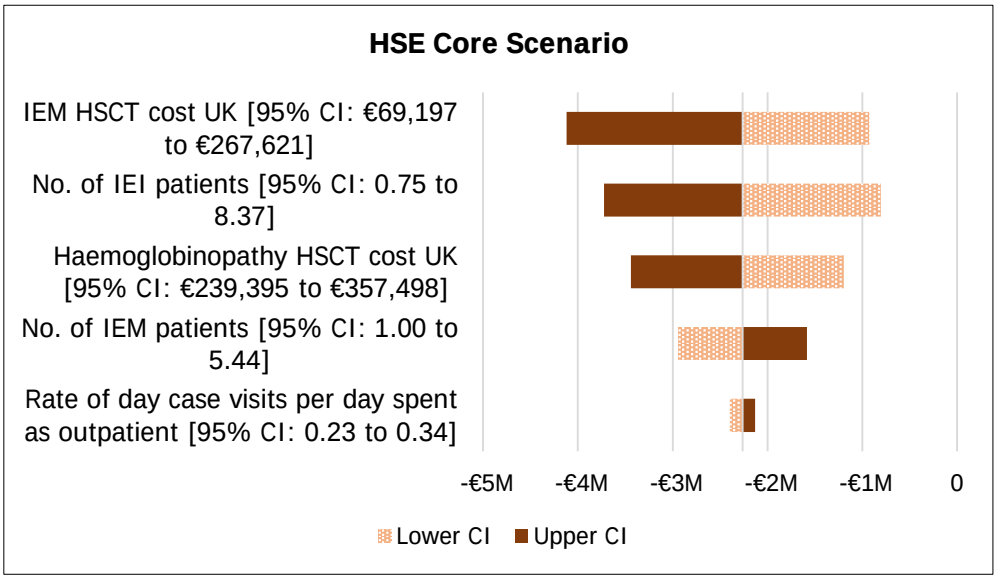
HSE perspective

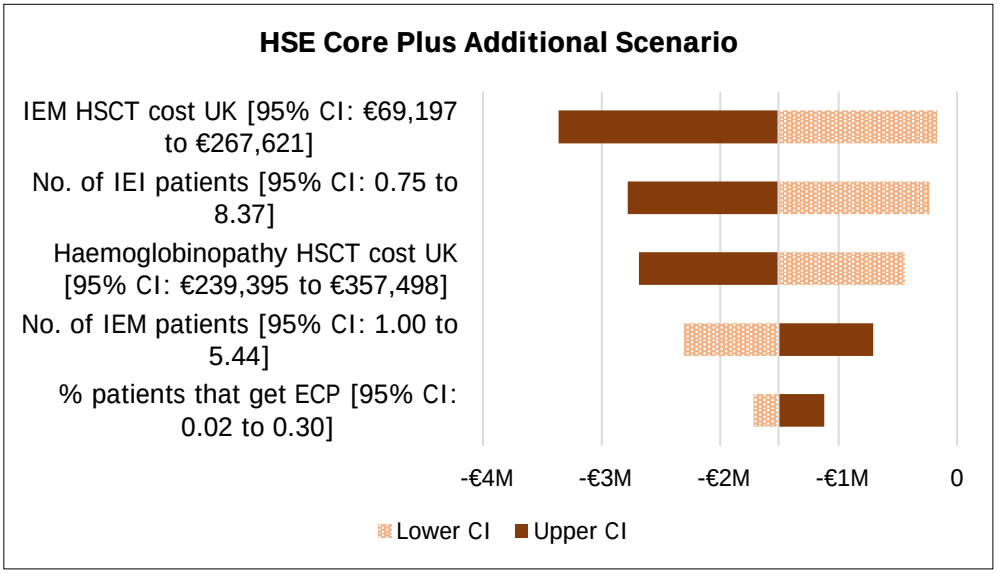
From the HSE core perspective, the input parameters that, when set at their lower and upper bounds, had the largest impact on the five-year incremental budget impact were the:

- cost of HSCT for IEM patients in the UK
- number of IEI patients
- cost of HSCT for haemoglobinopathy patients in the UK
- number of IEM patients
- day case rate (applied in Ireland and the UK).

When these parameters were set at their lower and upper bounds the five-year incremental budget impact percentage variation ranged between 6% and 141%. When the costs of ECP and procedures aimed at preserving fertility were considered, the top four parameters that had the largest impact remained the same, but the percentage of patients receiving ECP replaced the day case rate as the parameter that had the fifth highest impact. Under this perspective, the five-year incremental budget impact percentage variation ranged between 13% and 151%. These results are summarised in Figure 5.4.

Figure 5.4 One-way sensitivity analysis of budget impact from HSE perspective





Key: CI – confidence interval; ECP extracorporeal photopheresis; HSCT – haematopoietic stem cell transplantation; HSE – Health Service Executive; IEI - inborn errors of immunity; IEM – inborn errors of metabolism; no – number.

Note: For legibility, only the five parameters that, when set at their lower and upper bounds, resulted in the largest change in the estimated budget impact are presented.

Note: 'HSE Core' Scenario reflects the incremental budget impact to the HSE excluding the cost of ECP and fertility-sparing treatments. 'HSE Core plus Additional Scenario reflects the incremental budget impact to the HSE including these costs.

Department of Defence, Irish family accommodation provider and patient perspectives

From the Department of Defence perspective, the input parameters that, when set at their lower and upper bounds, had the largest impact on the five-year incremental budget impact were the:

- number of IEM patients
- cost of Air Corps travel for IEI patients
- proportion of IEI patients that require Air Corps transport from the UK
- proportion of IEI patients that require Air Corps transport to the UK
- number of IEI patients.

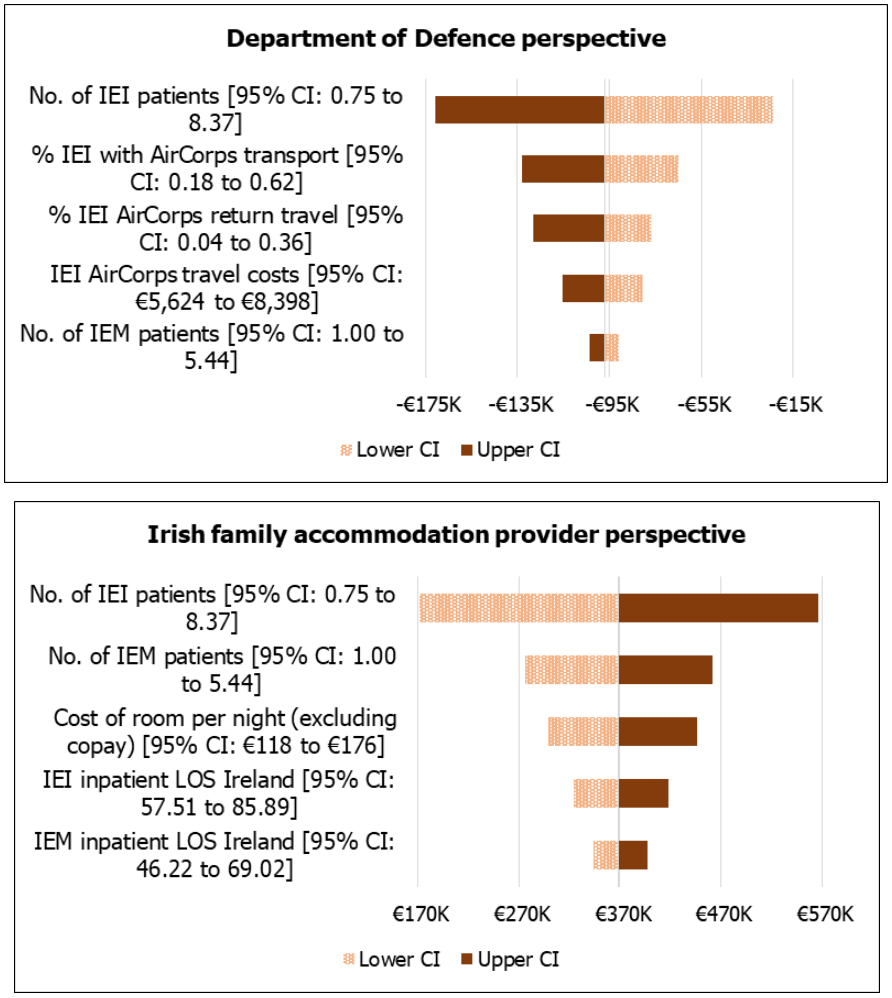
When these parameters were set at their lower and upper bounds the five-year incremental budget impact varied between 13% and 151% (see Figure 5.5).

From the Irish family accommodation provider perspective, the input parameters that, when set at their lower and upper bounds, had the largest impact on the five-year incremental budget impact were the:

- length of stay in inpatient care in Ireland for IEM patients
- length of stay in inpatient care in Ireland for IEI patients
- cost per night of accommodation (excluding co-payment)
- number of IEM patients
- number of IEI patients.

When these parameters were set at their lower and upper bounds the five-year incremental budget impact varied between 14% and 107% (see Figure 5.5).

Figure 5.5 One-way sensitivity analysis of budget impact from Department of Defence and Irish family accommodation provider perspectives



Key: CI – confidence interval; IEI - inborn errors of immunity; IEM – inborn errors of metabolism; LOS – length of stay; No. – number.

Note: For legibility, only the five parameters that, when set at their lower and upper bounds, resulted in the largest change in the estimated budget impact are presented.

Scenario Analyses

Scenario analyses were conducted to examine the impact of alternative parameters on the incremental budget impact. The results are shown in Table 5.10 below. None of the scenarios examined influenced the budget impact under the Irish family accommodation provider, patient perspective or the Department of Defence perspective. Therefore, these perspectives are not presented below.

Conversion of GBP to Irish Euro based on Purchasing Power Parity (PPP)

Treating hospitals abroad invoice the TAS section of the HSE in GBP sterling. Therefore, currency fluctuations will influence the cost to the HSE. In this HTA, prices are presented in 2021 Irish Euro. The purchasing power parity for that year (£1 = €1.14) represents the strongest PPP for the Irish Euro over the past 10 years. As it may not be reflective of future years, an alternative value of £1 = €1.20 was examined in scenario analysis which represents the weakest PPP for the Irish Euro during this time period. In this scenario, the weaker Euro increases the cost of transplants abroad which increases the potential savings associated with repatriation. This would translate into a reduction in costs of €3.1 million over five years instead of €2.3million (or €2.4 million instead of €1.5 million when costs of ECP and fertility-sparing treatments are included).

Variation in costs associated with ECP and procedures aimed at preserving fertility

Increasing the number of additional ECP cycles reduces the incremental budget impact, as, under the model assumptions, ECP is less expensive in Ireland. However, these assumptions are based on limited data and may not be borne out in practice. Incorporating the cost of 30 years of gamete and gonadal tissue storage increases the cost by €95,000 under the model assumptions.

Table 5.10 Five-year incremental budget impact for scenario analyses

			HSE Core			HSE Core plus additional		
Scenario	Base case value	Scenario Value	5 year Incremental Budget Impact	Absolute Change	% change	5 year Incremental Budget Impact	Absolute Change	% change
Base-case			-€2,263,534			-€1,506,063		
£ to € PPP	€1.14	€1.20	-€3,146,987	-€883,45	-39	-€2,398,706	-€892,643	-59
Cost of additional ECP cycles	TAS lower bound	TAS Upper bound	N/A	N/A	N/A	-€1,737,422	-€231,359	-15
Cost of gonadal tissue and gamete storage	Five year costs only	30 year cost in year 1	N/A	N/A	N/A	-€1,411,234	€94,829	+6

Key: HSE - Health Service Executive; ECP - extracorporeal photopheresis, TAS – treatment abroad scheme.

Note: 'HSE Core' reflects the incremental budget impact to the HSE excluding the cost of ECP and fertility-sparing treatments. 'HSE Core plus Additional' reflects the incremental budget impact to the HSE including these costs.

In the budget impact model, the mean cost of an allogeneic HSCT in Ireland is assumed to be €215,162. This is the inlier price paid by the HSE to CHI for each transplant. However, if a transplant stay is longer than 69 days, additional payments of €4,435 per day are paid to the hospital to account for the additional resource use. Incorporation of these additional payments for extended length of stay increases the mean cost of a transplant. To account for this, a threshold analysis was undertaken to estimate the maximum mean cost of a HSCT for the budget impact to be neutral (that is, the cost of repatriated service would be the same as the cost of care through the TAS assuming all other factors remain unchanged). The estimated maximum mean cost at which the budget impact would be neutral was €254,256; if the additional costs associated with provision of ECP and fertility-sparing treatments are included, the maximum mean cost was estimated at €241,173 for the HSE core perspective and the HSE core and additional perspective, respectively.

5.3.2 Vignettes illustrating the financial impact of treatment abroad on patients and their families

Two vignettes are presented below which illustrate the potential financial stress that travelling abroad for treatment may place on an individual family. In both vignettes, the family circumstances of a fictional family are first described. While the families are fictional, the types of financial challenges documented have been described to the review team as lived experiences by families who have travelled abroad for treatment and by medical social workers who assist such families.

Regardless of where a transplant takes places, significant costs are incurred by families. These include the cost of travel for hospital appointments, additional childcare costs, additional costs relating to sustenance while attending the hospital setting, and wages foregone. In the tables below, only the costs specifically attributable to travelling abroad for treatment are described. However, the financial impact associated with treatment abroad should be considered in the context of wider financial challenges that may be faced by families.

5.3.2.1 Vignette 1: Claudia

Anne and Barry's daughter, Claudia, (age 6 months) has just been diagnosed with a genetic condition and requires an allogeneic HSCT. They have two other daughters, Danielle (age 6) and Emily (age 2). Their eldest daughter Danielle is a suitable graft donor for Claudia.

Family circumstances: Anne and Barry live in Meath. Anne's parents, Frances and Greg, are pensioners. They live close by and sometimes help out with childcare.

Baseline Financial circumstances: Anne is on maternity leave from her job. She was planning to go back to work soon but has chosen not to return at this time in order to care for Claudia and her other children. Barry is unemployed and receives Job Seeker's Allowance.

Decision: Anne and Barry both wish to travel to Manchester with Claudia (the transplant recipient) and Danielle (the donor). Anne's mother, Frances, will also travel with them so that she can return home with Danielle once she has recovered from the stem cell donation procedure. Frances and Greg will care for Claudia's siblings while their parents are in Manchester. They want Danielle to return to school as soon as possible given she already missed so much school as a result of COVID-19.

Before they go, their medical social worker advises them to apply for the Domiciliary Care Allowance and for Carer's Allowance for Anne. If they were receiving a transplant in Ireland, these supports would also be available. The medical social worker also applies to a charity on their behalf seeking financial assistance given their circumstances. They receive a donation from a charity of approximately €1,400 to help with their situation. No family member currently has passports.

Table 5.11 Vignette 1: costs incurred by family due to treatment abroad

Item	Expenditure/lost income associated with treatment abroad	Expenditure under a repatriated service	Notes
Two adult passports and three child passports	€210		
Return ferry journey to Manchester	€400		Cost of ferry is reimbursed by TAS.
Cost of personal car journey from Holyhead to Manchester	€84		Not eligible for reimbursement from TAS.
Return flight home for grandparent and donor	€200		While they are entitled to claim back the cost of travel for the donor and travelling companion as the child is under 18, the family is unaware that this is possible and they therefore incur the cost themselves.
Transplant recipient remains in hospital for 57 days. One parent stays on the ward throughout this time. Another stays in hospital-affiliated family accommodation close to the hospital. There is no charge for this. However, the accommodation was unavailable for the first two nights in Manchester so the family paid for a hotel.	€200	€570	In Ireland, for corresponding family accommodation needs, there is a €10 co-pay per night for accommodation.
The transplant recipient's father's Job Seeker's Allowance is stopped unexpectedly for the duration of the time abroad as the father is unavailable for work. With three children, this represents a loss of at least €288 per week for the duration of the time abroad.	€2,624		
The family needs to purchase more clothes for the infant undergoing the transplant as the baby has grown while they have been away. They have	€50		

Item	Expenditure/lost income associated with treatment abroad	Expenditure under a repatriated service	Notes
spare clothes at home, but they must buy new clothes in Manchester.			
The transplant recipient's grandparent brings the child's two siblings to visit their sister and parents; two visits are made over the eight weeks.	Flights €450 (three people x 2 trips). Accommodation €400 (€200 per night).		
Cost of driving from Manchester to the ferry port at Holyhead, to take the ferry back to Ireland once treatment has concluded.	€84		
Total Costs	€4,702	€570	
Costs reimbursed by TAS	(€400)		Cost of international travel is reimbursed by TAS.
Total	€4,302	€570	
Excess expenditure associated with treatment abroad	€3,732		

Key: CI – confidence interval, TAS – treatment abroad scheme.

Variability in costs as listed in Vignette 1

It is important to note that in the example above, it is assumed that the payment of Job Seeker's Allowance was stopped while abroad and was not replaced with another alternative form of allowance. Medical social workers stated that, in some cases, this payment has been replaced with Supplementary Welfare Allowance for affected families; however, this experience has been very variable and requires the family to make an application after the Jobseeker's Allowance has been stopped. Furthermore, payment of Supplementary Welfare Allowance is based on the family's individual circumstances and is at the discretion of the community welfare officer, with strict income limits applied. Therefore, as it is not paid in all circumstances, we have not included the payment of Supplementary Welfare Allowance in this vignette. Regardless of whether or not this payment is made, if the Job Seeker's Allowance is cancelled in this way, the family's income would be significantly disrupted at what is likely to be a challenging time.

It is expected that some charitable support may also be received if the transplant were conducted in Ireland. The additional charitable support available to families going abroad is unclear.

5.3.2.2 Vignette 2: Heather

Heather is 11 years old and needs a transplant to treat her genetic condition.

Family Circumstances: Heather lives in Clonmel with her brother Luke (age 5) and parents, Mary and Nathan. They have no family members nearby who can assist with childcare.

Financial Circumstances: Mary has a part-time role and Nathan works full-time.

Decision. Mary takes parental leave from her role to be with Heather during her transplant. Nathan decides to stay at home in Ireland to care for Luke and so that he can stay in employment to reduce the financial stress on the family. While Mary is away, Nathan takes the equivalent of one day of parental leave for each week that Mary and Heather are abroad in order to care for Luke.

The family did not receive a charitable grant to help with the costs of transplant. The family already had passports.

Table 5.13 Vignette 2: costs incurred by family due to treatment abroad

Item	Additional expenditure under TAS	Additional Expenditure if repatriated.
Flight	Reimbursed by TAS: €147 Not reimbursed by TAS €64: ■ Airline baggage fees for 2 x 10kg bags each way: €52[151] ■ Reserved seats: €12*[151]	
Flight 2	Reimbursed by TAS: €387 Not reimbursed by TAS: €100: ■ Airline baggage fees for 2 x 20 kg bags each way: €88 ■ Reserved seats: €12	
Taxi from airport to Newcastle hospital x2	€41x 2 = €82	
For the duration of the inpatient stay (71 days), Mary stays with Heather in the patient's hospital room. For the duration of the outpatient stay abroad (46 days) they stay in an apartment arranged by the hospital. There is no cost to the family associated with this.	No charge.	Co-pay of €10 per night for in-patient stay = €710
Excess Parental leave If the service were repatriated, Mary would be available at home to care for Luke during the outpatient phase and Nathan would not need to take as much parental leave. Nathan would still have to take some parental leave as Mary would still have to take Heather to outpatient appointments in Dublin. It is assumed that Nathan will take 0.5 days parental leave per week for these 6.5 weeks.	€871.62 average weekly wages = 87.16 per 0.5 days x 6.5 weeks = €566[152]	

Item	Additional expenditure under TAS	Additional Expenditure if repatriated.
For the four months that they are away, Nathan and Luke visit every second weekend. For half of the visits, they stay in family accommodation provided by the hospital free of charge. For the other half, they pay for accommodation themselves.	Flight for Adult and Child 147 x 7 = €3,087 Accommodation for adult and child for three nights x 4 times = €150 x 44 = €600**[153]	
Excess sustenance and travel. 46 days as outpatient in Newcastle would be spent at home if the service were repatriated to Ireland. However, the family would have to travel to Dublin for outpatient appointments (Estimated average of 2 visits per week).	Assume 33 days extra days sustenance required compared to repatriation scenario = €990	If repatriated – families incur cost of driving to Dublin for hospital appointments. 334km x 43.4 cent = €145 per return trip 13.14 trips required x €145 = €1,905
Total	€5,573	€2,615
Reimbursed by TAS	€534	
Total patient	€5,039	€2,615
Excess expenditure associated with treatment abroad	€2,424	

Key: CI – confidence interval, TAS – treatment abroad scheme.

* Have to pay for one reserved seat if an adult is with a child so that they can sit together.

** Off peak weekend costs.

5.3 Discussion

This chapter aimed to assess the financial consequences of providing HSCT in Ireland for the additional indications of IEM, IEI and haemoglobinopathies for which treatment is currently provided abroad. The BIA was calculated from the point from pre-transplant until the point at which the transplant recipient and family would return to Ireland and require no further visit abroad. Only aspects of the service that are expected to change in a repatriated service are included. Therefore, the figures presented here should not be taken to represent the full cost of care.

The target population for this model is paediatric patients with IEM, IEI, or haemoglobinopathies for whom a HSCT has been indicated. The BIA estimated the incremental cost associated with the repatriation of paediatric HSCT to Ireland over a five-year time horizon relative to accessing treatment abroad through the TAS. Repatriation of the HSCT service would involve a change in the cost of providing HSCT to the HSE, but also a shift in some of the financial burden between different stakeholders. Therefore, the budget impact was considered under multiple perspectives, including; the HSE, the Department of Defence, charities providing family accommodation in Dublin and the patient perspective. Two types of analyses were considered under the patient perspective; (1) the minimum travel and accommodation costs that would directly change under repatriation, and which are independent of a family's personal financial and social circumstances, were quantified using standard methods, and (2) two vignettes have been provided which describe the potential impact of repatriation on the financial circumstances of hypothetical families. Descriptions are hypothesised from interviews with healthcare professionals and patients' family members.

For the base case analysis, the five-year incremental budget impact of repatriating HSCT services was found to result in lower costs from the perspective of the HSE. The projected reduction in costs to the HSE were mostly driven by the reduction in transplant costs. Such cost reductions would be offset by additional costs relating to the potential adoption of ECP and procedures aimed at preserving fertility. Repatriation would also reduce costs for the Department of Defence as the need for air ambulance transfer to the UK would be removed.

The budget impact analysis was subject to substantial uncertainty. One-way sensitivity analysis showed that the incremental budget impact was sensitive to changes in the numbers of IEM and IEI patients undergoing HSCT as well as the estimated cost of the HSCT procedure for these patients in the UK. When these parameters were set at their lower and upper bounds, the five-year incremental budget impact varied between 6% and 141%. The interpretation of the cost of HSCT

through the TAS must be also considered in the context of currency fluctuations: even if the cost per HSCT by the NHS is fixed, currency fluctuations will impact the actual cost to the HSE. There were no costing data available for the new treatment pathway for patients with haemoglobinopathies. Therefore, it was assumed to be the same as the cost for IEI patients undergoing HSCT in the UK. The incremental budget impact remained cost neutral when the cost of HSCT in the UK was reduced by 20%.

The BIA highlights potential issues associated with requirements for family accommodation; while all families require access to accommodation for the duration of the transplant episode when HSCT is provided through the TAS, if services are repatriated, this requirement may only apply to families that do not live within easy commuting distance of CHI. If provided through the hospital, this accommodation is heavily subsidised and is largely reliant on the charitable sector for its provision with no government financing. As outlined in their 2021 statement of accounts, the Ronald McDonald House charity does not normally receive government funding, the exception being COVID-19 supports.[145] The provision of family accommodation for this cohort of families is likely to represent an opportunity cost rather than an accounting cost given that no increase in the number of family accommodation rooms beyond that planned in the national children's hospital is expected.

Under the patient perspective, the estimated additional cost per family associated with repatriation is €120. The patient perspective in the formal budget impact analysis is limited as it only considers the costs associated with the minimum level of transport and accommodation required. While patients may claim the cost of this travel from TAS, many patients do not.

In a repatriated scenario, a patient co-pay per family per night of €10 was assumed for any accommodation that would be provided. While the cost of accommodation is heavily subsidised, the long stay associated with transplant mean that cumulative costs can represent a significant burden for some families. Co-pays may be waived or patients may receive social welfare allowances to help with these costs. The formal BIA does not capture the total impact of going abroad for treatment on a family's financial situation. Two vignettes were developed from interview data and describe the potential impact of repatriation on the financial circumstances of hypothetical families. These outline the range of costs to which families may be exposed both in the context of treatment abroad and if care is repatriated. Consistent with other chronic conditions that require extensive hospital care, families may be exposed to substantial out-of-pocket costs irrespective of where care is provided. However, it is noted that extended stay abroad, as necessitated when HSCT is provided through the TAS, poses particular challenges in relation to the

payment of Job Seekers Allowance and may contribute to a reduction in income for those who are employed due to additional leave requirements. The latter may be less likely to arise if care were to be repatriated.

This BIA is an analysis of the best available data on the costs associated with the repatriation of HSCT for IEM, IEI and haemoglobinopathies. Data availability was particularly challenging for this small group of patients; to bridge some of the gaps, HIQA undertook a comprehensive series of interviews with health system staff and the parents of children who had accessed the TAS for HSCT. Multiple data sources were also pursued within the health system including the TAS at HSE and the children's hospitals. However, important limitations exist in relation to the currently available data and the findings of the BIA must be interpreted in that context.

Further, for the cost of transplant the inlier ABF price list price was used in the base case analysis. However, ABF prices for specialist paediatric hospitals including Crumlin are adjusted to account for the fact that the cost of treating patients in a specialist paediatric hospital tends to be higher than the cost of treating those same patients in a general hospital setting.[154] Further patients with lengths of stay significantly longer than average will also attract additional payments from the HSE. Scenario analysis indicated that repatriation remained cost saving from the HSE perspective provided the cost of transplant to the HSE is no more than 12% higher than the modelled ABF price. Given the small patient numbers, heterogeneity in treatment response and clinical practice, and the indefinite treatment duration, estimating parameters for the BIA was difficult and there is a large degree of uncertainty around the estimates.

Costs were estimated in the event that ECP and procedures aimed at preserving fertility are funded. However, if these procedures are made available for patients with IEI, IEM and haemoglobinopathies, this would contribute to inequities in the system as they are not routinely available within the public health system for other patients. Consideration of the clinical and cost effectiveness of these procedures or their feasibility was beyond the scope of this HTA. However it is noted that the budget impact would likely increase if there were to be wider application of these procedures.

To estimate the number of HSCT procedures, and the associated costs, analysis was conducted of anonymised claims data provided by the TAS section of the HSE, describing paediatric HSCT episodes of care abroad from 2012 to 2021. For some treatments, the invoiced cost of treatment may differ from the estimated cost of treatment at the time of application. To ensure the data were representative and to reduce the administrative burden on the HSE, more detailed cost data were

systematically provided for the years 2018 to 2020 only. As invoices are received in arrears, treatment costs were not available for every patient at the time of analysis. Therefore, the budget impact may be over or underestimated. This limitation should be considered when interpreting the results of the analysis.

For patients with an IEI, the proportion of patients who transfer and return to the UK by Air Corps was derived from a clinician analysis of patient records between 2017 and 2021. During this time period, travel by Air Corps may have been more frequent than usual because of travel disruptions due to COVID-19, leading to a potential overestimate of the costs. This therefore is a limitation of the present analysis.

5.4 Conclusions

The repatriation of HSCT services is likely to be cost neutral and may be cost saving for the HSE. A major limitation of the analysis is that, as patient numbers are low, many parameter estimates are derived from small patient numbers and clinical opinion, resulting in large uncertainty in the estimated BIA. While the extensive hospital care associated with transplant care would continue to impose a financial burden on many families, repatriation of HSCT services may ease some of this burden.

6 Patient and social considerations

Key points

- The patient and social considerations associated with the repatriation of HSCT services to Ireland were informed by meetings with parents, clinicians, specialist nurses, and medical social workers. The key considerations identified are summarised in the following points.
- The transplant journey is a period of substantial stress and uncertainty for patients, parents and families, irrespective of the requirement to travel abroad.
- The additional burden that travelling abroad places on families is multifaceted:
    - Parents need to manage a significant administrative and logistical burden arising from the need to travel abroad.
    - There is a considerable financial burden placed on families due to incurring up-front costs and living expenses while abroad. In addition, there may be a disruption to or a reduction in family income given the requirement for a parent to travel abroad with the child for an extended duration. This may exacerbate the financial burden, although the impact of this will vary depending on the individual circumstance of each family.
    - The experience of living abroad for between two and six months, separated from family, can be an isolating and an emotionally burdensome experience for parents.
- In Ireland, family-centred integrated care is a core consideration of the national model of care for paediatric healthcare services. Currently, the separate delivery of care across the two healthcare jurisdictions of Ireland and the UK may make it challenging for Children's Health Ireland to ensure that continuity of family-centred care to the patient, parents and siblings is provided. The current separation of siblings and other family members can be very difficult for families. Repatriation of HSCT services may improve the delivery of family-centred care for those receiving these services.
- The repatriation of HSCT services to Ireland may allow greater scope for the immediate and wider family to provide support to the patient and primary caregiver. This may help reduce the emotional impact on families during this time.
- Although repatriation would not eliminate the financial burden arising from the treatment pathway, there would be a reduction in the up-front costs that families are required to pay, which may reduce reliance on charitable sources of funding and offer families more control over their financial resources.

- Certain minority or ethnic groups may find the burden of travelling abroad to access HSCT services additionally challenging, beyond that of the general population. Issues such as financial insecurity, language, literacy or numeracy difficulties, and cultural values may mean that they are disproportionately impacted by challenges associated with travelling abroad to access transplant services.
- Extracorporeal photopheresis for the treatment of graft-versus-host disease and procedures aimed at preserving fertility in children undergoing HSCT services are not currently available within the publicly funded healthcare system in Ireland. There was an expressed desire from some parents and healthcare professionals that patients be given the opportunity to access procedures aimed at the preservation of fertility. It is important that appropriate information is provided to parents in relation to the indications for these procedures, and their associated benefits and risks. Consideration should be given to the potential impact of the change in availability of these services to Irish patients if HSCT is repatriated to Ireland, and the acceptability of such changes for patients and families.

6.1 Introduction

Regardless of where a haematopoietic stem cell transplant (HSCT) takes place, it is a challenging and stressful experience for the patient and their family. The aim of this chapter is to look at the additional burden that undergoing a transplant abroad places on families compared to undergoing a transplant in Ireland. Understanding the stresses associated with a transplant is an important element of this.

This chapter was structured broadly in line with the guidance described in the European Network of HTA (EUnetHTA) Core Model.[100] The focus here is on patients and their families who have travelled abroad to receive a transplant and the additional burden that travelling abroad placed on them. This chapter has been informed by interviews with parents, clinicians, specialist nurses, and medical social workers. The parents and family members were drawn from a convenience rather than a representative sample. Parents were provided with a plain English information leaflet prior to consenting to participate in the process. Informed consent was given by each individual prior to participating in the interview.

It is recognised that a child in need of a transplant will be in the care of one or both parents or guardians. For simplicity, we refer to parents in the subsequent text, but this can be interpreted as guardians.

6.2 Practical considerations of transplant

There are several practical considerations that require action prior to, during, and after the patient undergoes transplant. The following sections outline and describe the practical aspects of availing of transplant as experienced by families of children undergoing HSCT.

6.2.1 Administrative burden and transport

The administrative burden relates primarily to the documentation that is required prior to travel or prior to reimbursement. This documentation can be wide-ranging and the workload can vary from family to family depending on individual circumstances and need. Where required, the parents of paediatric patients can receive considerable support from medical social workers.

The administrative tasks that need to be completed prior to travelling abroad for transplant can include applications for: a medical card; a passport; a visa for non-Irish nationals; the Health Service Executive's (HSE's) Treatment Abroad Scheme (TAS) application form; relevant welfare supports; financial aid from charities; and accommodation services in the country where the transplant will be taking place.

The administrative burden associated with reimbursement of expenses includes keeping track of and providing receipts and proof of purchase for travel costs incurred by parents, but covered under the TAS.

There are numerous reasons why these administrative tasks may be particularly challenging. Urgent cases with short notice of a transplant can create significant time pressure for parents and medical social workers to have the applications for financial support from charities, and the Department of Social Protection processed as quickly as possible. In some cases, the parents of patients may not have passports, so passport applications may need to be processed for both the parent(s) and the patient. Additional challenges may arise in the case of patients and or family members who are non-nationals, particularly for those in whom visa status in Ireland has not been regularised, for example, undocumented migrants. Parents who do not hold Irish passports may require a visa from the Department of Foreign Affairs to enable them to travel abroad with the patient requiring a transplant. Similar visa or passport requirements may need to be arranged for siblings, in the event of a sibling acting as a donor for a patient.

It is also important that families receiving social welfare payments are made aware of what alternative payments are available to them before they travel abroad. Certain social welfare payments are stopped when the recipient leaves the country. As such, there is an urgency associated with informing families of additional welfare supports that may be relevant, such as Domiciliary Care Allowance, carer's leave and additional needs payment supports. Moreover, families may be dependent on financial support from charities to cover upfront costs incurred prior to travelling abroad. The medical social workers typically put the families in touch with relevant charities and assist them with the application for such supports. The day-to-day role of medical social workers includes providing emotional support to parents and helping with administrative tasks. Depending on the context, the role of medical social workers may extend to carrying out a substantial portion of these applications on behalf of the families, leaving limited time available for the emotional support aspect of their role.

Applications require interacting with a variety of government departments, agencies and organisations. Navigating the system and successfully completing the various required forms can be challenging. The parents of patients may experience literacy, numeracy or language issues, presenting barriers to understanding and managing this administrative workload. Such issues may also result in difficulties for parents being aware of and accessing appropriate public or private sources of support available to them. For parents with one or more of these difficulties, medical social workers may need to spend additional time with them to provide reassurance and

communicate the necessary steps required. In cases requiring urgency, there may be limited opportunity to provide this support.

There are also considerable practical considerations that families must deal with when it comes to travelling abroad, beyond the administrative burden outlined above. These considerations mostly relate to the mode of transportation and to booking accommodation abroad. It should be emphasised that transplant candidates must be free of infection at the time of transplant. Modes of travel that involve mixing with large numbers of people increase the risk of exposure to infection and, as a consequence, the potential for transplant cancellation. There are typically three means of travel from Ireland to the UK used by families when travelling abroad for transplantation: commercial ferry, commercial airline, and travel by Air Corps or air ambulance. The latter option is usually reserved for emergency cases in need of urgent travel.

It should be emphasised that the circumstances of parents during this time are extremely stressful, irrespective of the travel requirement. Therefore, concerns associated with the factors outlined in this section are in addition to the existing burden of stress and anxiety experienced by families as they navigate how to manage and care for their child. Commercial travel by air or sea presents challenging issues for families to manage. Families can be informed of the provisional date of transplant several weeks in advance, but are often advised to wait until close to this date before booking their tickets to travel as the date of transplant may change. Consequently, the tickets to travel will often be more expensive, since they are booked very close to the date of travel. Although covered under the TAS, this upfront cost can be a significant financial burden for families. Meanwhile, the potential for the date of transplant to be cancelled and rearranged with little notice can add to existing levels of uncertainty or stress.

Commercial air travel presents specific difficulties and inconveniences for families. Airports are typically densely crowded locations where individuals spend substantial periods in close proximity to one another. This can be a source of significant stress and concern for parents, since during this time they will have been informed about ensuring infection prevention and control (IPC) practices in the home environment to minimise the risk of their child having an infection. Travelling by commercial air travel can lead to parents feeling that their child is vulnerable and exposed to infection risk. These concerns were accentuated during the SARS-CoV-2 pandemic. A concern specific to air travel is the baggage limitations imposed on passengers. Treatment abroad necessitates living in another country for a number of months and having access to the associated belongings required for day-to-day life. Parents can opt to pay additional fees for increased baggage allowances, but these costs are not

reimbursed by TAS. Likewise, priority boarding and access to less crowded waiting areas are not covered. These types of obstacles can prompt families to decide to take their car and travel to the UK by ferry. In travelling by car, they can bring additional luggage, such as clothes, toiletries, personal belongings, and food. During the SARS-CoV-2 pandemic, some parents preferred to travel by ferry and car to minimise close contacts with others while travelling. Bringing a car abroad can present other issues, such as the additional costs of running and parking the car, managing the experience of driving in a different country, and the potential need to service or repair the car while abroad.

Accommodation services need to be organised and booked before travelling abroad. Medical social workers assist families in securing accommodation for the duration of their stay abroad by linking in with the accepting hospitals for hospital-affiliated accommodation and relevant charitable organisations known to provide local accommodation to families availing of these medical services. However, sometimes families must travel abroad at short notice and this can lead to a delay between when the family arrives abroad and when such accommodation is available. In these cases, families may have to book into temporary accommodation, such as a hotel. When this happens, it presents an additional upfront cost incurred by the family, as well as added anxiety. With respect to booking accommodation services and flights to other countries, it must be recognised that some parents may have little or no previous experience of foreign travel.

6.2.2 Living abroad

The experience of living abroad for the parent and patient is typically divided into two stages; an inpatient period on the hospital ward and an outpatient period. The total time spent abroad can vary from patient to patient, depending on the success of stem cell engraftment and whether the patient experiences complications during or following the transplant procedure. As per chapter 4 (table 4.1) the inpatient period typically lasts approximately two months, and the outpatient period a further six weeks, bringing the total time abroad for the parent and patient to approximately 16 weeks.

Living abroad during this period of time can be difficult for families. Under the TAS, international transport costs for two parents are now covered financially The extent to which both parents can travel abroad and stay for the duration of the inpatient and outpatient periods of care is dependent on various factors, including whether the parents have other children to care for, the financial situation of the parents, and considerations regarding their employment and leave allowances. These factors can limit the ability of both parents to travel abroad for the duration, with one parent

typically travelling abroad and staying with the patient for the duration and the other parent limited to occasional visits. As a result, family members are separated for extended periods of time.

During the inpatient phase, at least one parent can typically stay on the ward with the patient for the duration of their stay. The expected facilities available to parents and patients during this phase can include access to a microwave, fridge, utensils, a shelf and locker. The parent and patient can also have their laundry done on the ward. There are additional services to support the parent and patient, such as play teams that may come in and engage with the patient for an hour each weekday. This service, and the proximity to health care workers on the ward, can make it easier for parents to take a break and leave the patient for enough time to go to a nearby shop or make a phone call. For many parents in this situation, phone and video calls are the main form of communication with their family in Ireland during their time abroad.

During the outpatient phase, the parent and patient live in temporary accommodation organised by the hospital or charitable organisation for approximately six weeks, visiting the hospital for appointments two to three times each week. Depending on the specific accommodation available, the facilities may include a small kitchen, sitting room, double room and en-suite. The cost of accommodation and local transport is typically covered as part of their care package provided by the treating hospital and not paid for by the parent.

Managing meals tends to be challenging for parents during both the inpatient and the outpatient phase, as there may be limited grocery shopping options near to the hospital and or accommodation, and limited facilities for cooking. A parent may not be able or willing to leave their child for long, meaning that they must use nearby facilities for shopping and eating. As a result, parents may feel obliged to buy food that is either more expensive or less healthy than preferable, and are restricted to microwavable or ready-to-eat meals.

During this outpatient period, the parent assumes considerable responsibility as the primary caregiver of their child during recovery, managing their day-to-day needs and closely monitoring their condition each day. Handling this substantial responsibility can be a significant physical and mental burden for the parent, especially if they are alone for the duration of the outpatient phase and separated from their support network of family. Parents may regard reaching the outpatient phase as a significant milestone in the recovery of the patient, but at the same time also describe it as being much more difficult to manage compared to the inpatient phase, as they feel alone and feel that they do not have the same reassurance as

when on the hospital ward with access to health care workers whenever they have a concern about their child. In addition, parents describe feeling vulnerable and concerned in case their child develops complications during the outpatient phase, preventing them from returning home to their other children and family in Ireland. These concerns can be especially upsetting and difficult for parents as they are already feeling isolated and deeply missing their family at home.

It should be noted that the inpatient and outpatient phases can be significantly longer in duration if the transplant recipient experiences complications. In the case of children that develop graft-versus-host disease (GvHD) after HSCT, extracorporeal photopheresis (ECP) is a therapy option that may be offered in the UK if clinically indicated, but it is not available in Ireland. This may involve an extended stay in the UK or travel over and back to the UK after discharge. Although treatment regimens vary in terms of frequency and duration, the UK Photopheresis Society recommend one 1.5 hours session on two consecutive days, repeated weekly for a minimum of eight weeks.[47, 49]

6.2.3 Employment and other caring responsibilities

Another important consideration is the employment situation of the parents and any other caring responsibilities they may have. One or both parents may be in full- or part-time employment and therefore may need to exhaust whatever personal leave allowances (such as annual leave or sick leave) they may have available to them, or leave their job on a temporary or permanent basis. Individuals in this context rely on their employer to show understanding and support to facilitate their leave requirements. Only one parent is entitled to go on carer's leave at any one given time. The associated reduction in income that follows leaving one's employment can bring financial uncertainty and stress to parents.

Parents may have additional children or other family members who need to be cared for and looked after while their other child travels abroad to receive a transplant. Both parents may be able to travel abroad with the patient initially, if they have a family member or other person that can look after their other children while they do so. Where this may not be possible, one parent may stay in Ireland to manage the household and caring responsibilities while the other parent travels abroad. It is important to note that family dynamics are not always straightforward, and that some individuals may not have close or extended family members available to care for or support their other children while they are abroad, or in some cases their other children may have additional needs or care requirements that mean they may require one parent to remain with them.

6.2.4 Implications of repatriation

Repatriation of HSCT is expected to considerably reduce families' administrative burden in organising travel documents, travel arrangements and accommodation.It should also reduce the administrative burden placed on medical social workers, allowing them to devote more time to providing emotional support to families.

Travelling abroad can be a source of substantial stress and anxiety for families. Repatriation will not completely eliminate the need to travel large distances, as the service would be located in Dublin. However, it would reduce the need to bring children through crowded settings and the associated risk of infection prior to transplant. It would also give parents greater control over travel arrangements and the ability to make use of family supports for the journey. It would also reduce the burden associated with making travel arrangements at short notice.

A repatriated service would give parents greater flexibility to manage their employment and care responsibilities. For example, it would provide greater scope for parents to take turns in staying with their child in hospital or to return to work for periods. It would also likely reduce the periods of family separation as travel would be simplified and generally less costly. For family members that must move to Dublin for the transplant period, and indeed for family members that live within commuting distance of the hospital, challenges with respect to managing meals persist and are common to many families of children with serious chronic illnesses that require extensive hospital-based care. While repatriation of HSCT services does not fully address this issue, families may have greater flexibility and support than when abroad as well as a greater familiarity with the options available to them.

As noted in section 6.2.2, ECP, which is available in the UK for the management of GvHD, is not currently a therapy option available in Ireland. Access to ECP for patients may be impacted if transplant services are repatriated to Ireland.

6.3 Financial impact of treatment abroad

Travelling abroad for treatment incurs a number of costs and expenses that have a financial impact on families. The TAS support covers the cost of both parents travelling abroad with the patient receiving transplantation services. For parents who are working, one parent may go on carer's leave to enable them to provide full-time care for their child. A parent may use up any personal leave entitlements they have from their employers, such as annual leave and sick leave allowances, to limit their working hours while maintaining income to support the family. In addition to the immediate effect of reduced working on their total income, families may experience feelings of concern or uncertainty about the security of their employment or the

impact that extended periods of leave may have on their career prospects with their given employer. Likewise, any changes to income or employment can worsen feelings of stress for families as it may impact their financial security and ability to pay for bills in the short-to-long term.

When preparing to travel abroad, families may need to pay charges for various types of documentation required for travelling, such as visas or passports. Tickets to travel by air or sea typically need to be paid for upfront by parents, and are later reimbursed through the TAS. As mentioned previously, in the case of air travel, additional baggage allowance, seat selection or priority boarding are not generally covered by the TAS and so the cost of these additions are incurred by the family. These various travel costs are paid by the parents twice: when travelling abroad and also returning home to Ireland after the transplant. Tickets for travel may have to be bought at short notice, in which case they are typically more expensive. Accommodation is normally provided for parents and patients. Where there is a delay in accommodation being available, parents may have to source temporary accommodation for the first nights abroad, presenting an additional upfront cost to be paid by the parents of the patient.

The TAS covers transport costs of the patient and up to two parents going abroad for transplant services. For parents who may be unable to leave a child at home for whatever reason, such as specific needs or care requirements or family support being unavailable, the costs associated with this child are not covered, and must be paid for by the parents. Depending on the type and size of the accommodation provided abroad, additional family members may not be able to stay, or may even be prohibited from staying there. In these instances, parents may have to source and pay for alternative accommodation for the duration of their stay abroad. Similar costs apply to extended family members who may choose to travel abroad to visit the parent(s) or patient to provide emotional and practical support.

Additional day-to-day costs that are incurred by the parents are manifold and include currency exchange rate fees, food and drink, mobile phone and internet data costs, laundry costs during the outpatient period, purchasing new clothes for the patient if needed, toiletries and hygiene products, and costs of fuel or public transport. There is uncertainty for parents as they do not how long they will be staying abroad and how long they need to budget for. Some families may experience difficulties in accessing funds while abroad, either because of limited bank access or because they may be more reliant on cash. A lack of funding has immediate implications for buying food, but also has clear implications for paying for accommodation and travel.

6.3.1 Resources available

There are different financial resources available to parents of a patient who has to travel abroad to receive a transplant. These financial supports can be broadly separated into those provided by the government through the HSE or Department of Social Protection, and private sources of assistance from charitable organisations. The TAS is applied for through the HSE and covers the cost of travel for the patient and two parents, subject to availability of funding. Additional costs and expenses relating to travel or subsistence while abroad are not provided for under this scheme. The TAS does not cover accommodation costs. However, accommodation costs may be included as part of the public patient access in the other country and, as such, may be included within the invoiced treatment cost.

Transport costs that are covered by the TAS may be incurred upfront by parents and reimbursed at a later time. The process for seeking reimbursement can be difficult or time-consuming to complete for some, and the time between seeking reimbursement and receiving funds can be very slow, further compounding the financial burden for families. Social welfare supports may be available for eligible parents, such as carer's leave payments, domiciliary care allowance, or additional needs payments. Eligibility to receive these payments will be dependent on the specific circumstances of individuals and the duration of time the patient will have spent at home, in hospital, and abroad. For example, Domiciliary Care Allowance allows for payment to continue for up to 26 weeks if the child is receiving medical or other treatment in hospital, after which time the payment may be stopped.[155] In addition, parents who are receiving social welfare supports such as Jobseeker's Allowance who spend extended periods of time in the UK may have their payments suspended as per the usual restrictions that apply to such schemes. Therefore, there is an urgency for these parents to apply for alternate supports from the Department of Social Protection before travelling abroad. This uncertainty and risk of very significant financial hardship is an additional burden for these parents to endure while managing and caring for their sick child.

There are private charitable organisations that provide grants and funding to support parents who need to travel abroad with their child. Medical social workers typically contact these organisations on behalf of parents and help them with their applications to receive support. Often the funding received from these charities is used by parents to cover many of the upfront costs that have been discussed, such as travel costs and applications for documents such as passports or visas, meaning there is little money left for families to use towards the additional day-to-day costs incurred while abroad. It should be noted that charities can limit how often each family can receive support. This means that families with other children who have

the same or similar condition and subsequently require a transplant abroad may not be able to avail of the same supports for these children, leaving them with financial uncertainty and reduced resources available to them.

Apart from applications for funding from charitable organisations, families may also fundraise to cover costs associated with going abroad for treatment. Some families may feel obligated to fundraise to cover costs associated with going abroad for treatment. This can present an additional source of stress for parents during what is a difficult time. Families may be uncomfortable with reaching out to the wider community or general public in this way and, or with having to sacrifice the privacy of their daily life. Families may not want to sacrifice their privacy and the normalcy of their daily life in this way. A decision such as this can present an additional source of stress for parents during what is already a considerably difficult time for them and their family.

6.3.2 Implications of repatriation

When undergoing transplant in the UK, families are typically split: the members that travel and those that remain in Ireland. The need to effectively run two households creates inefficiencies that generate additional costs for families that are not reimbursed. While abroad, the inability to easily access belongings from home also leads to buying additional items, such as clothes. A repatriated service would enable families to more easily access belongings from home and thereby reduce the financial burden in that regard.

While treatment in Ireland would not eliminate travel costs, it can substantially reduce them for many families, particularly in relation to additional family members coming to visit and provide support. Parents and families may also be able to leverage their wider support networks to minimise some costs. It should be noted that some of the supports that may be provided in the UK, such as transport from accommodation to the hospital, may not be covered in a repatriated service. In most cases, it is likely that a parent would choose to stay in accommodation close to the hospital in Dublin, and this can incur a co-payment for an extended period of time that would place a financial burden on families in a repatriated service. Furthermore, families staying in Dublin for treatment will incur costs for a range of needs including food, transport, laundry and car parking. Given the lengthy duration of treatment, these costs can cumulatively become a significant financial burden.

If based in Ireland, parents would have greater clarity about what financial supports they can avail of and how to access them. Access to banking abroad can be challenging for some families, and may create difficulties in funding day to day

expenses while abroad. A repatriated service would reduce or eliminate such problems for families.

Finally, a repatriated service may reduce the reliance of families on charitable sources of support, leading to greater stability and certainty of their financial resources.

6.4 Personal and family impact of treatment abroad

The personal and family impact of treatment abroad refers to the physical, emotional and mental challenges placed on family members during this time. In Ireland, child and family-centred care is an aspect of the integrated care pathway for the treatment of children and young people, as outlined in the national model of care for paediatric healthcare services.(156) Currently, the provision of care for patients who must travel to access HSCT is divided across the two healthcare jurisdictions of Ireland and the UK. This may represent a challenging barrier to the continuity of family-centred care to the patient, parents and siblings for Children's Health Ireland. Travelling abroad for treatment has a considerable impact on the entire family unit: the patient receiving the transplant, the parent acting as primary caregiver, the other parent, siblings, and members of the extended family.

Travelling abroad for an extended period of time means that family members are separated from one another during what it is an exceptionally difficult time. The realisation that they have to travel abroad and be apart from family is an additional source of stress for families who are already dealing with the concern and uncertainty of caring for a child with a serious illness. The important role of partners, other family members, and friends in providing emotional support and practical help to families with a child in hospital in Ireland has been reported previously.(157) Examples of how travelling abroad for treatment impacts different members of the family are discussed in the following sections.

6.4.1 Person receiving the transplant

The age of the patient receiving the transplant can vary, depending on the condition and the time to diagnosis. Depending on the type and severity of the condition, the patient could be any age from newborn to a teenager when they go abroad for transplant. For very young patients, such as newborns or infants, they may miss important bonding moments with one parent and with siblings. For older children, it can be a very isolating experience, as they are separated from one parent, siblings, extended family and friends for anywhere between two to six months. According to discussions with parents, having access to home comforts and supports such as their siblings or family pet makes a big difference to how the patient feels during

recovery, particularly during the outpatient phase of treatment. However, they have to do without these comforts while abroad, which can be upsetting and may make the experience more challenging.

6.4.2 Primary caregiver

Typically, one of the parents of the patient will act as their primary caregiver. This person will travel abroad with the patient and stay with them for the duration of the time spent abroad. During the inpatient phase, the primary caregiver can stay on the ward with the patient, while during the outpatient phase, they are responsible for managing the day to day needs of the patient, including basic medical needs, in between hospital visits. This is a significant responsibility and can be emotionally, mentally and physically draining for parents. In addition, parents have described this time spent abroad as a very isolating experience. The emotional impact of being separated from their partner, other children, family, and friends is substantial. Some parents commented that they missed the physical connection that they would have had at home, and instead their main source of contact with family was through phone calls. Likewise, it can be upsetting and difficult for parents being separated from their other children, and missing important milestones in their growth and development.

The outpatient phase is a significant one for the primary caregiver. The patient reaching this phase after having undergone a transplant represents an important milestone in the recovery process. However, this can also be a significantly isolating and stressful time for the primary caregiver. Compared with the inpatient phase, it can be more challenging, as the parent is alone and does not have the same reassurances as when they were on the hospital ward where they had access to healthcare workers whenever they had a concern about the health of their child.

Things like being near healthcare workers on the ward and play teams visiting to engage with the child allowed parents to feel as though they had opportunities to take a short break from time to time. Similarly, some parents may meet other parents of children while on the ward who are going through the same experience, which may provide some degree of support. In contrast, the outpatient phase is a lonelier experience. Managing this substantial responsibility, often alone, can place a significant physical and mental burden on the parent, separated from their support network back home in Ireland. Parents described feeling vulnerable, uncertain and concerned in case their child developed complications during recovery that prevented them from returning home to the rest of the family in Ireland. At the same time, some parents expressed feeling afraid to share too much information with their partner when things were going badly abroad.

For families with the financial means or supports, it is possible for family to travel and visit for a short period of time to provide support. However, this is not possible for all families, who instead are limited to phone calls with family for moments of support.

6.4.3 Other parent or guardian

Two parents are now supported under the TAS to travel with the patient to receive a transplant abroad, as described previously. This being said, there may be reasons, financial or other, why one parent may remain in Ireland while the other parent travels abroad with the patient. The parent may remain in Ireland for financial reasons, for employment reasons, or to remain at home and take care of their other children or other dependents.

For parents who do remain in Ireland, it is emotionally difficult for them to be separated from their partner and their child during an intense period of medical uncertainty abroad. In addition, the parent who remains at home may find themselves taking on new responsibilities as the primary caregiver for their other children at home, or making personal sacrifices to support their family while their partner is abroad.

6.4.4 Donor

The requirement for the donor to travel abroad is dependent on the donor type. Unrelated donors are sourced through international bone marrow registries and are not typically required to travel to provide a stem cell donation. Related donors can be a parent, sibling or extended family member. While these related donors can be evaluated in Ireland, the sample donation will typically occur in the accepting hospital abroad. Transport costs associated with the related donor family member are covered under the TAS.

As with the patient undergoing transplant, the accommodation costs of a family member that accompanies the related donor are not covered under the TAS unless such costs are included within the treatment costs of a public patient in the other country. The donor or parents of a child donor may experience similar practical, financial and emotional concerns associated with travelling abroad as outlined previously.

6.4.5 Siblings

For children who remain in Ireland while one or both parents are abroad with their sibling, it may be a very upsetting experience. According to reports from parents,

their children in Ireland struggled with not having one of their parents at home. In addition, these children may be worried and concerned about their sibling receiving a serious health intervention abroad. These concerns and feelings of uncertainty caused by separation can have negative impacts on siblings.

In some cases, a sibling may be a suitable donor match for the patient. In this instance, these siblings are covered to travel abroad under the TAS, as they are patients in their own right.

Some challenges observed by families of children receiving HSCT abroad are consistent with those observed more broadly by families of children who require hospital-based care. Findings published in 2020 by Children in Hospital Ireland reported that families felt an additional need for mental health support services while their child was in hospital;[(157)] 21% (n=69) respondents had sought mental health support for themselves, 11% (n=35) for their partner and 8% (n=27) for siblings of the patient in hospital. According to the same report, a considerable number of families felt that they had needed mental health services, but were unable to access these because of financial costs (23%), long waiting lists (7%) or distance of the service from home or the hospital (8%).

In the context of this HTA, issues reported included a perception that insufficient support services were available to their family back in Ireland during this time to help them cope with a parent and sibling being abroad. Also noted was a risk of attachment issues with their other children at home in Ireland during this time, as a result of periods of prolonged separation from one or both parents. Children can react in numerous ways to the experience. Older children may be asked to take on more responsibility to compensate for one parent being away, which can be difficult for them to understand and accept. After the parent and child return home, it can take time for the family unit to readjust to being together and living all together again. Some children may want to move on and try to forget about this upsetting time being separated from a parent, and may experience moments that trigger upsetting memories down the line, in school or elsewhere.

6.4.6 Extended family

For extended family members, relatives and friends it can be a very difficult and upsetting time as they are separated from the patient and their parent(s). In some cases, these family members can provide support to the children and partner at home in Ireland, assisting them with responsibilities and helping to mind children. As many of these genetic conditions may be common in families in Ireland, there may be family members or relatives who have similar conditions and also require care

and assistance. This may reduce the availability of family members to provide additional support and assistance to each other. In addition, for financial and practical reasons it can be difficult for family members to travel abroad to visit the parent and patient.

Communicating complex health matters and updates from a distance by phone or video calls can be difficult, resulting in an inability of family members such as grandparents to understand certain aspects of care, adding to the difficulty of this experience. In this way, parents may have to manage what information they share, representing an additional burden during a considerably challenging time.

6.4.7 Implications of repatriation

Repatriation of transplant services to Ireland may improve the delivery of family-centred care for those family units receiving HSCT services. The separation from family and other children could be managed and mitigated if parents did not have to travel abroad with the patient to receive a transplant. Travelling to and from Dublin is a much more manageable experience for most than travelling abroad. There would be fewer barriers for family members to overcome in order to travel to visit the parent and patient in Dublin, although appropriate infection prevention and control precautions would apply.

The outpatient phase of recovery could be done at the patient's home, enabling them to experience home comforts during this time and be connected with their siblings and family. However, commuting over long distances within Ireland to CHI may pose other difficulties. The experience of related donors would also be more straightforward if transplant services were repatriated to Ireland, as it would remove the requirement of them to travel abroad and lesson the burden associated with what is an altruistic act.

It was noted that there is a lack of dedicated support for the family members that remain in Ireland while the patient is being treated abroad. In a repatriated service, the need for such services would not be eliminated, as families will continue to be separated for lengthy periods. However, there may be greater scope for visits and for parents to swap duties for periods, potentially reducing the emotional impact on the family and reducing the need for psychological support.

6.5 Additional topics for consideration

6.5.1 Irish Travelling community

Irish Travellers are an indigenous minority group in Ireland who have their own distinct culture, language and value system.[158] Compared with the general population in Ireland, there is an increased prevalence of inborn errors of immunity (specifically, ADA-SCID) and inborn errors of metabolism (specifically Hurler syndrome) within the Irish Traveller Community, as described in chapter 3. The requirement for a paediatric patient to travel abroad to receive a transplant can present distinct challenges for individuals within the Irish Traveller Community due to practical, financial and cultural considerations.

Many of the practical and financial issues relate to those discussed in sections 6.3 and 6.4 of this chapter. As outlined previously, there is a significant administrative burden placed on parents once their child has received a diagnosis for a genetic condition requiring the child to travel abroad to receive transplant services. This burden can be significantly greater for Irish Travellers. Specific obstacles that have been documented by the All-Ireland Traveller Health Study (AITHS) include literacy and numeracy issues, experiences of prejudice by service providers, and low expectations from health services.[159]

Parents with literacy issues may find completing the relevant documentation challenging. This may result in delays or problems obtaining passports or TAS approval. According to the AITHS, a significant number of Irish Travellers are unemployed or dependent on social welfare payments. Parents in receipt of certain social welfare payments, such as Jobseeker's Allowance or Benefit, may have their payments suspended when they spend extended periods of time abroad, due to usual restrictions that apply to these schemes. Uncertainty or concerns regarding the continuation of their social welfare payments can be an additional source of stress for parents who have to travel abroad with their child to receive transplant services. Disruption to income may place these parents at risk of significant financial hardship.

Furthermore, the Irish Traveller Community has a distinct culture in which considerable value is placed on immediate and wider family networks and community togetherness.[159] Findings from the AITHS demonstrated that members of the Irish Traveller Community find it very difficult to be housed in an area isolated from family and friends. Similar issues were noted in the discussions with parents of patients from the Irish Traveller Community who travelled abroad to receive a transplant. The lack of access to extended family during treatment abroad is therefore particularly challenging for members of the Irish Traveller community. There is a cultural expectation that families are expected to visit sick relatives in hospital. However, due to financial and practical issues, it may not be possible for the wider family to provide the same level of support to patients who are treated abroad. The weight of expectation and perceived duty to visit family members in

hospital may impel the wider family to travel abroad to visit the patient and primary caregiver despite the financial or practical consequences. However, it may be difficult for family members to source affordable accommodation adjacent to the hospital where the patient was being treated. As a result, family members have sometimes slept in their vehicles for the duration of the patient's stay in hospital because they felt compelled to be there to provide support. In addition, a commonly reported barrier to accessing health services for individuals from minority groups, such as Irish Travellers, is discrimination.[160] Such concerns may be worsened by the requirement to be separated from their support network in Ireland to travel abroad for the patient to access transplant services.

6.5.2 Immigrant Populations

Many patients with haemoglobinopathies are first generation immigrants. That is, the parents of the affected children were not born in Ireland. Accordingly, consideration should be given to parents, and or primary caregivers, of patients from migrant or immigrant populations. Language barriers, literacy issues and financial concerns can add to the burden associated with the practical considerations of travelling abroad, such as difficulties in completing or paying the upfront costs for the appropriate application forms for passports or visas.

As noted in section 6.5.1, discrimination, including discrimination when accessing health services, is a commonly reported barrier for individuals from minority groups,[160] with the potential for such concerns to be worsened by the requirement to travel abroad to access transplant services.

6.5.3 Impact of HSCT treatment on fertility

Procedures aimed at preserving fertility are considered ancillary to the provision of HSCT, and as such are not always available to patients undergoing HSCT treatment. However, such procedures are often considered part of the standard HSCT package of care in the UK and have therefore been made available to some patients who have travelled there for transplant.

The choice of conditioning approach will potentially impact on fertility. Avoiding full conditioning can reduce the incidence of subfertility and infertility in patients. Parents may have fewer concerns relating to the requirement for fertility-related procedures when the patient receives a less intense conditioning regimen. Some parents felt strongly that fertility-related procedures should be offered to children, as they do not want their child's options limited later in life. The severity of the patient's condition and health state can influence the urgency of a decision to consent their child for HSCT from the parents' perspective. In cases with less urgency to

transplant, parents may pause to consider options for procedures aimed at preserving fertility before proceeding to transplant. When fertility preservation is presented as an option for parents, the decision to proceed with transplant may be easier.

Although there are a number of procedures available which are intended to preserve fertility, it should be noted that the effectiveness of some of these procedures is not supported by evidence. There may be a perception among parents that HSCT will impair their child's fertility regardless of true clinical risk and there may similarly be a perception that these procedures are effective. Therefore, it is important that appropriate information is provided to parents in relation to the indications for these procedures, and their associated benefits and risks.

6.5.4 Mortality abroad

BSBMTCT registry data report non relapse mortality at 100 days post-transplant for paediatric allogeneic transplant as 5% (95% CI 4% to 7%) for patients who were transplanted between 2014 and 2018.[47] An important reality of the transplant experience that therefore requires appropriate consideration is the potential for the patient not to survive the HSCT treatment episode. The impact and burden of this on the immediate and wider family network is substantial, and heightened by the separation of being apart from the patient if it occurs while they are abroad. There are additional complications and complexities associated with cultural differences between the approach to mourning periods and undertaker practices between the UK and Ireland, and this can be difficult for parents and families. Likewise, the process of transfer back to Ireland can be traumatic for parents due to the logistical issues associated with transportation, such as the requirement to be separated from their child during the journey back to Ireland. Reimbursement of transportation expenses in these cases by TAS is discussed in section 4.2.1.

6.5.5 Implications of repatriation

Specific ethnic and minority groups in Ireland face particular challenges when travelling abroad to receive transplant services, beyond that of the general population. Specific consideration is warranted of the burden that the current treatment pathway places on them, and the potential for repatriation of transplant services to alleviate some of this burden.

Irish Travellers and other ethnic or minority groups in Ireland may be disproportionally impacted by practical and financial challenges associated with travelling abroad, due to having less financial security, lower income, receiving social welfare support, or language, literacy and numeracy issues. Repatriation of

transplant services would considerably reduce the financial and administrative burden for these families.

The Irish Traveller Community has a distinct culture system in which considerable value is placed on immediate and wider family networks and community togetherness. Repatriation of transplant services to Ireland would remove current barriers to family members visiting the patient and primary caregiver in hospital to provide support, which is of significant importance and cultural value to these families.

In addition, removing the travel requirement by repatriating transplant services to Ireland eliminates certain complicated and upsetting additional steps that families need to take in the event whereby the patient does not survive the treatment pathway and needs to be brought back to Ireland from abroad.

Fertility preservation services are considered ancillary to the provision of HSCT, but are sometimes included within the overall package of care provided to patients who travel to the UK for transplant. If transplant services are repatriated to Ireland, fertility preservation may not be available to families as part of the package of care.

6.6 Discussion

The purpose of this chapter was to consider and describe the additional burden that undergoing a transplant abroad places on families compared to undergoing a transplant in Ireland. With reference to the experiences of parents and family members who have travelled abroad, a number of important considerations emerged.

Irrespective of where the procedure takes place, the transplant journey places a considerable burden on parents and families. This burden includes:

- stress, anxiety and uncertainty relating to the health condition of their child
- the preparation and steps required to ensure their child receives a transplant
- understanding and dealing with the associated risks and potential complications of the procedure
- taking on the responsibility of acting as the child's primary caregiver and managing their daily care needs during recovery following the procedure.

Many of these challenges are not unique to families of children requiring HSCT, but represent common challenges for the families of children requiring hospital-based

care for serious health conditions.[157] However, it is recognised that the requirement to travel abroad for transplant presents an additional burden for parents and families during what is already a difficult experience. Similarly, the current delivery of care across the two healthcare jurisdictions of Ireland and the UK may present a challenge to Children's Health Ireland in ensuring that continuity of family-centred care is provided.[156]

The additional burden placed on parents and families, arising from the requirement for the patient to travel abroad to receive transplant services, has been framed and presented in three broad domains: the practical considerations for parents and families, the financial impact felt by parents and families, and the personal impact on the immediate and extended family. The requirement to travel abroad can be viewed as an additional complexity and complication for families. The specific impact of each set of considerations is different for each family and depends on individual circumstances, such as the extent of their immediate and wider support network, their financial and employment situation, and additional caring responsibilities beyond those of the patient. Repatriation of transplant services to Ireland would considerably reduce the burden on families associated with travelling abroad, but it will not eliminate all challenges.

In research conducted by Children in Hospital Ireland, more than half of parents (58%) reported that they had experienced a strong or extreme negative financial impact associated with their child's hospital stay in Irish hospitals.[157] Families may experience difficulties travelling to, and temporarily staying in, Dublin if transplant services were repatriated to Ireland. However, while not eliminating all challenges, repatriation would provide greater scope for the immediate and wider family to provide support to the patient and primary caregiver during this time.

In addition, the requirement to travel abroad for transplant can disproportionately affect certain minority or ethnic groups, beyond the burden experienced by that of the general population. The increased prevalence of financial uncertainty and language, literacy or numeracy barriers among such groups can make the current transplant journey much more challenging. Moreover, there can be specific cultural considerations relevant to the experiences of various ethnic groups. For example, the Irish Traveller population place considerable cultural importance on the ability and requirement of the immediate and extended family to provide support to one another during difficult times, such as while in hospital. When judging the merits and challenges of repatriation of transplant services to Ireland, appropriate consideration should be given to the impact of the decision on such ethnic or minority groups.

Despite the prospective reduction in burden on the family, repatriation of transplant services may result in changes to currently available care arrangements for the patient. Currently, procedures aimed at preserving fertility are considered ancillary to the provision of HSCT, and as such are not available to patients undergoing HSCT in Ireland. There have been instances, however, where some patients have been offered fertility preservation procedures as part of their HSCT package of care in the UK. Similarly, some patients may experience GvHD complications after transplant. In the UK, ECP therapy may be provided as second-line treatment when clinically indicated, with this treatment also offered to patients from Ireland undergoing HSCT in the UK. It was reported that, between 2017 and 2021, 11.7% of IEI patients from Ireland who underwent HSCT in the UK received ECP.[108]

At present, the HSE does not provide funding for procedures aimed at preserving fertility or for ECP treatment in CHI at Crumlin. Consideration should be given to the potential impact of the change in availability of these services to Irish patients if HSCT is repatriated to Ireland, and the acceptability of such changes for patients and families.

7 Ethical issues

Key points

- The purpose of this chapter was to outline the ethical considerations associated with the potential repatriation of paediatric HSCT services to Ireland.
- The impact of repatriation on the family of children who currently receive this service abroad was noted to be a key consideration. Under the current pathway:
    - There is the potential for considerable employment, financial and administrative strain on the parents of the child, which may not be equitable in terms of resilience when considering families on lower incomes.
    - The need to travel is associated with a separation of the family unit and reduced access to support from wider family and community networks. This burden is likely exacerbated when considering single parent families.
    - HSCT is available and provided in Ireland for children with selected indications. In the absence of clear clinical rationale for the difference in treatment pathways for conditions which require HSCT, the distinction may appear arbitrary and unjust from the patient perspective.
- The requirement to engage with healthcare systems abroad for the provision of HSCT services necessitates that clinical responsibility and oversight is transferred to the host country. The HSE is furthermore reliant on the capacity and prioritisation of care in that country, with a risk to care provision should current agreements change. There are further ethical considerations relating to the child and their family in this context, including:
    - the protection of autonomy and variations in processes of information provision and obtaining of informed consent internationally.
    - ensuring respect for persons in terms of a family being unfamiliar with a healthcare system outside of Ireland, and the potential for privacy challenges with the sharing of data with host countries and those outside of the European Union.

- The sustainability and benefits of a repatriated service would depend on the investment in staff resources and availability of clinical facilities. As HSCT is currently provided in Ireland for certain indications, repatriation of the remaining indications would increase demand for such services in Ireland.
    - The unpredictable nature of when transplants will be required makes it challenging to project demand. If demand exceeds capacity in a repatriated service, then some patients may still be required to access treatment abroad. To ensure equity and fairness, a transparent system would be required to determine which patients are referred abroad for treatment.
    - In the event of a decision to repatriate, consideration should be given to ongoing monitoring and evaluation to ensure that access (as reflected by time to transplant) and outcomes are maintained for these patient cohorts.
- In terms of the ethical consequences of the HTA itself, given the rarity of the genetic conditions under consideration, there are challenges relating to the availability of data to inform these types of assessments. Furthermore, the findings of the HTA may be impacted by prospective changes in elements such as the availability of alternative treatments, service level agreements, and family support packages. Lastly, the approach of the assessment was based on the assumption that the procedure as delivered in Ireland would be equivalent to that delivered in the UK. However, there may be distinct differences such as the availability of publicly funded options for fertility-related procedures and access to ECP as a second line treatment for GvHD.

7.1 Introduction

This chapter outlines the main ethical issues that should be considered in the decision-making process in relation to the repatriation of paediatric haematopoietic stem cell transplant (HSCT) services to Ireland. The chapter content was developed broadly in line with the structure described in the European network of HTA (EUnetHTA) Core Model.[100] The ethical issues relating to a technology should be assessed with reference to the prevalent social and moral norms relevant to the technology, and also with respect to the HTA itself. While governments have an obligation to protect the health and wellbeing of the population, this must be achieved in a manner that is equitable, non-discriminatory, transparent, and, as far as possible, non-coercive. The moral value that societies attribute to the consequences of implementing a technology is affected by socio-political, cultural, legal, religious and economic differences. It must be also borne in mind that the balance of benefits and harms to individuals and the wider population may be viewed differently over time as a reflection of societal and cultural changes.

HSCT is available in Ireland for paediatric patients with haematological malignancies and selected benign conditions, while paediatric patients with genetic conditions requiring HSCT currently travel abroad to avail of this treatment provided through the Treatment Abroad Scheme (TAS) operated by the Health Service Executive (HSE). The requirement for travel abroad can place a significant psychological, financial and logistical burden on families, and the addition of another healthcare system in the treatment pathway can raise challenges in terms of autonomy, respect for persons, justice and equity.

7.2 Impact on families

HSCT is a medical procedure that requires a lengthy hospitalisation and an extended period of intensive outpatient follow-up after patient discharge. As a consequence, the parents and guardians of paediatric HSCT patients can experience psychological, financial and logistical burden (as outlined in chapter 6).

One of the notable burdens faced by families is the disruption to employment and income during the transplant period that may extend over a period of years following the transplant procedure. Loss or disruption of income can contribute to substantial financial hardship and distress among families of paediatric HSCT recipients. Financial resources are essential for caregivers of paediatric patients undergoing HSCT due to the need to cover not only living costs during the extended treatment and recovery periods, but also to cover the upfront costs of travel for treatment abroad.[161]

Since the SARS-CoV-2 pandemic, some employers have brought in initiatives to support working remotely, which could give eligible parents more flexibility to maintain their employment during the transplant and post-transplant period. However, travelling abroad for a transplant may restrict or eliminate the option of remote working. Furthermore, many occupations are not amenable to remote working and the parent is unlikely to be able to work during key phases of their child's treatment.

The changes to income in a household may affect some families more than others. Families with more substantial financial resources have more resilience to manage the various upfront costs that are incurred, irrespective of whether or not they are reimbursed later through the TAS. As such, the system of accessing HSCT abroad leads to inequities as it may inadvertently bias against those on lower incomes or with fewer financial resources such as savings. Indeed, a lack of funding could present a considerable barrier to some families to avail of the service to the extent that charitable support or requests for support otherwise (for example, from family or from the public at large) are necessary. A reliance on such supports to avail of a service can be associated with stigma for some, and or an invasion of their private lives, particularly where individuals feel under pressure to resort to fundraising initiatives.

The administrative burden associated with travel abroad potentially includes making numerous applications and bookings (for example, in relation to passports, visas, social welfare payments, travel tickets, accommodation). Aside from financial resources, families with poor literacy and or limited experience of travel may face greater barriers to accessing the service in the UK. Those additional barriers could adversely impact a family's resilience and ability to cope during the transplant process, and may disproportionately affect families of lower socioeconomic status.

It was also highlighted in chapter 6 that treatment abroad could also be stressful for parents due to loss of sharing of responsibilities within households as one of them takes on responsibility as the primary caregiver for the duration of treatment abroad. At the same time, the other parent remains in the country for work and or to take care of their other children. In the case of a repatriated service, families would not be separated for long periods of time and they may also be able to leverage support from their extended families or community.[161] They may also be able to better balance employment and caregiving responsibilities in a repatriated service. Single parent families or those with a greater number of dependents, or dependents with more complex care needs, may be particularly disadvantaged by the current treatment pathway. Another relevant issue occurs when the donor for the paediatric

patient is a sibling, which effectively creates a second patient in the household which may add more physical and psychological implications and stress for parents.

A considerable ethical issue is that the HSCT procedure is available in Ireland for patients with certain conditions. The families of those patients are not faced with the impact of having to travel abroad to avail of the service. Hence a subgroup of patients are disadvantaged because of limited treatment capacity in Ireland. For both patient groups, care is initiated and completed in Ireland. However, for those who undergo the procedure in the UK, care is partly being outsourced. To avail of the service they must face barriers to care in the form of additional stress, disruption and financial burden. The families who must travel to the UK for treatment are not receiving an equivalent service, and supports received do not eliminate the financial burden. In the absence of clear clinical rationale for the difference in treatment pathways for conditions which require HSCT, the distinction may appear arbitrary and unjust from the patient perspective.

Repatriation of the procedure may not eliminate inequities, but by reducing the travel burden and associated costs, and potentially increasing access to a family's support network, it may reduce them. However, whether the service continues as is or is repatriated, it must be acknowledged that accessing care places a significant burden on families that can have long-lasting financial and emotional effects.

7.3 Involvement of another healthcare system

When a treatment is delivered abroad the care process is not entirely under the control or responsibility of the national healthcare system but rather is outsourced in full or in part to another healthcare system. This outsourcing of care abroad usually occurs because a country does not provide the service in question or because the service cannot be provided within the time normally necessary for it to be received by the patient. In the case of HSCT, this service is currently provided in Ireland for specific conditions, which may be perceived as ethically unjust.

In terms of the benefit-harm balance, the risks of not providing the treatment in Ireland and continuing treatment abroad must be countered by those linked to travel and the associated risk of infection, particularly in the case of acutely unwell patients. If the service were delivered within Ireland, the need for travel to the treating hospital, potentially by public transport, would not be avoided, but may be lessened. The risk of infection occurring during transport of the patient is not inconsequential as it can jeopardise transplantation and associated outcomes; both the procedure and the associated travel must be considered.

Reliance on treatment abroad for the provision of HSCT also means that the service is dependent on available capacity in another healthcare system. The HSE has no control over service planning in that jurisdiction, and availability could in theory decrease at any time in the event of changes to or ending of service level agreements. While the National Health Service (NHS) in the UK may allocate capacity for international patients, the care of these patients may be considered more resource intensive because of the need to liaise with clinicians in other countries, for example. For international patients, hospitalisations may require a longer length of stay than is medically indicated to account for the need to organise travel and accommodation, and hence the associated care may be considered less resource efficient.[162] If international patients were to be considered lower priority and the service were constrained in terms of resources, this would potentially lead to reduced access to HSCT for Irish patients.

To date, procedures for patients in Ireland have been outsourced to hospitals in the UK. Attempts have also been made to reach an agreement with a hospital in Italy. In the event that procedures were to be outsourced to countries other than the UK, an additional concern would be the potential for language barriers. Should the service be provided by an institution where English is not the first language, there is a risk of miscommunication that could impact on the ability of parents to give properly informed consent. While some degree of support may be available from Irish clinicians, it is possible that parents will have to provide consent to procedures and therapies without having a full understanding of what they are agreeing to, or to the potential benefits and harms of the treatment. This would be particularly relevant if the patient were to develop complications and urgent intervention were to be required. Travel to a country other than the UK would likely also increase the administrative and financial burden on families, particularly as travel by ferry may not be an option, and may pose important sociocultural challenges.

7.4 Autonomy

Autonomy is the right of individuals to make informed decisions about their own medical care. Autonomy is the foundation of informed consent and requires the patient/guardian to be competent to make a voluntary decision having been provided with adequate information. The key components of informed consent are capacity, disclosure, understanding, voluntariness, and decision.[163] Adequate disclosure requires the provision of information about the diagnosis, the reason for a proposed intervention, anticipated benefits, potential risks, and acceptable alternatives. With HSCT, the assumption is that, as the treatment considered here is for a paediatric population, there is a tripartite relationship between the child, parents, and clinicians. Consent to undergo HSCT is affected by many different

factors, such as clinical effectiveness, the value systems of both physician and patient/parents/caregivers, the sociocultural and religious context, and the individual's emotions or personal or contextual features. All these factors could be even greater when HSCT involves the paediatric population coupled with the need to travel abroad for treatment. It should also be noted that in situations where there are two parents involved in care decisions but only one is present, as is often the case when treatment is accessed abroad, it creates challenges for informed consent and shared decision-making.

If the treatment is delivered abroad, the responsibility for ensuring that a proper informed consent is given for some aspects in the pre-transplant and transplant process is totally under the control of the country where treatment is being delivered. According to the World Health Organization (WHO) Aide-Mémoire[164] on the donation and transplantation of tissues and cells, national health authorities are responsible for defining the process of obtaining and recording consent for cell, tissue and organ donation in the light of international ethical standards, the manner in which organ procurement is organised in their country, and the practical role of consent as a safeguard against abuses and safety breaches.

7.5 Respect for persons

In terms of human dignity, patients and their families travelling abroad for HSCT find themselves away from home in a foreign country, with no direct family or community support. Considering the stress related to the HSCT process, parents may, depending on the location of healthcare (and local language used, should treatment be provided in countries other than the UK), experience difficulties in engaging with the healthcare system. For example, they may struggle with appointments, registration procedures or other medical requirements that are important for successful clinical management.[165] They may also feel that their culture will not be understood or approved of, and may fear judgement or discrimination. Moreover, it could be perceived by the family that Irish patients are prioritised differently to local patients in the country of their care. There may also be potential for privacy challenges with the sharing of data with host countries and those outside of the European Union, such as the UK, given Brexit.

7.6 The Irish healthcare system: capacity and availability

It is possible that repatriation of HSCT could increase the resilience of the Irish service in terms of staff and handover of expertise. Historically, the service has been dependent on a small number of individuals, and loss of staff through retirement, for example, has had a major impact on service provision. Repatriation would result in a

higher volume of patients, which could lead to greater expertise and a larger team with the requisite clinical expertise.

Conversely, accessing the service abroad has involved patients receiving care from international centres of excellence. Parents may perceive benefits or derive reassurance from knowing they were engaging with a centre with a long tradition of excellence in the care of these patient groups. It is unclear if an Irish-based service would be considered of lesser quality by parents.

Repatriation of the service may require the reallocation of human resources, training, or funding, which may be drawn from resources from other areas. As the reallocation of resources may jeopardise other patient groups, the manner in which this reallocation affects the existing health care system has to be considered. As HSCT is provided in Ireland for haematological malignancies and selected benign conditions, repatriation would result in a more equal provision of service.

However, repatriation may result in delays in treatment or the need to prioritise patients in order to manage bed availability. If demand exceeds capacity in a repatriated service, then it may also be necessary to continue to send some patients abroad, and for a system to be in place to determine which patients are referred abroad for treatment. In the event of a decision to repatriate care for the indications included in this HTA, consideration would need to be given to ongoing monitoring and evaluation to ensure that access (as reflected by time to transplant) and outcomes are maintained for these patient cohorts.

7.7 Impact on fertility

Parents of paediatric HSCT candidates are informed about the side effects of the procedure and the expected long-term outcomes in terms of the potential for fertility impairment. In addition to coming to terms with the newly diagnosed disease, parents must also process the risk of infertility for their child, which may increase concerns about the procedure. Fertility preservation counselling is a difficult task for clinicians and requires sensitivity regarding the ethnic and cultural background of the families. Concepts of fertility, child-bearing and parenthood are influenced by culture and may differ markedly across families depending on the ethnic and cultural background.

Procedures which may be performed with the aim of preserving fertility are described in chapter 4. These procedures vary with respect to their proven ability to enable a person to have a child, and are in some cases experimental. Furthermore, complications include surgical site infection, post-procedural fevers, delay in HSCT start, prolongation of hospital stay, or delayed engraftment.[122, 166, 167] From an

ethical standpoint, it is important that parents fully understand the expected level of benefit, and potential risks, associated with these procedures to provide consent for their child to undergo such a procedure.

Fertility-related procedures are currently offered to patients undergoing HSCT who are treated in the UK, while in Ireland adult HSCT patients may access fertility preservation procedures and paediatric cancer patients can also currently access some procedures under a research grant.[17] Grants from charities that specifically support paediatric patients with cancer would not be available to this repatriated cohort who have benign conditions. If HSCT procedures were repatriated, then access to fertility-related procedures may be contingent on charitable support, the availability of which, and in particular the long term availability of which, is unclear. There is no certainty that support would be available, or, for parents with multiple children receiving the same treatment, if a charity would support more than one child from the same family.

An important consideration is whether parents have received appropriate information and that the decision to undergo the procedure is driven by the patient's best interests. This is additionally important given that the procedures offered involve the long-term storage of gametes and preserved tissue, which also incurs associated costs. While the initial costs may be included in the procedure cost, and funded, for example, through charitable funding, it is unclear how long-term ongoing storage costs are funded and on whom such responsibility lies. If support is discontinued and families face the prospect of loss of tissue, they may feel they must take on payments that may be unaffordable. Furthermore, it is important to note that procedures involving the eventual use of these gametes and preserved tissue (that is, with a view to producing a child) are also not funded. The potential financial burden associated with accessing fertility-related procedures can give rise to inequities and disadvantage families with fewer financial resources.

7.8 Ethical consequences of the HTA

Given the nature of the research question – the repatriation of a procedure - this assessment has not looked at a number of the domains that are ordinarily considered in a HTA. Specifically, the assessment has not considered the clinical effectiveness, safety, or the cost effectiveness of repatriation of HSCT services. These domains were omitted under the assumption of equal effectiveness of the UK and Irish service. That is, it was assumed that clinical outcomes would be equivalent whether patients are treated in the UK or Ireland. This assumption is contingent on an equivalent approach to the procedure and any allied therapies. While this may be a reasonable assumption regarding the transplant procedure, access to some allied

procedures and therapies, for example extracorporeal photopheresis (ECP) and procedures intended to preserve fertility, may impact on the utility for patients. The former may be clinically indicated for some patients and may require travel to the UK for treatment unless an ECP service is developed in Ireland. Had the assessment included a cost-effectiveness analysis, it may have been possible to incorporate the potential benefits of differences in the service delivered, although any such results would have been subject to substantial uncertainty.

The findings of an assessment are also influenced by the available data. It is notable that this assessment is evaluating a procedure for a cohort with rare conditions. As such, there are very limited data on the numbers of patients, the outcomes of treatment, and the impact of travelling abroad for treatment compared to the alternative of a repatriated service. The rarity of the conditions means that year to year fluctuations in the number of patients requiring transplant may appear small, but are relatively large for a capacity-constrained service. While cost data relating to the UK-based service have been provided by the TAS, data on procedure costs in Ireland are based on a Diagnosis-Related Group (DRG) coding. The DRG is calculated based on a larger cohort of patients including indications and age groups outside the scope of this assessment. As a consequence, the procedure cost may misrepresent the true cost of treatment in Ireland. While the DRG reflects the cost reimbursed to the hospital, paediatric patients for the selected indications included in this assessment may, on average, have a longer length of stay which may increase the procedure cost and associated funding to the treating hospital. The costs accruing to families are not formally recorded. Through discussions with parents of patients, we were able to identify what aspects of treatment abroad generated out-of-pocket expenses for families (as documented in chapter 6), but the magnitude of those costs may vary from family to family depending on their individual contexts.

Finally, a HTA is conducted at a point in time and reflects the evidence and information available at that time. Important developments could occur that change the understanding of the implications of repatriating the service; these may include the availability of new or different treatments (for example, gene therapies), or changes to the existing service level agreements or the establishment of new agreements. For example, as of November 2022, no patient had completed the treatment pathway under the new service level agreement for patients with haemoglobinopathies as it has recently been established. For the purpose of this HTA it is also assumed that patients will be able to receive treatment whether in the UK or in a repatriated service, but there may be hidden barriers to treatment which have not been examined. Furthermore, rules regarding social welfare support and the extent of TAS support change over time. Supports that lessen the burden placed

on families when accessing HSCT treatment outside of Ireland could reduce the ethical issues associated with treatment abroad.

7.9 Discussion

This chapter considered the ethical issues in relation to the existing HSCT treatment service and the potential consequences of repatriation of the service.

As described in chapter 6, the HSCT procedure and treatment pathway have a significant impact on patients and their families. Undergoing the procedure in the UK places a substantial additional emotional and financial burden on families. A key ethical concern is that the financial burden in particular puts families on lower incomes at a disadvantage when accessing the service. A repatriated service may reduce inequities by reducing the travel burden and associated costs. The repatriation of HSCT services to Ireland would also align with the Sláintecare strategies set out by the Department of Health 2021-2023 to improve access to treatment for marginalised communities, such as the Traveller population.[(168)] This is particularly relevant given the higher prevalence of a number of the genetic conditions of relevance to this HTA (SCID, Hurler syndrome) in the Traveller community. In this regard, repatriation would also be consistent with the goals of the National Traveller Health Action Plan (2022-2027) to improve Travellers' equality of access, participation, and outcomes in health services.[(169)]

The outsourcing of a service to another jurisdiction not only increases costs for families, but may also result in parents being ineligible for some of the supports that are available when care is provided in Ireland. Given that the procedure is available and provided in Ireland for children with selected indications, families of children with genetic disorders may perceive it as discriminatory and an arbitrary decision that places them at a disadvantage. It is not clear that there is a clinical rationale for a subgroup of patients to have their care outsourced in this manner.

By availing of services provided in another country, the HSE is reliant on capacity and availability in that country, and also subject to price fluctuations in that country. Adverse changes in demand and capacity in the UK could create challenges in obtaining treatment in the UK, ranging from longer wait times for the procedure through to a failure to get treatment at all. By accessing treatment in another country, this can also generate difficulties in relation to language and cultural barriers that may impact on a parent's ability to give informed consent. The logistical challenges of treatment abroad often entail that only one parent stays with their child in the UK, creating additional challenges to making informed decisions

particularly when faced with urgent treatment decisions in response to complications.

The sustainability and benefits of a repatriated service would depend on the investment in staff resources and availability and access to the requisite facilities. HSCT is currently provided in Ireland for haematological malignancies and selected benign conditions; repatriation would therefore increase demand for services in Ireland. The unpredictable nature of when transplants will be required, and the variability in the complexity of individual cases, makes bed management challenging. If demand exceeds capacity in a repatriated service, then some patients may still have to access treatment abroad. To ensure equity and fairness, a transparent system would be required to determine which patients are referred abroad for treatment.

The side effects of HSCT treatment may include a reduction in fertility. For patients treated in the UK, procedures aimed at preserving fertility are generally included as part of the package of care. In Ireland, such procedures are not provided by the publicly-funded healthcare system in this context, although access may be possible through charitable support. This distinction is one aspect where HSCT treatment abroad provides perceived benefits over and above what is currently available in Ireland.

This chapter also considered the ethical aspects in relation to the assessment itself. The approach of the assessment was based on the assumption that the procedure as delivered in Ireland would be equivalent to that delivered in the UK. There are some notable differences, such as access to ECP and procedures aimed at preserving fertility in the UK. A repatriated service may also take time to develop sufficient capacity and expertise to be resilient. The assessment is also influenced by the available data. The conditions under consideration are rare, and hence the associated data reflect a small cohort and may be skewed due to variability in the patients treated. The effect of small numbers may impact on estimates of average treatment costs within a specific indication. Finally, the assessment is conducted at a point in time and reflects the information available and context at that point in time. Changes to available therapies or treatment pathways may influence the findings of the assessment.

8 Discussion

8.1 Introduction

HSCT is currently available in Ireland to paediatric patients with haematological malignancies and selected benign conditions; paediatric patients with other conditions requiring HSCT must travel to the UK to avail of this treatment. This includes those with inborn errors of metabolism (IEM) (currently being treated in Manchester), those with inborn errors of immunity (IEI) (currently being treated in Newcastle), and certain haemoglobinopathies (who historically have rarely undergone HSCT but an agreement for service provision has in 2022 been put in place with St. Mary's Hospital, London). A request was received by the Health Information and Quality Authority (HIQA) from the National Clinical Lead, Child Health Public Health, in the HSE, with support from specialist clinicians in Children's Health Ireland (CHI), to carry out a health technology assessment (HTA) of the repatriation of paediatric HSCT services for these non-malignant indications. This request was prioritised for inclusion in the HIQA HTA work plan.

The purpose of this discussion chapter is to summarise the key findings of the HTA, contextualise these findings, and present the strengths and limitations of the assessment.

8.2 Summary of key findings

In terms of the treatment pathway, for the majority of cases referred for treatment, HSCT for IEI, IEM, and haemoglobinopathies (that is, the collective disorders of interest to this HTA) is provided in the UK under the HSE Treatment Abroad Scheme (TAS). Following transplant, longer term post-procedure care for all three patient groups is transferred back to CHI. The proposed pathway of repatriated care for these patient groups would mean the transplant episodes themselves would now take place in Ireland without the requirement for the child, their family, or donor to travel abroad. Additional benefits may include reduced logistical and cost burden for families in relation to travel, accommodation, and sustenance, improved access to treatment for patients who may not be in a position to travel overseas, greater continuity of care, and reduced administrative burden for referrals abroad. However, there may be differences between the repatriated services and the existing treatment pathway due to differences in the package of care provided.

The epidemiology and burden of disease varies for conditions within and between the groups of disorders of relevance to this HTA. Severe combined immunodeficiency (SCID) represents the most common IEI historically referred for HSCT, while Hurler

syndrome made up the majority of IEM cases. The burden of the disease associated with each of these conditions was noted to be considerable, with both displaying higher incidence in the Irish Traveller population. Both conditions are associated with early morbidity and mortality in the absence of appropriate treatment, with HSCT considered the primary intervention for both. Sickle cell disease represents the most common form of haemoglobinopathy internationally with heterogeneous clinical presentation and outcomes. HSCT is typically reserved for more severe cases of sickle cell disease for whom the clinical benefit is considered to outweigh potential harm. Collectively, across the patient groups in this HTA and those treated in Ireland currently for other indications, the projected demands for allogeneic HSCT in a repatriated setting infers an average of between 21 to 25 procedures per year up to 2030.

In terms of the resilience of the current service, there is a risk to access to HSCT for these cohorts should there be a change to the current agreements in place, or in a scenario in which demand in the host country exceeds available capacity. To facilitate the provision of HSCT in Ireland for these patient groups, and to preserve resilience in such a service, a number of key resources and organisational changes would be required. It will be important to ensure there is sufficient bed capacity for those who receive care in Ireland currently and those who would require care in the context of a repatriated service.

The need for resilience will need to be factored into the capacity estimates in the context of potential variation in demand each year. Additional staff would be required to care for these additional patients who have complex care needs including specialist nurses (who require two years of training), a medical scientist, and health and social care professionals. There is a need to consider the availability of family accommodation and how this may be facilitated in the context of the new children's hospital. In terms of an equivalent service, special consideration is also required in relation to the provision of ECP and procedures aimed at preserving fertility; these services are not currently funded by the HSE for children undergoing HSCT in Ireland. Introduction of these services would have organisational and resource implications as well as implications beyond the repatriated cohort. Furthermore, any decision to provide these procedures in Ireland should be evidence-based and, in the context of a service providing procedures aiming at preserving fertility, would need to comply with national legislation. As capacity for transplant will be finite under a scenario of repatriation, consideration will need to be given to criteria for the selection and prioritisation of patients for transplant, and the use of contingencies at times where demand exceeds capacity (for example, continued agreements with centres abroad).

In terms of costs associated with a repatriated service, from the perspective of the HSE, while subject to substantial uncertainty, the estimated five-year incremental budget impact is expected to result in cost reductions. These are expected to range between a reduction of €1.5 million (95% CI -€5.0m to +€1.9m) and a reduction of €2.3 million (95% CI -€5.8m to +€1.1m) over a five-year time horizon, depending on whether costs arising from ECP and procedures which aim to preserve fertility are included. From the perspective of the Department of Defence, the reduction in costs was €100,000 over a five-year time horizon (accounting for those that require air ambulance transfer to the UK by Air Corps currently). From the perspective of the Irish family accommodation provider, the incremental five-year budget impact increased by €370,000. The budget impact associated with repatriation from the patient perspective is especially complex. The extent of the financial burden depends on family circumstances. Significant accommodation, travel and sustenance costs will be incurred by families regardless of treatment location. It is difficult to quantify how treatment abroad affects all of these costs.

The requirement to travel abroad for HSCT places a considerable financial burden on the parents and families of transplant candidates. Although repatriation would not eliminate this burden, and the range of supports that can be accessed may differ in a repatriated service, there would be a reduction in the upfront costs that families are required to pay. Therefore, families may be less reliant on charitable sources of funding and may have more certainty of their financial resources. Beyond the financial and logistical burden, the transplant journey is a period of substantial uncertainty for parents and families, irrespective of the requirement to travel abroad. Removing the requirement to travel abroad would remove many additional causes of anxiety and stress, which would be a significant benefit to the primary caregiver and family. This journey is also associated with potential isolation and emotional burden given necessary separation from family and community support networks. Such pressures are also unlikely to be equitable under the current pathway when considering lone parent families, and those from certain minority and ethnic groups.

Such logistical, financial, and emotional factors are associated with ethical challenges in the context of the current pathway of care. Additional ethical considerations include the requirement to engage with healthcare systems abroad for the provision of HSCT services, the transfer of clinical responsibility and oversight to the host country, and the reliance on the capacity and prioritisation of care in that country, with a risk to care provision should current agreements change. The current arrangements, whereby some patients are treated in Ireland and others are required to travel abroad, may appear unjust from a patient perspective.

The unpredictable nature of when transplants will be required makes it challenging to project demand. Given fluctuating levels of demand, there may be periods when demand for urgent transplant exceeds capacity in a repatriated service, whereby some patients may still need to undergo HSCT abroad to obtain timely access to care. To ensure equity and fairness, a transparent system would be required to determine which patients are prioritised first for transplant or referred abroad for treatment.

8.3 Context of key findings

In the context of paediatric HSCT, it is important to consider the impact on the family as a whole. The current pathway of care necessitates travel to the UK, potentially exacerbating the stress associated with caring for an unwell child. This places logistical and financial strain on the family unit, alongside a separation of emotional support systems. While a repatriated service may ease such burdens, it is important that appropriate supports are put in place to accommodate the needs of the family throughout the transplant journey.

The need for a repatriated HSCT service for the patient groups outlined in this HTA has previously been highlighted in the HSE paediatric model of care.[156] For those with IEI and IEM requiring HSCT, the model highlights the need to develop transplantation services in Ireland in the context of significant social cost, alongside the financial cost to the family and the state. A business case was further made for a dedicated transplant consultant, who has since been appointed. Specifically in the case of Hurler syndrome, it is highlighted that HSCT for these complex clinical cases was previously provided in Ireland, but ceased when the treating consultant retired, meaning children had to travel abroad to access this service. Again, this highlights the importance of considering the resilience of HSCT services currently, and in the context of repatriation.

Historically, children in Ireland with haemoglobinopathies have rarely undergone HSCT. In 2022, an agreement for service provision was established with St. Mary's Hospital, London. However, as of November 2022, no patient had yet completed the pathway. For the purposes of this HTA, it is assumed that these children will now have equitable access to HSCT in the context of travel abroad; however, how practical or effective this arrangement is will only be borne out as patients and their families begin to avail of the service.

In the context of equity of access to care, there is currently a separation of paediatric patient groups in terms of access to HSCT services, with some indications treated in Ireland while others must travel to the UK. Additionally, a number of the

conditions outlined within this HTA have higher incidence in the Irish Traveller population and those of non-Irish ethnicity. The repatriation of HSCT services to Ireland may align with strategies set out by the Department of Health 2021-2023[168] and in the National Traveller Health Action Plan (2022-2027)[169] to improve access to care and address health inequalities.

HIQA undertook a HTA of the addition of T-cell receptor excision circle (TREC)-based screening for all SCID subtypes to the NNBSP in Ireland to inform a recommendation by the National Screening Advisory Committee (NSAC).[63] In January 2023, the Minister for Health approved a recommendation from the NSAC to add these conditions to the NNBSP.[64]

This HTA summarised the clinical benefits associated with the earlier detection of cases of SCID in terms of improved survival and clinical outcomes. These improved outcomes rely largely on earlier detection through screening facilitating earlier initiation of preventative strategies for infections and optimising the clinical condition of the child before transplant. In the context of screening for SCID being introduced, dependent on the final recommendation and ministerial decision, access to timely HSCT may be improved in the context of a repatriated service.

Additionally, this HTA noted that there may be an increase in the need for HSCT given that there may be an increase in the post-screening prevalence of SCID (that is, in the absence of screening there may be proportion of children who die prior to identification). However, it is challenging to reliably estimate the number of children who may be affected.

The potential for a repatriated service must be considered in light of the anticipated opening of the new children's hospital on the St James's Hospital Dublin campus and the planned increase in transplant bed numbers at that location. As the required bed capacity for a repatriated service is likely to be facilitated only at this new location, the completion date of the new children's hospital will have implications for the timing of repatriation.

Of note, any increase in transplant activity is contingent on the ability to recruit trained staff. Recruitment challenges have been identified for many disciplines. In particular, the limited and fluctuating number of trained HSCT nurses available to the unit has been identified by nursing management as a risk to the expansion of the service.

In terms of ancillary services such as ECP and those aimed at fertility preservation (which are currently offered as part of care received in the UK), it was highlighted that a business case has already been submitted by the HSCT and Cellular Therapy

Unit in CHI for development of a paediatric ECP service for the existing HSCT population.

With regard to procedures aimed at fertility preservation, it is noted that a number of these are experimental in nature. While they may represent the best available option at this time, all procedures should be evidence-based with experimental procedures only provided in the context of a research programme. Furthermore, provision of these procedures must be compliant with Irish legislation. Also, as with ECP, any decision by the HSE to provide access to procedures aimed at fertility preservation would have implications beyond the repatriated cohort with potential for considerable resource and organisational impacts. The issues associated with the provision of fertility preservation in children and young people is being examined by the NCCP for patients with cancer.[170] Consideration could be given to expanding the scope of this group to include patients with benign conditions such as those considered in this HTA.

Internationally, there is an increasing demand for HSCT given the improvement in techniques and technology, and the extension of clinical indications. As highlighted in section 8.2, in the context of the rare diseases considered in this HTA, there is expected variation in demand each year. There is also potential for an increase in HSCT requirements for the population with malignancies given proposals to increase the maximum age of patients with cancer treated at CHI from 16 to 20 years. Even in the context of a repatriated service, there may be periods when demand for urgent transplant exceeds the available six-bed capacity, necessitating contingencies to be considered. These include a requirement for some patients to travel abroad for HSCT in order to obtain timely access to care. Fair and transparent decision-making would be required as to what clinical indications avail of such a service at each phase, and patient prioritisation across groups and the rationale for same clearly articulated. Additionally, there may be reciprocal ethical obligation to treat patients from other countries or Northern Ireland when their demand outweighs capacity. Such factors emphasise the importance of maintaining professional relationships and agreements with international HSCT centres to facilitate shared capacity and expertise.

While the context of HSCT would be repatriation to extend an existing service in Ireland rather than the establishment of a new service, it is important to note that this would still require significant time to implement fully.

8.4 Strengths and limitations

The findings of this assessment should be considered in light of its overall strengths and limitations. Firstly, a robust approach to the assessment was employed with

publication of a protocol for the HTA),[171] and the assessment was conducted in accordance with national and international HTA guidelines.[100, 139] An Expert Advisory Group (EAG) comprising a broad range of key stakeholders was established to support the assessment, and stakeholders outside of EAG members were consulted to ensure the perspectives of those impacted by the current and proposed pathway were appropriately represented in the assessment.

The collective patient cohorts of interest to this HTA largely represent rare conditions which are clinically heterogeneous. As such, there are challenges in reliably estimating the demand for, and costs of, HSCT, and to adequately account for the variation that may be seen year on year. Assumptions regarding the epidemiological and cost implications of the repatriation of HSCT services were therefore frequently guided by expert opinion and the international literature. However, these estimates were validated across sources wherever possible and extensively tested in sensitivity and scenario analyses to quantify the impact of uncertainty. Nonetheless, these limitations present a risk that decision-making in the Irish context may be relying on estimates which could under- or overstate the potential benefits or costs.

For the ancillary services provided as part of the current treatment pathway, namely ECP and those aimed at preserving fertility, it was beyond the scope of this HTA to consider the evidence base for their clinical effectiveness and safety. Additionally, while associated with significant resource implications in the context of the patient groups for a repatriated service, the introduction of these services in Ireland may have resource implications beyond these patient groups, which have not been considered by this assessment.

Lastly, this HTA did not assess the clinical effectiveness, safety, or the cost effectiveness of repatriation of HSCT services. These domains were omitted under the assumption of equal effectiveness of the UK and Irish service. That is, it was assumed that clinical outcomes would be equivalent whether patients are treated in the UK or Ireland. This assumption is contingent on an equivalent service, the availability of supportive services, and care being provided in accordance with appropriate local quality assurance process and international standards.

Conclusion

The results of this assessment suggest that repatriation would reduce the financial, logistical and emotional burden on families at a time that is already unavoidably stressful for families. In total, it is estimated that repatriation would mean an average of between 10 and 13 additional allogeneic HSCT procedures each year, potentially doubling the number of such procedures currently provided by CHI. While

there will be potential fluctuation in demand, on average, there would be sufficient capacity for all patients when services move to the new National Children's Hospital and the number of dedicated transplant beds increases from four to six. Under the modelled assumptions, from the perspective of the HSE, provision of the service in Ireland is unlikely to cost more than the current arrangement of travelling abroad for treatment and may be cost-saving.

It would also reduce demand for air ambulance services provided by the Department of Defence, but would increase demand for family accommodation close to CHI. If a decision were made to repatriate HSCT services for these conditions, it would be necessary to ensure appropriate resources are in place before changes are made to the existing provision of services. A decision to repatriate HSCT services for these conditions may warrant a phased approach to implementation, which would support the build-up of sustainable capacity within the service.

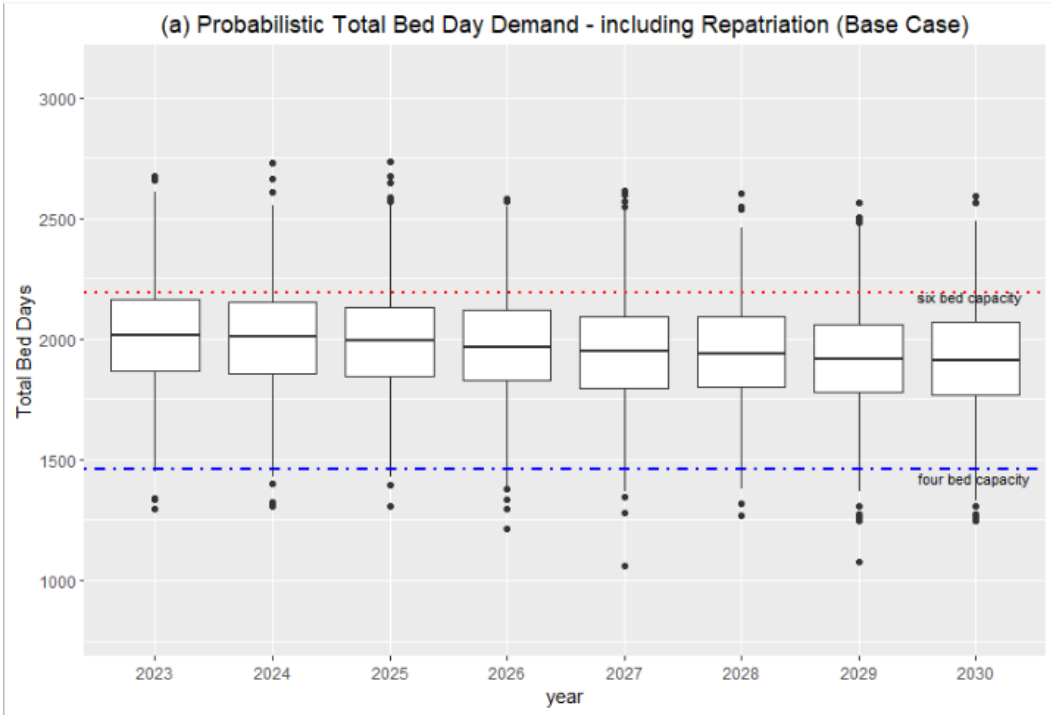
Appendix

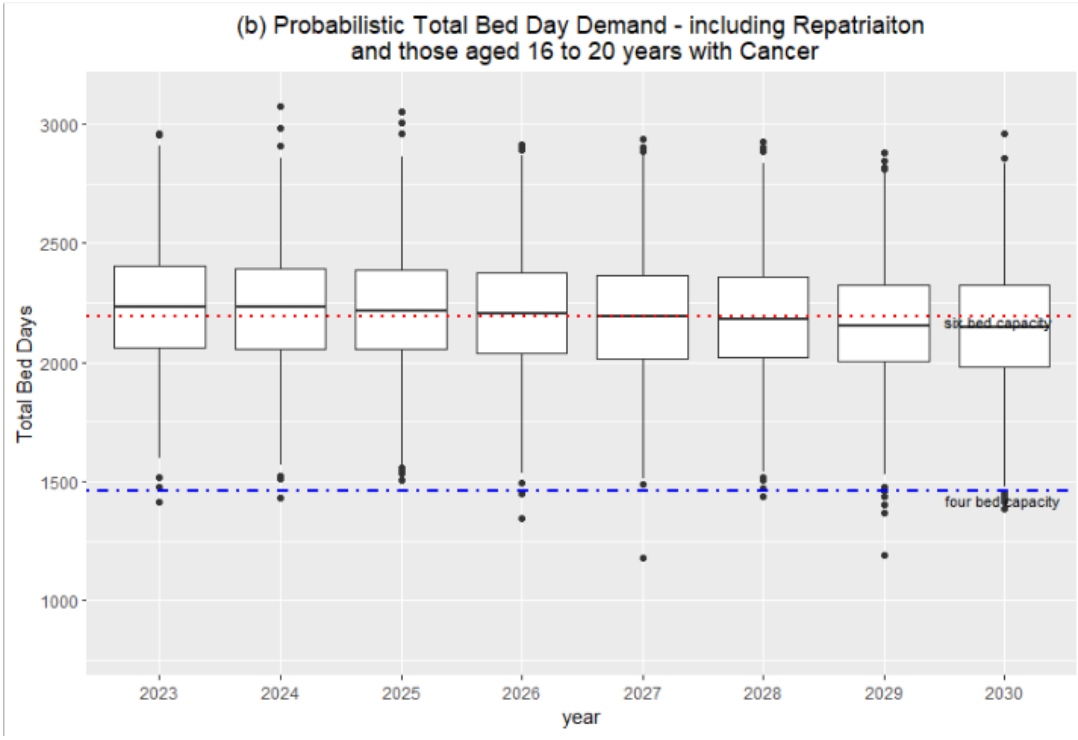
Probabilistic total bed day demand estimates derived using the methods described in section 4.3.2 are presented in Figure A1 below. To account for random variation in the number of patients presenting for HSCT every year, a probabilistic analysis was conducted whereby the number of patients presenting for autologous or allogeneic HSCT was varied using a normal distribution over 1,000 simulations. The estimated average lengths of stay were applied to the projected number of procedures to calculate the probabilistic total bed day demand. Due to a lack of data, no variation was made in the length of stay or the number of patients with haemoglobinopathies undergoing HSCT. The number of patients presenting for CAR-T therapy was also not varied as the unit is currently only funded for a maximum of five procedures pe

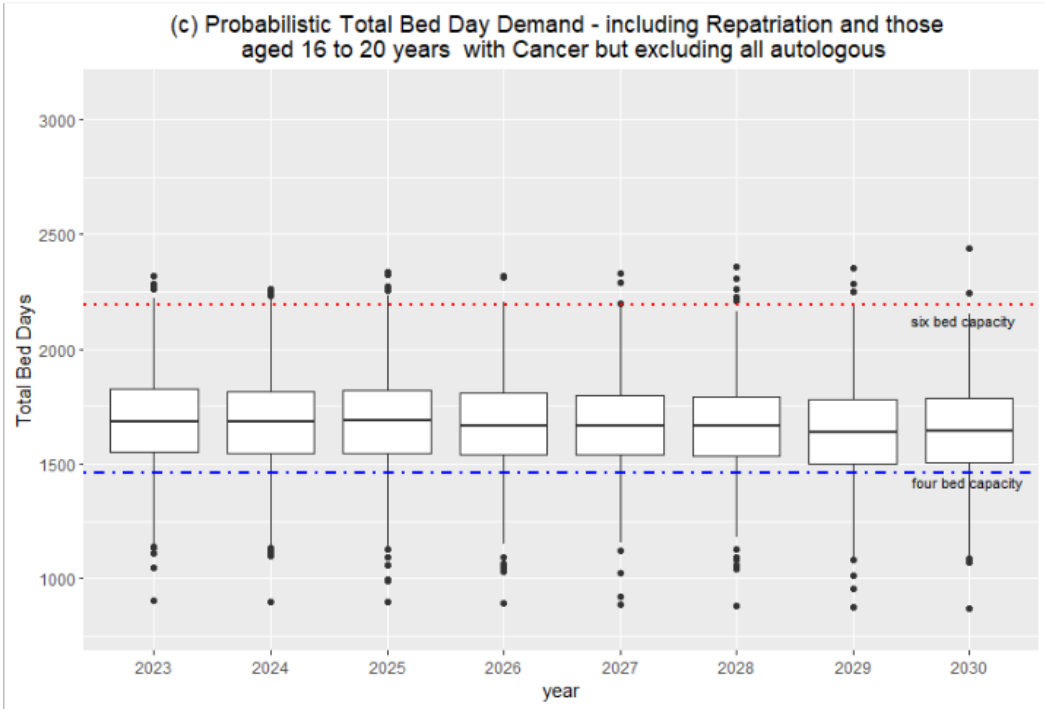
r annum and it was assumed that all five procedures would occur.

- The base case (a) includes demand for allogeneic and autologous HSCT for malignant and other indications currently transplanted at CHI as well as CAR-T cell therapy.
- Scenario (b) also includes potential demand from patients aged 16 to 20 years with malignant indications for allogeneic and autologous HSCT.
- Scenario (c) is equivalent to scenario (b) with the exception that all autologous indications are removed.

Figure A1 Probabilistic Total Bed Day Demand by scenario and year







Note: Each box represents the interquartile range (IQR) for the probabilistic total bed day demand distribution. The horizontal line in each box represents the median. The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Data beyond the end of the whiskers are called "outlying" points and are plotted individually.

References

1. Lead Consultant in Haemoglobinopathies at Children's Health Ireland at Crumlin. Personal Communication: Management of patients with haemoglobinopathies. 2022.
2. Lead Consultant in Inborn Errors of Metabolism at Children's Health Ireland at Temple Street. Personal Communication: Management of patients with inborn errors of metabolism. 2022.
3. Lead Consultant in Inborn Errors of Immunity at Children's Health Ireland at Crumlin. Personal Communication: Management of patients with inborn errors of immunity. 2022.
4. Murphy K, Weaver C. Janeway's immunobiology. Abingdon: Garland science; 2016.
5. National Health Service. Stem cell and bone marrow transplants [Internet]. 2022 [cited 2022 November 1]. Available from: https://www.nhs.uk/conditions/stem-cell-transplant/.
6. Hutt D. Engraftment, Graft Failure, and Rejection. In: Kenyon M, Babic A, editors. The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT. Cham (CH): Springer; 2018.
7. EBMT. JACIE Accreditation [Internet]. 2022 [cited 2022 May 12]. Available from: https://www.ebmt.org/jacie-accreditation.
8. EBMT. JACIE Accredited Centres [Internet]. 2022 [cited 2022 May 12]. Available from: https://www.ebmt.org/jacie-accredited-centres.
9. Consultant Haematologists (CHI Crumlin). Personal Communication: Management of patients receiving allogeneic HSCT. 2022.
10. HSE. Treatment Abroad Scheme [Internet]. 2022 [cited 2022 May 12]. Available from: https://www2.hse.ie/services/treatment-abroad-scheme/.
11. Lankester AC, Albert MH, Booth C, Gennery AR, Güngör T, Hönig M, et al. EBMT/ESID inborn errors working party guidelines for hematopoietic stem cell transplantation for inborn errors of immunity. Bone Marrow Transplantation. 2021;56(9):2052-62.
12. HSE. Travel Policy for E112 Applicants [Internet]. 2021 [cited 2022 November 15]. Available from: https://assets.hse.ie/media/documents/travel-policy-for-treatment-abroad-scheme-applicants-e112_wpypo4H.pdf.
13. Galgano L, Hutt D. HSCT: How Does It Work? In: Kenyon M, Babic A, editors. The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT. Cham (CH): Springer; 2018.
14. Ní Chonghaile M. Donor Selection. In: Kenyon M, Babic A, editors. The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT. Cham (CH): Springer; 2018.
15. Irish Blood Transfusion Service. Irish Unrelated Bone Marrow Registry [Internet]. 2022 [cited 2022 May 12]. Available from: https://www.giveblood.ie/clinical-services/bone-marrow-registry/.
16. Fuchs EJ, Luznik L. HLA-haploidentical hematopoietic cell transplantation [Internet]. UpToDate; 2022 [cited 2022 May 12]. Available from: https://www.uptodate.com/contents/hla-haploidentical-hematopoietic-cell-

transplantation.
17. Lead Consultant in HSCT at Children's Health Ireland at Crumlin. Personal Communication: Management of HSCT transplant recipients. 2022.
18. Clinical Lead Clinical Programme for Children and Adolescent/Young Adults with Cancer. Personal Communication: Management of patients peceiving a HSCT. . 2022.
19. Krishnamurti L. Hematopoietic Cell Transplantation for Sickle Cell Disease. Frontiers in Pediatrics. 2021;8:551170.
20. Tan EY, Boelens JJ, Jones SA, Wynn RF. Hematopoietic Stem Cell Transplantation in Inborn Errors of Metabolism. Front Pediatr. 2019;7:433.
21. Kanter J, Liem RI, Bernaudin F, Bolaños-Meade J, Fitzhugh CD, Hankins JS, et al. American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. Blood Advances. 2021;5(18):3668-89.
22. Babic A, Trigoso E. Cell Source and Apheresis. In: Kenyon M, Babic A, editors. The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT. Cham (CH): Springer; 2018.
23. Irish Blood Transfusion Service. Donation Process [Internet]. 2022 [cited 2022 May 12]. Available from: https://www.giveblood.ie/bone-marrow/bone-marrow-donation-process/.
24. NHS Blood and Transplant. Donating cord blood [Internet]. NHS 2022 [cited 2022 May 12]. Available from: https://www.blood.co.uk/news-and-campaigns/the-donor/latest-stories/donating-cord-blood/.
25. Hubel K. Mobillization and Collection of HSC. In: Carreras E, Dufour C, Mohty M, Kroger N, editors. The EBMT Handbook - Hematopoietic Stem Cell Transplantation and Cellular Therapies. Cham: EBMT; 2019.
26. Zulu S, Kenyon M. Principles of Conditioning Therapy and Cell Infusion In: Kenyon M, Babic A, editors. The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT. Cham (CH): Springer; 2018.
27. Haddad E, Hoenig M. Hematopoietic Stem Cell Transplantation for Severe Combined Immunodeficiency (SCID). Front Pediatr. 2019;7:481.
28. NIH National Cancer Institute. Stem Cell Engraftment [Internet]. 2022 [cited 2022 May 13]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/stem-cell-engraftment.
29. NHS England. B04/S/B 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Children) [Internet]. NHS England; 2013 [cited 2022 May 12]. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/06/b04-haema-child.pdf.
30. Bader P. Documentation of Engraftment and Chimerism After HSCT. In: Carreras E, Dufour C, Mohty M, Kroger N, editors. The EBMT Handbook - Hematopoietic Stem Cell Transplantation and Cellular Therapies. Cham: EBMT; 2019.
31. Immune Deficiency Foundation USA. Guide to Hematopoietic Stem Cell Transplantation. Towson: Immune Deficiency Foundation U, 2018.
32. Miyamoto S, Umeda K, Kurata M, Nishimura A, Yanagimachi M, Ishimura M, et al. Hematopoietic Cell Transplantation for Severe Combined Immunodeficiency

Patients: a Japanese Retrospective Study. Journal of clinical immunology. 2021;41(8):1865-77.
33. Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. The New England journal of medicine. 2014;371(5):434-46.
34. Vogelsang GB. How I treat chronic graft-versus-host disease. Blood. 2001;97(5):1196-201.
35. Toubai T, Sun Y, Reddy P. GVHD pathophysiology: is acute different from chronic? Best Practice & Research Clinical Haematology. 2008;21(2):101-17.
36. FACT-JACIE. International Standards For Hematopoietic Cellular Therapy Product Collection, Processing, and Administration [Internet]. FACT-JACIE; 2021 [cited 2022 May 12]. 8.1. Available from: https://www.ebmt.org/sites/default/files/2021-12/STS_5_2_041_FACT-JACIE%20Standards%20Eighth%20Edition_8_1_R2_12142021_ForWeb.pdf.
37. The Royal Marsden NHS Foundation Trust. JACIE Accreditation [Internet]. Chelsea: The Royal Marsden NHS Foundation Trust; 2022 [cited 2022 May 13]. Available from: https://www.royalmarsden.nhs.uk/about-royal-marsden/quality-and-safety/regulatory-information/jacie-accreditation.
38. EBMT. About JACIE [Internet]. EBMT; 2022 [cited 2022 May 12]. Available from: https://www.ebmt.org/accreditation/about-jacie.
39. FACT-JACIE. International Standards For Hematopoietic Cellular Therapy Product Collection, Processing, and Administration Accreditation Manual [Internet]. FACT-JACIE; 2021 [cited 2022 May 21]. 8.2. Available from: https://www.ebmt.org/sites/default/files/2021-12/STS_5_2_042_FACT-JACIE%20AccreditationMANUAL%20Eighth%20Edition_8_2_R3_12142021_ForWeb.pdf.
40. BSBMTCT. Annual Activity 2020 [Internet]. BSBMTCT; 2022 [cited 2022 May 13]. Available from: https://bsbmtct.org/activity/2020/.
41. NHS England. Clinical Commissioning Policy: Haematopoeitic Stem Cell Transplantation (HSCT) (All Ages): Revised Reference: NHS England B04/P/a [Internet]. NHS England; 2021 [cited 2022 December 12]. Available from: https://www.england.nhs.uk/wp-content/uploads/2022/10/Haematopoietic-Stem-Cell-Transplantation-HSCT-All-Ages.pdf.
42. NHS England. Clinical Commissioning Policy: Allogeneic Haematopoietic Stem Cell Transplant for Primary Immunodeficiencies (all ages) [Internet]. NHS England,; 2019 [cited 2022 May 12]. Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/07/Clinical-Commissioning-Policy_Allogeneic-Haematopoietic-Stem-Cell-Transplant-for-Primary-Immunodeficiencies.pdf.
43. Children's Health Ireland at Crumlin. Red Cell and Haemoglobinopathy Service [Internet]. Dublin: Children's Health Ireland; 2022 [cited 2022 May 13]. Available from: https://www.olchc.ie/services/departments-a-z/children-s-cancer-services/red-cell-and-haemoglobinopathy-service/.
44. National Centre for Inherited Metabolic Disorders. National Centre for Inherited Metabolic Disorders

[Internet]. 2022 [cited 2022 May 12]. Available from: www.metabolic.ie.
45. HSE. How to apply [Internet]. HSE; 2018 [updated 2018 January 24; cited 2022 November 11]. Available from: https://www2.hse.ie/services/schemes-allowances/treatment-abroad/how-to-apply/.
46. Bompoint C, Castagna A, Hutt D, Leather A, Stenvall M, Schroder T, et al. Transplant Preparation. In: Kenyon M, Babic A, editors. The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT. Cham (CH): Springer; 2018.
47. BSBMTCT. BSBMTCT Executive Summary of Transplant & Cellular Therapy Outcomes in UK/ROI A report for Commissioners 12th edition BSBMTCT, 2021.
48. BSBMT. BSBMT 8th Report To Specialist Commissioners. BSBMT, 2017.
49. Alfred A, Taylor PC, Dignan F, El-Ghariani K, Griffin J, Gennery AR, et al. The role of extracorporeal photopheresis in the management of cutaneous T-cell lymphoma, graft-versus-host disease and organ transplant rejection: a consensus statement update from the UK Photopheresis Society. British journal of haematology. 2017;177(2):287-310.
50. Administrator HSE. Personal communication: Administration of the Treatment Abroad Scheme. 2022.
51. Genetic Alliance The New York-Mid-Atlantic Consortium for Genetic Newborn Screening Services. Understanding Genetics: A New York, Mid-Atlantic Guide for Patients and Health Professionals. Washington (DC): Genetic Alliance; 2009.
52. Currier R, Puck JM. SCID newborn screening: What we've learned. The Journal of allergy and clinical immunology. 2021;147(2):417-26.
53. Murphy AM, Lambert D, Treacy EP, O'Meara A, Lynch SA. Incidence and prevalence of mucopolysaccharidosis type 1 in the Irish republic. Arch Dis Child. 2009;94(1):52-4.
54. Lobitz S, Telfer P, Cela E, Allaf B, Angastiniotis M, Backman Johansson C, et al. Newborn screening for sickle cell disease in Europe: recommendations from a Pan-European Consensus Conference. British journal of haematology. 2018;183(4):648-60.
55. BSBMTCT UK Paediatric BMT Group. Indications for HSCT in Children- UK Paediatric BMT Group 2015 [Internet]. BSBMTCT; 2015 [cited 2022 May 12]. Available from: https://www.bsbmtct.org/wp-content/uploads/2020/01/UK-Paed-BMT-Gp-HSCT_Indications_15Oct2015.pdf.
56. Angelucci E, Matthes-Martin S, Baronciani D, Bernaudin F, Bonanomi S, Cappellini MD, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. Haematologica. 2014;99(5):811-20.
57. McCusker C, Warrington R. Primary immunodeficiency. Allergy, Asthma & Clinical Immunology. 2011;7(1):S11.
58. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022:1-35.
59. Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Human Inborn Errors of Immunity: 2019 Update on the Classification

from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2020;40(1):24-64.
60. Fischer A, Notarangelo LD, Neven B, Cavazzana M, Puck JM. Severe combined immunodeficiencies and related disorders. Nature Reviews Disease Primers. 2015;1(1):15061.
61. European Society for Immunodeficiencies. Working definitions for clinical diagnosis of PID [Internet]. 2019 [cited 2022 November 12]. Available from: https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria.
62. National Newborn Bloodspot Screening Laboratory. A Practical Guide to Newborn Bloodspot Screening In Ireland [Internet]. HSE; 2022 [cited 2022 November 11]. 9th Edition. Available from: https://www.hse.ie/eng/health/child/newbornscreening/newbornbloodspotscreening/information-for-professionals/a-practical-guide-to-newborn-bloodspot-screening-in-ireland.pdf.
63. Health Information and Quality Authority. HTA of the addition of severe combined immunodeficiency (SCID) to the National Newborn Bloodspot Screening Programme [Internet]. Cork: Health Information and Quality Authority; 2023 [updated 2023 January 18; cited 2023 January 20]. Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/hta-addition-severe-combined-immunodeficiency.
64. Department of Health. Minister for Health approves 10th condition for the National Newborn Bloodspot Screening Programme, [Internet]. Dublin: Government of Ireland; 2023 [updated 2023 January 19; cited 2023 January 20]. Available from: https://www.gov.ie/en/publication/c9a66-minister-for-health-approves-10th-condition-for-the-national-newborn-bloodspot-screening-programme/#:~:text=The%20Minister%20for%20Health%20Stephen,Bloodspot%20Screening%20(NBS)%20Programme.
65. Marciano BE, Huang CY, Joshi G, Rezaei N, Carvalho BC, Allwood Z, et al. BCG vaccination in patients with severe combined immunodeficiency: complications, risks, and vaccination policies. The Journal of allergy and clinical immunology. 2014;133(4):1134-41.
66. Shearer WT, Dunn E, Notarangelo LD, Dvorak CC, Puck JM, Logan BR, et al. Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: the Primary Immune Deficiency Treatment Consortium experience. The Journal of allergy and clinical immunology. 2014;133(4):1092-8.
67. Puck JM. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia. Immunological reviews. 2019;287(1):241-52.
68. Rivers L, Gaspar HB. Severe combined immunodeficiency: recent developments and guidance on clinical management. Arch Dis Child. 2015;100(7):667-72.
69. NHS. Overview - Stem cell and bone marrow transplants [Internet]. NHS; 2022 [updated 7 Sept 2022; cited 2022 November 14]. Available from: https://www.nhs.uk/conditions/stem-cell-transplant/.
70. Haddad E, Logan BR, Griffith LM, Buckley RH, Parrott RE, Prockop SE, et al. SCID genotype and 6-month posttransplant CD4 count predict survival and

immune recovery. Blood. 2018;132(17):1737-49.
71. Chiesa R, Wynn RF, Veys P. Haematopoietic stem cell transplantation in inborn errors of metabolism. Current Opinion in Hematology. 2016;23(6):530-35.
72. de Vasconcelos P, Lacerda JF. Hematopoietic Stem Cell Transplantation for Neurological Disorders: A Focus on Inborn Errors of Metabolism. Frontiers in Cellular Neuroscience. 2022;16:895511.
73. Kruszka P, Regier D. Inborn Errors of Metabolism: From Preconception to Adulthood. American family physician. 2019;99(1):25-32.
74. Taylor M, Khan S, Stapleton M, Wang J, Chen J, Wynn R, et al. Hematopoietic Stem Cell Transplantation for Mucopolysaccharidoses: Past, Present, and Future. Biology of Blood and Marrow Transplantation. 2019;25(7):e226-e46.
75. Moore D, Connock M, Wraith E, Lavery C. The prevalence of and survival in Mucopolysaccharidosis I: Hurler, Hurler-Scheie and Scheie syndromes in the UK. Orphanet journal of rare diseases. 2008;3:24.
76. Ghosh A, Miller W, Orchard PJ, Jones SA, Mercer J, Church HJ, et al. Enzyme replacement therapy prior to haematopoietic stem cell transplantation in Mucopolysaccharidosis Type I: 10 year combined experience of 2 centres. Molecular genetics and metabolism. 2016;117(3):373-7.
77. Wynn R, Schulz A. Inborn Errors of Metabolism and Osteopetrosis. In: Carreras E, Dufour C, Mohty M, Kröger N, editors. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies. Cham: Springer Nature; 2019.
78. Aldenhoven M, Jones SA, Bonney D, Borrill RE, Coussons M, Mercer J, et al. Hematopoietic cell transplantation for mucopolysaccharidosis patients is safe and effective: results after implementation of international guidelines. Biol Blood Marrow Transplant. 2015;21(6):1106-9.
79. Trent RJ. Diagnosis of the haemoglobinopathies. Clinical Biochemist Reviews. 2006;27(1):27-38.
80. Halim-Fikri BH, Lederer CW, Baig AA, Mat-Ghani SNA, Syed-Hassan SR, Yusof W, et al. Global Globin Network Consensus Paper: Classification and Stratified Roadmaps for Improved Thalassaemia Care and Prevention in 32 Countries. Journal of personalized medicine. 2022;12(4):552.
81. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. Lancet (London, England). 2017;390(10091):311-23.
82. Piel FB, Steinberg MH, Rees DC. Sickle Cell Disease. New England Journal of Medicine. 2017;376(16):1561-73.
83. Cappelli B, Gluckman E, Ghanem K, Abboud MR. Hemoglobinopathies (Sickle Cell Disease and Thalassemia). In: Carreras E, Dufour C, Mohty M, Kröger N, editors. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies. Cham: Springer Nature; 2019.
84. Wastnedge E, Waters D, Patel S, Morrison K, Goh MY, Adeloye D, et al. The global burden of sickle cell disease in children under five years of age: a systematic review and meta-analysis. Journal of global health. 2018;8(2):021103.
85. Streetly A, Sisodia R, Dick M, Latinovic R, Hounsell K, Dormandy E. Evaluation of newborn sickle cell screening programme in England: 2010-2016. Arch Dis

Child. 2018;103(7):648-53.
86. Public Health England. SCT screening: handbook for newborn laboratories [Internet]. Public Health England; 2021 [cited 2022 October 12]. Available from: https://www.gov.uk/government/publications/sct-screening-handbook-for-newborn-laboratories.
87. Leonard A, Bertaina A, Bonfim C, Cohen S, Prockop S, Purtill D, et al. Curative therapy for hemoglobinopathies: an International Society for Cell & Gene Therapy Stem Cell Engineering Committee review comparing outcomes, accessibility and cost of ex vivo stem cell gene therapy versus allogeneic hematopoietic stem cell transplantation. Cytotherapy. 2022;24(3):249-61.
88. Walters MC, De Castro LM, Sullivan KM, Krishnamurti L, Kamani N, Bredeson C, et al. Indications and Results of HLA-Identical Sibling Hematopoietic Cell Transplantation for Sickle Cell Disease. Biology of Blood and Marrow Transplantation. 2016;22(2):207-11.
89. Gluckman E, Cappelli B, Bernaudin F, Labopin M, Volt F, Carreras J, et al. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. Blood. 2017;129(11):1548-56.
90. Expert Advisory Group. Personal Communication: Results of analysis of patient data. 2022.
91. BSBMTCT. Annual Report 2021 For transplants performed 2014 to 2018 and snapshot data for 2019: OLHSC Dublin CIC 774 Rep of Ireland. 2021.
92. Children's Health Ireland at Temple Street. Personal Communication: Results of analysis of patient data. 2022.
93. Central Statistics Office. Population [Internet]. Central Statistics Office; 2022 [cited 2022 November 12]. Available from: https://www.cso.ie/en/statistics/population/.
94. Department of Health. National Cancer Strategy 2017 - 2026 [Internet]. Dublin: Department of Health; 2017 [cited 2022 December 16]. Available from: https://www.gov.ie/en/publication/a89819-national-cancer-strategy-2017-2026/#:~:text=This%20Cancer%20Strategy%20aims%20to,Ireland%20for%20the%20next%20decade.&text=This%20strategy%20aims%20to%20reduce%20the%20number%20of%20cancer%20cases%20in%20Ireland.
95. National Cancer Control Programme. Framework for the Care and Support of Adolescents and Young Adults (AYA) with Cancer in Ireland 2021 - 2026 [Internet]. HSE; 2022 [cited 2022 December 16]. Available from: https://www.hse.ie/eng/services/publications/framework-for-the-care-and-support-of-adolescent-and-young-adults-in-ireland.pdf.
96. Central Statistics Office. Census of Population 2016 – Profile 8 Irish Travellers, Ethnicity and Religion [Internet]. Cork: Central Statistics Office; 2016 [cited 2022 November 7]. Available from: https://www.cso.ie/en/releasesandpublications/ep/p-cp8iter/p8iter/p8itd/.
97. European Medicines Agency. EU/3/05/313: orphan designation for the treatment of severe combined immunodeficiency (SCID) due to adenosine deaminase (ADA) deficiency [Internet]. London: European Medicines Agency; 2016 [cited 2022 August 15]. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-

05-313.
98. Snowden JA, Sánchez-Ortega I, Corbacioglu S, Basak GW, Chabannon C, de la Camara R, et al. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. Bone Marrow Transplantation. 2022;57(8):1217-39.
99. Yesilipek MA. Hematopoietic Stem Cell Transplantation in Patients with Hemoglobinopathies. Hemoglobin. 2020;44(6):377-84.
100. European Network for Health Technology Assessment (EUnetHTA). HTA Core Model Version 3.0 [Internet]. 2016 [cited 2022 November 12]. Available from: https://eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf
101. HSE. About the scheme [Internet]. HSE; 2018 [updated 8 Nov 2018; cited 2022 November 11]. Available from: https://www2.hse.ie/services/schemes-allowances/treatment-abroad/about/.
102. HSE. Performance Profile January-March 2021. Dublin, Ireland: 2021.
103. Treatment Abroad Scheme. Treatment Abroad Scheme records. 2022.
104. Medical Social Worker at Crumlin. 2022.
105. Clinicans at Children's Health Ireland. Developing a Comprehensive Paediatric Haematopoietic Stem Cell Transplantation Service for the Republic of Ireland [Unpublished business case]. 2018.
106. O'Regan E. New national children's hospital due to open its doors to patients in late 2024 as costs set to exceed €1.4bn. The Irish Independent,. 2022 October 05 2022
107. Children's Health Ireland at Crumlin. Clinics and Wards [Internet]. 2022 [Available from: https://www.olchc.ie/services/departments-a-z/chi-haematopoietic-stem-cell-transplant-and-cellular-therapy-service/clinics-and-wards/.
108. Consultant immunologist (CHI Crumlin). Personal Communication: Management of patients receiving HSCT. 2022.
109. Children's Health Ireland. A revolutionary cancer treatment, CAR-T cell therapy now available to children in Ireland [Internet]. Dublin: Children's Health Ireland; 2022 [updated 27 Apr 2022; cited 2022 December 19]. Available from: https://www.cuh.ie/2022/04/a-revolutionary-cancer-treatment-car-t-cell-therapy-now-available-to-children-in-ireland/.
110. Healthcare Pricing Office. ABF 2022 Admitted Patient Price List [Internet]. HSE; 2022 [cited 2022 November 12]. Available from: https://www.hpo.ie/abf/ABF2022AdmittedPatientPriceList.pdf.
111. AnthonyNolan.org, Ernst & Young LLP. Analysis of hospital activity and costs following allogeneic stem cell transplantation in England [Internet]. London: Ernst & Young LLP; 2021 [Available from: https://www.anthonynolan.org/sites/default/files/2021-03/analysis-of-hospital-activity-and-costs.pdf.
112. HSCT coordinator at Children's Health Ireland at Crumlin. Personal Communication: Managment of HSCT transplant recipients. 2022.
113. Chief medical scientists HSCT laboratory at CHI Crumlin. Personal Communication. 2022.

114. Children's Health Ireland at Crumlin. Parents Accomodation Unit Information Pack [Internet]. No date [cited 2022 November 12]. Available from: https://www.olchc.ie/children-family/parent-patient-information-leaflets/parents-accommodation-unit-information-pack.pdf.
115. Ronald McDonald House Charities (Ireland). What We Do [Internet]. Dublin Ronald McDonald House Charities,; 2022 [cited 2022 November 12]. Available from: https://rmhc.ie/what-we-do/.
116. Department of Health. Minister for Health announces appointment of Ronald McDonald House Charities as the designated charity partner for the proposed Family Accommodation Unit at the new Children's Hospital [Internet]. Dublin: Department of Health; 2021 [cited 2022 November 12]. Available from: https://www.gov.ie/en/press-release/bb768-minister-for-health-announces-appointment-of-ronald-mcdonald-house-charities-as-the-designated-charity-partner-for-the-proposed-family-accommodation-unit-at-the-new-childrens-hospital/.
117. Lawitschka A, Lucchini G, Strahm B, Dalle JH, Balduzzi A, Gibson B, et al. Pediatric acute graft-versus-host disease prophylaxis and treatment: surveyed real-life approach reveals dissimilarities compared to published recommendations. Transplant international : official journal of the European Society for Organ Transplantation. 2020;33(7):762-72.
118. NHS England. Clinical Commissioning Policy: Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation [Internet]. NHS England,; 2017 [cited 2022 November 12]. Available from: https://www.england.nhs.uk/publication/treatments-for-graft-versus-host-disease-gvhd-following-haematopoietic/.
119. Greinix H. Photopheresis in Adults and Pediatrics. In: Carreras E, Dufour C, Mohty M, Kroger N, editors. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies. 7th ed. Cham: Springer Nature; 2019.
120. Brown L, Xu-Bayford J, Allwood Z, Slatter M, Cant A, Davies EG, et al. Neonatal diagnosis of severe combined immunodeficiency leads to significantly improved survival outcome: the case for newborn screening. Blood, The Journal of the American Society of Hematology. 2011;117(11):3243-6.
121. Railey MD, Lokhnygina Y, Buckley RH. Long-term clinical outcome of patients with severe combined immunodeficiency who received related donor bone marrow transplants without pretransplant chemotherapy or post-transplant GVHD prophylaxis. The Journal of pediatrics. 2009;155(6):834-40.e1.
122. Balduzzi A, Dalle JH, Jahnukainen K, von Wolff M, Lucchini G, Ifversen M, et al. Fertility preservation issues in pediatric hematopoietic stem cell transplantation: practical approaches from the consensus of the Pediatric Diseases Working Party of the EBMT and the International BFM Study Group. Bone Marrow Transplant. 2017;52(10):1406-15.
123. NHS. What happens -IVF [Internet]. NHS; 2021 [updated 2021 October 18; cited 2022 November 12]. Available from: https://www.nhs.uk/conditions/ivf/what-happens/.
124. Hussein AA, Tran ND, Smith JF. Fertility preservation for boys and adolescents facing sterilizing medical therapy. Translational Andrology and Urology.

2014;3(4):382.
125. Mulder RL, Font-Gonzalez A, Green DM, Loeffen EA, Hudson MM, Loonen J, et al. Fertility preservation for male patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. The Lancet Oncology. 2021;22(2):e57-e67.
126. Mulder RL, Font-Gonzalez A, Hudson MM, Van Santen HM, Loeffen EA, Burns KC, et al. Fertility preservation for female patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. The Lancet Oncology. 2021;22(2):e45-e56.
127. Lotz L, Dittrich R, Hoffmann I, Beckmann MW. Ovarian Tissue Transplantation: Experience From Germany and Worldwide Efficacy. Clinical medicine insights Reproductive health. 2019;13:1179558119867357.
128. Dolmans M-M, von Wolff M, Poirot C, Diaz-Garcia C, Cacciottola L, Boissel N, et al. Transplantation of cryopreserved ovarian tissue in a series of 285 women: a review of five leading European centers. Fertility and Sterility. 2021;115(5):1102-15.
129. Mayo Clinic. Primary ovarian insufficiency [Internet]. Mayo Foundation for Medical Education and Research; 2021 [Available from: https://www.mayoclinic.org/diseases-conditions/premature-ovarian-failure/symptoms-causes/syc-20354683.
130. Oxford Tissue Cryopreservation Service. Ovarian Tissue Cryopreservation: Patient [Internet]. Oxford, England: Oxford University Hosptials NHS Foundation Trust; 2016 [cited 2022 November 12]. Available from: https://www.ouh.nhs.uk/patient-guide/leaflets/files/12856Povarian.pdf.
131. Lakhoo K, Davies J, Chakraborty S, Berg S, Tennyson R, Fowler D, et al. Development of a new reproductive tissue cryopreservation clinical service for children: the Oxford programme. Pediatr Surg Int. 2019;35(11):1271-8.
132. Irish Cancer Society. Irish Cancer Society Pre-Budget Submission 2022 [Internet]. Dublin, Ireland: Irish Cancer Society; 2022 [cited 2022 November 12]. Available from: https://www.cancer.ie/sites/default/files/2021-09/Real%20Cost%20Of%20Childhood%20Cancer%20and%20Prebudget%202022.pdf.
133. Latif S, Martins Da Silva S, Davies M, Mavrelos D, Foo X, Sangster P, et al. Fertility preservation provision in the NHS: a national assessment of care policies. Human Fertility [Internet]. 2022 [cited 2022 November 12]:1-6. Available from: https://doi.org/10.1080/14647273.2022.2045519.
134. Newton HL, Picton HM, Friend AJ, Hayden CM, Brougham M, Cox R, et al. Inconsistencies in fertility preservation for young people with cancer in the UK. Archives of Disease in Childhood. 2022;107(3):265.
135. Irish Cancer Society. Childhood Cancer Fertility Project update [Internet]. Irish Cancer Society; 2021 [updated 2021 September 21; cited 2022 16 Dec]. Available from: https://www.cancer.ie/about-us/news/childhood-cancer-fertility-project-update.

136. Houses of the Oireachtas. Health (Assisted Human Reproduction) Bill 2022 [Internet]. Dublin: Houses of the Oireachtas; 2022 [cited 2022 May 12]. Available from: https://www.oireachtas.ie/en/bills/bill/2022/29/.
137. National Office of Clinical Audit. Irish Paediatric Critical Care Audit National Report 2017-2019 [Internet]. Dublin: HSE; 2021 [cited 2022 November 12]. Available from: https://www.noca.ie/documents/irish-paediatric-critical-care-audit-national-report-2017-2019.
138. National Clinical Programme for Critical Care and National Clinical Programme for Paediatrics. Model of Care for Paediatric Critical Care [Internet]. Dublin: Children's Health Ireland; 2019 [Available from: https://www.hse.ie/eng/about/who/cspd/ncps/critical-care/moc/model-of-care-for-paediatric-critical-care.pdf.
139. Health Information and Quality Authority. Guidelines for the Budget Impact Analysis of Health Technologies in Ireland [Internet]. Cork: HIQA; 2018 [updated 2018 January 17; cited 2022 November 13]. Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/guidelines-budget-impact-analysis-health.
140. Revenue. Search VAT rates [Internet]. 2022 [updated 2022 Feb 21; cited 2022 November 12]. Available from: https://www.revenue.ie/en/vat/vat-rates/search-vat-rates/vat-rates-database.aspx.
141. HSE. Pay scales [Internet]. HSE; 2022 [cited 2022 May 12]. Available from: https://healthservice.hse.ie/staff/benefits-services/pay/pay-scales.html.
142. Burns H, Collins A, Marsden P, Flood TJ, Slatter MA, Booth C, et al. Severe Combined Immunodeficiency (SCID)-the Irish Experience. J Clin Immunol. 2021;41(8):1950-3.
143. Department of Defence. Organisation information: Routinely Published Information [Internet]. Dublin: Department of Defense; 2019 [updated 2019 October 15; cited 2022 November 9]. Available from: https://www.gov.ie/en/organisation-information/e8132-routinely-published-information/#.
144. St. Vincent's University Hospital. Patient Charges [Internet]. Dublin: St. Vincent's University Hospital; 2022 [cited 2022 November 9]. Available from: https://www.stvincents.ie/for-patients/patient-charges/.
145. Ronald McDonald House Charities (Ireland). Ronald McDonald House Charities (IRL) Annual Report and Audited Financial Statements for the financial year ended 31 December 2021 [Internet]. Dublin, Ireland: Ronald McDonald House Charities (Ireland),; 2021 [cited 2022 November 12]. Available from: https://rmhc.ie/wp-content/uploads/2022/05/RMHC-IRL-Signed-Financial-Accounts-2021-SORP.pdf.
146. Merrion Fertility Clinic. Pricelist [Internet]. Dublin: Merrion Fertilty Clinc; 2022 [cited 2022 November 9]. Available from: https://merrionfertility.ie/pricelist/.
147. Beacon Care Fertility. IVF Costs / Pricing [Internet]. Dublin: Beacon Care Fertiliy; 2022 [cited 2022 Nov 9]. Available from: https://www.beaconcarefertility.ie/ivf-costs/.
148. Therapie Fertility. Treatments and testing price list [Internet]. Dublin: Therapie Fertility; 2022 [updated 2022; cited 2022 November 9]. Available from:

https://www.therapiefertility.com/pricing/.
149. Kitko CL, Abdel-Azim H, Carpenter PA, Dalle J-H, Diaz-de-Heredia C, Gaspari S, et al. A Prospective, Multicenter Study of Closed-System Extracorporeal Photopheresis for Children with Steroid-Refractory Acute Graft-versus-Host Disease. Transplantation and Cellular Therapy. 2022;28(5):261.e1-.e7.
150. NHS England. Integrated Impact Assessment Report for Clinical Commissioning Polcies: Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation [Internet]. NHS England,; 2016 [cited 2022 November 9]. Available from: https://www.engage.england.nhs.uk/consultation/clinical-commissioning-wave8/user_uploads/f01x08-impact-assessment.pdf.
151. Ryanair.com. Search for flights [Internet]. Ryanair; 2022 [cited 2022 November 14]. Available from: https://www.ryanair.com/ie/en.
152. Central Statistics Office. Earnings and Labour Costs Q2 [Internet]. Cork: Central Statistics Office; 2022 [cited 2022 November 14]. Available from: https://www.cso.ie/en/statistics/earnings/earningsandlabourcosts/.
153. booking.com. Find your next stay [Internet]. Booking.com; 2022 [cited 2022 November 14]. Available from: https://www.booking.com/.
154. Healthcare Pricing Office. ABF Pricing Framwork for the 2022 Price List [Internet]. Dublin: HSE; 2022 [cited 2022 November 14]. Available from: https://www.hpo.ie/abf/HPOABFPricingFramework2022-28June2022.pdf.
155. Citizens Information Board. Domiciliary Care Allowance [Internet]. Citizens Information Board; 2022 [updated 2022 September 28; cited 2022 November 11]. Available from: https://www.citizensinformation.ie/en/social_welfare/social_welfare_payments/disability_and_illness/domiciliary_care_allowance.html#:~:text=Domiciliary%20Care%20Allowance-,What%20is%20the%20Domiciliary%20Care%20Allowance%3F,It%20is%20not%20means%20tested.
156. HSE. A National Model of Care for Paediatric Healthcare Services in Ireland [Internet]. Dublin: HSE; 2015 [cited 2022 October 14]. Available from: https://www.hse.ie/eng/about/who/cspd/ncps/paediatrics-neonatology/moc/chapters/.
157. Children in Hospital Ireland. Childhood Illness, Financial Stress: The Hidden Costs of Hospital Care for Children [Internet]. Dublin: Children in Hospital Ireland; 2020 [cited 2022 December 1]. Available from: https://childreninhospital.ie/wp-content/uploads/2021/09/Children-in-Hospital-Report_1-FINAL.pdf.
158. McKey S, Quirke B, Fitzpatrick P, Kelleher CC, Malone KM. A rapid review of Irish Traveller mental health and suicide: a psychosocial and anthropological perspective. Irish Journal of Psychological Medicine. 2022;39(2):223-33.
159. All Ireland Traveller Health Study Team. All Ireland Traveller health study: Summary of findings [Internet]. Dublin: School of Public Health, Physiotherapy and Population Science, University College Dublin; 2010 [cited 2022 November 8]. Available from: https://assets.gov.ie/18859/d5237d611916463189ecc1f9ea83279d.pdf.

160. McFadden A, Siebelt L, Gavine A, Atkin K, Bell K, Innes N, et al. Gypsy, Roma and Traveller access to and engagement with health services: a systematic review. European Journal of Public Health. 2018;28(1):74-81.
161. Biddell CB, Kasow KA, Killela MK, Page KM, Wheeler SB, Drier SW, et al. Understanding the financial and psychological impact of employment disruption among caregivers of pediatric HSCT recipients: a mixed methods analysis. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2022;30(6):4747-57.
162. Benedetti DJ, Golshan M, Kesselheim JC. Going the Distance: Ethical Issues Arising When Patients Seek Cancer Care From International Settings. Journal of global oncology. 2018;4:1-4.
163. del Carmen MG, Joffe S. Informed Consent for Medical Treatment and Research: A Review. The Oncologist. 2005;10(8):636-41.
164. World Health Organization. Access to Safe and Effective Cells and Tissues for Transplantion - AIDE-MEMOIRE for National Health Authorities [Internet]. World Health Organization,; 2006 [cited 2022 November 14]. Available from: https://www.notifylibrary.org/sites/default/files/WHO%20Aide%20Memoire%20for%20National%20Health%20Authorities%20on%20Safety%20and%20Quality%20of%20Tissues%20and%20Cells.pdf.
165. Liso A, Neri M, Maglietta F, La Russa R, Turillazzi E. Hematopoietic Stem Cell Transplantation: A Bioethical Lens. Stem cells international. 2017;2017:1286246.
166. Dalle JH, Lucchini G, Balduzzi A, Ifversen M, Jahnukainen K, Macklon KT, et al. State-of-the-art fertility preservation in children and adolescents undergoing haematopoietic stem cell transplantation: a report on the expert meeting of the Paediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT) in Baden, Austria, 29-30 September 2015. Bone Marrow Transplant. 2017;52(7):1029-35.
167. Mulder RL, Font-Gonzalez A, van Dulmen-den Broeder E, Quinn GP, Ginsberg JP, Loeffen EAH, et al. Communication and ethical considerations for fertility preservation for patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. The Lancet Oncology. 2021;22(2):e68-e80.
168. Department of Health. Department of Health Statement of Strategy 2021 - 2023 [Internet]. Dublin: Department of Health,; 2021 [cited 2022 December 2]. Available from: https://www.gov.ie/en/organisation-information/0fd9c-department-of-health-statement-of-strategy-2021-2023/.
169. HSE. National Traveller Health Action Plan (2022 - 2027) [Internet]. HSE; 2022 [cited 2022 December 2]. Available from: https://www.hse.ie/eng/services/publications/socialinclusion/national-traveller-health-action-plan-2022-2027.pdf.
170. National Cancer Control Programme. NCCP Child, Adolescent and Young Adult (CAYA) Cancer Annual Report [Internet]. HSE; 2021 [cited 2022 December 5]. Available from: https://www.hse.ie/eng/services/list/5/cancer/news/child-

adolescent-and-young-adult-caya-cancer-annual-report.pdf.

171. Health Information and Quality Authority. Repatriation of paediatric haematopoietic stem cell transplant services to Ireland: Protocol for a Health Technology Assessment [Internet]. Cork: Health Information and Quality Authority; 2022 [cited 2022 December 2]. Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/hta-repatriation-paediatric-haematopoietic.

Published by the Health Information and Quality Authority (HIQA).

For further information please contact:

Health Information and Quality Authority

George's Court

George's Lane

Smithfield

Dublin 7

D07 E98Y

+353 (0)1 8147400

info@hiqa.ie

www.hiqa.ie