BMJ Open Effectiveness of immunosuppression minimisation, conversion or withdrawal strategies in paediatric solid organ and haematopoietic stem cell transplantation: a protocol of a systematic review and meta-analysis

Carlos Martin Saborido ⁽¹⁾, ¹ Alberto M Borobia ⁽¹⁾, ^{2,3} Javier Cobas, ⁴ Lorenzo D'Antiga, ⁵ Esteban Frauca, ⁶ Francisco Hernández-Oliveros, ⁷ Paloma Jara, ⁶ Eduardo López-Granados, ⁸ Jose María Muñoz, ⁹ Emanuele Nicastro, ⁵ Jose Jonay Ojeda, ¹⁰ Antonio Pérez-Martínez, ¹¹ Juan Manuel Torres, ¹ Antonio Carcas²

ABSTRACT

To cite: Martin Saborido C, Borobia AM, Cobas J, *et al.* Effectiveness of immunosuppression minimisation, conversion or withdrawal strategies in paediatric solid organ and haematopoietic stem cell transplantation: a protocol of a systematic review and meta-analysis. *BMJ Open* 2020;**10**:e037721. doi:10.1136/ bmjopen-2020-037721

Prepublication history and additional materials for this paper is available online. To view these files, please visit the journal online (http://dx.doi. org/10.1136/bmjopen-2020-037721).

Received 14 February 2020 Revised 31 October 2020 Accepted 06 November 2020



© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Carlos Martin Saborido; carlos.martin@transplantchild. eu

Introduction Paediatric transplantation is the only curative therapeutic procedure for several end-stage rare diseases affecting different organs and body systems, causing altogether great impact in European children's health and quality of life. Transplanted children shift their primary disease to a chronic condition of immunosuppression to avoid rejection. Longer life expectancy in children poses a greater risk of prolonged and severe side effects related to longterm immunosuppressive (IS) disabilities and secondary cancer susceptibility. The goal remains to find the best combination of IS agents that optimises allograft survival by preventing acute rejection while limiting drug toxicities. This systematic review will aim to determine the optimal IS strategy within the so-called minimisation, conversion or withdrawal strategies.

Methods and analysis We will search the following databases with no language restrictions: Cochrane Central Register of Controlled Trials in the Cochrane Library, OvidSP Medline and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; OvidSP Embase Classic+Embase; Ebsco CINAHL Plus, complete database; WHO International Clinical Trials Registry Platform search portal. We will include controlled and uncontrolled clinical trials along with any prospective or retrospective study that includes a universal cohort (all participants from a centre/region/city over a certain period). Cases series and cross-sectional studies are excluded. Two review authors will independently assess the trial eligibility, risk of bias and extract appropriate data points. The outcomes included in this review are: patient survival, acute graft rejection, chronic graft rejection, diabetes, graft function, graft loss, chronic graft versus host disease, acute graft versus host disease, surgical complications, infusion complications, post-transplant lymphoproliferative disease, liver function, renal function, cognition, depression, healthrelated quality of life, hospitalisation, high blood pressure,

Strengths and limitations of this study

- The search strategies and lack of dates and language restriction will provide an exhaustive review of the topic.
- The review will cover all types of study designs aiming to capture all relevant information.
- A large number of studies with high risk of bias are expected and they will be clearly analysed.

low blood pressure, cancer—other, cancer—skin, cardiovascular disease, bacterial infection, Epstein-Barr infection, cytomegalovirus infection, other viral infections and growth.

INTRODUCTION Background

The treatment of choice for end-stage solidorgan failure in children in most cases is solid organ transplantation (SOT) or haematopoietic stem cell transplantation (HSCT) for the treatment of haematological malignancies, immune-deficiency illnesses or inherited metabolic disorders or haemoglobinopathies. Both SOT and HSCT offer the chance **s** of a cure, but at the same time raise the risk of treatment-related mortality and long-term side effects.

Between 2012 and 2016, 7741 solid organ transplants were performed on children in 23 European Union (EU)¹ countries and 4041 paediatric patients received HSCT.^{2 3} The clinical consequences of transplantation can be understood as those (i) directly related to

BMJ

the transplanted organ (acute or chronic allograft rejection, native disease within the allograft, surgical complications), (ii) arising primarily from post-transplant therapies (infection, malignancy, pharmacological toxicity, growth retardation), (iii) linked to the underlying disease (recurrence of original disease in some allografts) and (iv) being multifactorial.

Despite the rate of graft success has improved along with the patient's clinical outcomes by development and improvements of surgical techniques, anaesthetic procedures and post-transplant care, especially immunosuppression, the patients still need immunosuppressive (IS) agents to prevent rejection of the transplanted organ to a greater or lesser extent whether SOT or HSCT. Therefore, transplanted children have shifted to a chronic condition dependent on IS treatment to avoid grafted organ rejection or graft versus host disease. Consequences of posttransplant IS in children fall into two broad categories: direct organ toxicity and non-specific IS action (ie, infection and malignancy). This chronic condition requires proper monitoring and care of post-transplant complications such as infections, malignancy and chronic rejection, which is even more important in children as they have higher pretransplantation and post-transplantation mortality and morbidity rates than adults.

Challenges in paediatric transplantation

IS management is challenging in infants, children and young people. It requires tailored post-transplant management to the unique needs of the youngster. Physiological immaturity of many systems including the immune system, growing and development and other considerations make paediatric transplantation a singular entity when compared with adult transplantation. Diagnostic and therapeutic advances achieved in adult transplant are not necessarily applicable to paediatric transplantation and require a distinct pipeline of development. Specialised clinical and laboratory resources that support the transplantation procedure in common processes such as immunosuppression, immune reconstitution, rejection, tolerance, risk of infection and secondary malignancies are needed in order to accelerate research and new therapies. In addition, other areas of non-medical supportive care are demanded for children and their families, due to severe psychological and socioeconomic issues that extend to adulthood. A paediatric disease affects the whole family, as impairments of a child's function are a source of emotional distress for parents. Parents of transplanted children have been found to show post-traumatic stress disorder, feeling particularly distressed during the post-transplantation phase.⁴ These problems may affect the child's daily-life function and include a broad spectrum of somatic, psychological and social problems.

Furthermore, despite improvements in short-term graft survival, the immunosuppressive regimens have failed to prolong long-term graft survival, being estimated between 5 and 20 years for SOT and 1–2 years for HSCT.⁵ The paediatric transplantation demands even more expertise

BMJ Open: first published as 10.1136/bmjopen-2020-037721 on 3 December Ensei ignem 2020. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l gnement Superieur (ABES) (ABE ≥ technologies

in reference centres connecting multidisciplinary medical expertise, transfer of knowledge and innovative medicine.

Minimisation, conversion or withdrawal strategies in paediatric transplantation recipients

The optimal immunosuppressive regimen maintains graft function (GF), minimising rejection and graft versus host disease while limiting the potential for infection and organ toxicity. The IS treatment for SOT have not changed during the last years. It remains calcineurin inhibitors (CNI) mostly in association with steroids in the short-term and mycophenolate mofetil or mammalian target of rapamycin inhibitors (everolimus, sirolimus) in the mid-term or long term. As mentioned, CNI such as tacrolimus have improved short-term but not long-term graft survival. Prolonged use of IS drugs leads to nephrotoxicity, metabolic disorders, infections and cancer. Biomarkers of tolerance will help us to stratify patients at different stages, tailor and individualise treatment, considering the special characteristics of paediatric patients. In HSCT, IS is withdrawn in most of the patients 1-2 years post-transplantation. Furthermore, limited availability of fully match human leucocyte antigen donors has uses developed strategies of graft engineering to overcome mismatch related and unrelated donors. In this setting, total T cell depletion, as CD34⁺ selection, CD3CD19 depletion or partial T cell depletion as $\alpha\beta$ T-cell/CD19 B-cell depletion and CD45RA⁺ depletion, have shown 5 promising clinical results in paediatric patients. The most e important issue is that this kind of graft engineering allows the absence of post-HSCT pharmacological prophylaxis early after HSCT.⁶⁷

Strategies to limit the impact of prolonged IS include protocols of drug minimisation towards individualisation of organ-specific immunosuppression regimens, development of new non-nephrotoxic agents and trials of tolerance induction. The lack of consensual and standardised post-transplant care in paediatric patients is also a limitation for the design of clinical trials and for drawing conclusions that can be used in the clinical settings. The small number of SOT and HSCT performed in paediatric patients per year remains a challenge for research in this field, which is even more evident when the analysis is focused on certain organs such as heart and lungs. Some of the limitations of paediatric transplantation are associated with the inability to translate the results obtained from adult studies to paediatric studies examining similar diseases and procedures.

European reference networks

The EU, through the 2009 recommendation, advised on the identification of centres of expertise in rare diseases in order to overcome some of the challenges that they face: scarcity of patients, resources and expertise. The multidisciplinary approach of the centres of expertise will improve patient diagnosis, treatments and quality of life (QoL). In March 2017, the EU⁸ launched 24 European Reference Networks (ERNs), which are virtual networks involving healthcare providers across Europe. ERNs were created to tackle rare diseases and complex conditions requiring highly specialised healthcare by gathering knowledge and expertise that will result in better patient care.

ERN TransplantChild is one of the 24 ERNs established in a European legal framework.⁹ ERN TransplantChild is the only ERN focused on a complex and highly specialised process, the paediatric transplantation of both SOT and HSCT with a process approach rather than an organ approach. Eighteen healthcare providers from 11 Member States of the EU integrate ERN TransplantChild. The reasoning behind is that paediatric transplantation requires highly specialised centres with highly dedicated and multidisciplinary teams with different transplantation programmes and teams involved including common aspects to all transplants and favouring the implementation of new diagnostic tools and treatments. The network addresses the entire transplant process: pretransplant, transplant and post-transplant phases, dealing with a new chronic condition and preventing secondary transplantassociated diseases. ERN TransplantChild aims at the empowerment and the improvement of life expectancy and QoL for EU paediatric patients requiring a SOT or HSCT or transplanted patients and patients' families.

In this framework, ERN TransplantChild executive committee decided to develop a clinical practice guideline on the effects of the minimisation, conversion or withdrawal immunosuppression strategies in paediatric SOT and HSCT. To address this issue, the ERN defined the question to be answered through a systematic review. In the present article, we describe the protocol of this particular systematic review registered in PROSPERO with ID: CRD42019136524.

OBJECTIVE

To determine the effects of the minimisation, conversion or withdrawal immunosuppression strategies in paediatric solid organ and haematopoietic stem cell transplantation.

METHODS AND ANALYSIS

This systematic review started in April 2020 and was intended to be finished by July 2020.

Criteria for considering studies for this review Type of studies

This review will consider controlled and uncontrolled clinical trials along with any prospective or retrospective study that includes a universal cohort (all participants from a centre/region/city over a certain period). Cases series and cross-sectional studies are excluded.

Type of participants

The systematic review will include studies on paediatric population (0-18 years) in any stage of the transplantation process: pretransplantation or post-transplantation.

Type of interventions

Any immunosuppression strategy at any stage of the transplantation process, that is, any IS medication used such as steroids, calcineurin inhibitors, mycophenolic acid, sirolimus, everolimus... prescribed to the patients on different regimens or strategies as withdrawal, minimisation or conversion. Biological treatments should be excluded as these are out of the review's scope. Evaluation of conditioning regimens only should be excluded

The comparators could be any intervention defined **p** previously or any control. We included, as well, no controlled trials so in this case no comparator could be possible. The uncontrolled cohorts will be used by the CPG panel of experts as complementary information, copyright, including but the data extracted from those uncontrolled cohorts will not be summarised nor included in the summary of finding tables.

Type of outcome measures Primary outcomes

- Patient survival: proportion of subjects who are alive after transplantation at any timepoint.
- Acute graft rejection: clinically diagnosed or through biopsy of histological samples so they are not solely g based on time of occurrence, are based on the definiated to text tion from investigators in each of the studies or based on histological samples or clinical diagnose. We will use T-cell-mediated rejection and antibody-mediated rejection, rather than acute and chronic, according to the new Banff classification whenever will be possible. an At at least within 6 months from transplantation.
- data Chronic graft rejection: clinically diagnosed or through biopsy of histological samples so they are not solely based on time of occurrence, are based on the definition from investigators in each of the studies or **a** based on histological samples or clinical diagnose. ⊳ We will use T-cell-mediated rejection and antibodymediated rejection, rather than acute and chronic, according to the new Banff classification whenever , and will be possible. At at least within 6 months from transplantation.
- Diabetes measured based on A1C criteria or plasma glucose criteria, either the fasting plasma glucose or the 2-hour plasma glucose value after a 75g oral glucose tolerance test at any time.
- GF:
 - GF kidney: glomerular filtrate rate at any timepoint.
 - GF liver: at least liver transaminases+bilirubin at any timepoint+prothrombin time (PT)+international normalised ratio (INR)+serum lactate+ammonia levels.
 - GF lung: forced expiratory volume in 1 s+forced vital capacity at any timepoint.
 - GF heart: at least ejection fraction at any timepoint and graft vasculopathy.
 - GF intestine: at least citrulline+absorption faecal test at any timepoint.

ſe

- GF HSCT: count of leucocytes+platelet+haemoglobin+lymphocytes at any timepoint.
- Graft loss: defined as any medical or surgical condition requiring re-transplantation, such as primary graft dysfunction or non-function and death at any timepoint.
- Acute graft versus host disease: biopsy of histological sample at any timepoint.
- Chronic graft vs host disease: biopsy of histological sample at any timepoint.
- Surgical complications: any complication identified by the investigators.
- Infusion complications: any complication identified by the investigators during the infusion process for stem cell transplantation.
- Post-transplant lymphoproliferative disease (PTLD): biopsy of histological sample at any timepoint.
- Liver function: liver transaminases+bilirubin at any timepoint+PT+INR+serum lactate+ammonia levels.
- Renal function: glomerular filtration rate at any timepoint.
- Cognition measured by the IQ at any timepoint.
- Depression change in depression score from baseline to 6 or 12 months.
- Health-related quality of life (HRQoL): measured using any validated HRQoL scale for children or caregivers.
- Hospitalisation: number of hospitalisations from transplantation at any time point.
- High blood pressure: defined by investigators at any timepoint.
- Low blood pressure: defined by investigators at any timepoint.
- Cancer-other (not skin not PTLD): any cancer identified by investigators at any timepoint.
- Cancer-skin: any skin cancer identified by investigators at any timepoint.
- Cardiovascular disease: any cardiovascular disease identified by investigators at any timepoint.
- Bacterial infection: positive culture.
- Epstein-Barr infection: at least two positive determinations of EBV DNA-emia by PCR in blood test and confirmed histologically without evidence of EBV-PTLD. EBV-PTLD should be based on at least two of the following histological features defined by WHO¹⁰: (i) disruption of underlying cellular architecture by a lymphoproliferative process, (ii) presence of monoclonal or oligoclonal cell populations as revealed by cellular and/or viral markers, (iii) evidence of EBV infection in many of the cells, that is, DNA, RNA or protein. Detection of EBV nucleic acid in blood is not, eo ipso, sufficient for the diagnosis of EBV-PTLD.
- Cytomegalovirus infection/disease: PCR in blood test and confirmed histologically.
- Other viral infections: identified by investigators using PCR, histology, culture or serology.
- Growth: measured using at least height and weight from transplantation to any timepoint.

Secondary outcomes

- Age at transplantation.
- Age of participants at any analysis of primary outcomes provided by the authors of included studies.

Search methods for identification of studies

We will search for all published studies and will review the list of references as well of included studies to find potential relevant studies. All searches will be done from inception until end of March 2019.

Electronic searches

Protected In accordance with the Cochrane handbook, we launched search strategies search for the following electronic ŝ databases:

- copyright, 1. Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 3) in the Cochrane Library.
- 2. OvidSP Medline and Epub Ahead of Print, In-Process including & Other Non-Indexed Citations and Daily.
- 3. OvidSP Embase Classic+Embase.
- 4. Ebsco CINAHL Plus, complete database.
- 5. Trial registers:
 - 1. WHO International Clinical Trials Registry Platform search portal.¹¹

uses related to text Search strategy for Medline is in online supplemental Annex I.

Data collection and analysis

Selection of studies

At least two authors from the following list will independently screen titles and abstracts and assess full-text articles from potentially eligible studies:

Dr Carlos Martín Saborido. IdiPAZ

data mining, Al Dr Antonio Carcas Sansuán. Hospital Universitario La Paz

Dr Juan Torres. IdipAZ

Dr Alistair Baker. King's College London KCH Trust

Caroline Lindemans. Wilhelmina Children's Dr Hospital

ing, and Dr Daniela Liccardo. Ospedale Pediátrico Bambino Gesú

- Dr Emanuele Nicastro. Ospedale Papa Giovani XXIII Dr Elisa Benetti. Azienda Ospedaliera di Padova
- Dr Lucía Martínez. Hospital Universitario La Paz

similar tecl Dr Jaime Montserrat Villatoro. Hospital Universitario La paz

nologies Dr Elena Sánchez Zapardiel. Hospital Universitario La Paz

Dr Luz Yadira Bravo. Hospital Universitario La Paz Dr María Francelina Lopes. Centro Hospitalar e Universitario de Coimbra

Dr Carmen Capito. Hôpital Necker-Enfants Malades Dr Alastair Baker. Kings College London KCH Trust

Dr Dominique Debray. Hôpital Necker-Enfants Malades

Dr Jacek Toporski. Children's Hospital, Skåne University Hospital

Dr Esther Ramos. Hospital Universitario La Paz Dr Florance Lacaille. Hôpital Necker-Enfant Malades trair

ę

Dr Imeke Goldschmidt. Hannover Medical School Dr Lars Pape. Hannover Medical School

Dr Ulrich Baumann. Hannover Medical School

If there is no consensus between both authors involved in the screening or assessment, a third one, Carlos Martín Saborido (CMS) will intervene to solve the disagreement. We will use COVIDENCE as a screening and extraction tool to implement the selection process.¹² We will document the reasons for the exclusion of the full-text articles we assessed.

We will construct a flow chart to illustrate selection of studies included in this review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Data extraction and management

We will use a standard form to extract data from the included studies. This form will consist of the following fields, but the list could be longer if necessary:

- ► Study identification.
- Study methods including design, inclusion and exclu-sion criteria.
- Study population including baseline characteristics.
- Description of the intervention.
- Description of comparator.
- Information for assessment of the risk of bias (RoB).
- Organ/s involved.
- End points.
- Results.

We will use different prespecified forms for each type of study (randomised controlled trial (RCT), non-RCT, uncontrolled trial, cohort studies and case-control studies) and type of outcome (dichotomous or quantitative) in order to capture all relevant information.

One review author will extract data and another one will check all data have been properly extracted. Discrepancies will be identified and resolved through discussion (with a third author where necessary). Missing data will be requested from study authors.

Assessment of risk of bias in included studies

Due to the variety of designs we will find, we have planned to use several tools to assess the RoB. These tools are listed in the table 1.

Two review authors will independently assess each included study for RoB. We will resolve disagreements by discussion and when necessary by consultation with a third review author.

Measures of treatment effect

For continuous data, we have planned to compare the values in the intervention and control groups at final follow-up timepoint. We expect to use mean differences (MDs) with 95% CIs as summary statistics. If studies had used different measurement instruments or units to measure an outcome, we plan to use the standardised mean difference (SMD).

Table 1 Risk of bias (RoB) tools by study design	
Name of the tool	Study design
Cochrane RoB tool ¹³	Randomised controlled trials
RoB criteria for EPOC Reviews ¹⁴ (guide for review authors on assessing study quality)	Quasi-randomised trials
RoB criteria for EPOC Reviews ¹⁴ (guide for review authors on assessing study quality)	Controlled before and after (CBA) studies
RoB criteria for EPOC Reviews ¹⁴ (guide for review authors on assessing study quality)	Interrupted time series studies
Risk of Bias in non-randomised Studies of Interventions (ROBINS I) ¹⁵	Cohorts studies
Risk of Bias in non-randomised Studies of Interventions (ROBINS I) ¹⁵	Case-controls studies
Risk of Bias in non-randomised Studies of Interventions (ROBINS I) ¹⁵	Uncontrolled before and after (CBA) studies

For dichotomous data, we will calculate Mantel-Haenszel OR from the numbers of events in control and intervention groups. In the case of uncontrolled trials, we will account the number of events in the only group. We also collect 95% CIs or any statistic which allow to calculate the 95% CIs.

If some studies had reported an outcome as a dichotomous measure and others as a continuous measure for the same construct, we will convert results from a relative risk to an SMD, if an approximately normal distribution could be assumed for the underlying continuous measure.

Assessment of heterogeneity

We will explore clinical and statistical sources of heterogeneity among the different groups of studies (RCT, non-RCTs and uncontrolled trials). We will assess statistical heterogeneity using I² statistics and χ^2 test. We will consider a result to be statistically significant if p<0.1. We will consider values of $I^2 > 60\%$ to be an indication of 'moderate' heterogeneity and values above 85% to be 'considerable' heterogeneity. We may not carry out a meta-analysis if I² is high and will document the rationale for our decision.

Data synthesis

Where we consider studies sufficiently homogenous in terms of participants, interventions and outcomes, we plan to synthesise results in a meta-analysis using the randomeffects model within each of the following groups:

- RCT;
- Non-RCT:
- Uncontrolled trials.

We will perform statistical analysis using the Cochrane Collaboration's statistical software, Review Manager.

ā

Open access

Given the nature of the intervention included, we assume that clinical heterogeneity is very likely to impact on the results of our review, so we will report the randomeffects model results, regardless of statistical evidence of heterogeneity in effect size.

Provided we are including three types of interventions/ comparators, we will analyse all possible combinations reported.

Subgroup analysis

Results will be analysed for the following subgroups:

- Type of organ: heart, intestine, kidney, liver, lung, HSCT.
- ► Age groups: 0–4, 4–8, 8–12, 12–18 years.

Sex is not initially going to be considered, nevertheless if results are clearly disaggregated by sex, we could consider to do a subgroup analysis.

Overall quality of the body of evidence: summary of findings table

The quality of evidence for outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation approach. Quality will be determined as high, moderate, low or very low.

Patient and public involvement

Patient and public involvement (PPI) representatives worked with us to refine the list of outcomes, however, it was difficult to involve patients in other areas of the study design due to the very technical methods required to do design the protocol. PPI representatives will write a plain language summary and design a leaflet for dissemination of the final clinical practice guideline to their peers and distributing to patient groups.

Author affiliations

¹Institute for Health Research (IdiPAZ), La Paz University Hospital Biomedical Research Foundation, Madrid, Spain

 ²Clinical Pharmacology Department, Hospital Universitario La Paz, Madrid, Spain
³Pharmacology Department, Autonomous University of Madrid, Madrid, Spain
⁴Children's Hospital Manager, La Paz University Hospital, Madrid, Spain
⁵Centre for Pediatric Hepatology, Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy

⁶Department of Pediatric Hepatology, La Paz University Hospital, Madrid, Spain ⁷Department of Paediatric Surgery, La Paz University Hospital, Madrid, Spain ⁸Department of Clinical Immunology, La Paz University Hospital, Madrid, Spain ⁹General Hospital Medical Director, La Paz University Hospital, Madrid, Spain ¹⁰Quality Unit, La Paz University Hospital, Madrid, Spain

¹¹Pediatric Hemato-Oncology Department, La Paz University Hospital, Madrid, Spain

Twitter Carlos Martin Saborido @CMSaborido

Contributors CMS: write the protocol and the present manuscript. Coordination of the protocol development. AMB: outcome definition and review of protocol and manuscript. JC: outcome definition and review of protocol and manuscript. LD: definition of PICO question. Outcome definition and review of protocol and manuscript. EF: outcome definition and review of protocol and manuscript. EH-0: outcome definition and review of protocol and manuscript. EH-0: outcome definition and review of protocol and manuscript. EH-0: outcome definition and review of protocol and manuscript. EL-G: outcome definition and review of protocol and manuscript. SIME: outcome definition and review of protocol and manuscript. JMC: outcome definition and review of protocol and manuscript. JMC: outcome definition and review of protocol and manuscript. JMC: outcome definition and review of protocol and manuscript. JMC: outcome definition and review of protocol and manuscript. JMC: outcome definition and review of protocol and manuscript. JMC: outcome definition and review of protocol and manuscript. JMC: outcome definition and review of protocol and manuscript. JMC: outcome definition and review of protocol and manuscript. JMC: outcome definition and review of protocol and manuscript. JMC: outcome definition and review of protocol and manuscript. JMC: outcome definition and review of protocol and manuscript. JMC: outcome definition and review of protocol and manuscript. Coordination of the protocol development. AC: definition of P

question. Outcome definition and review of protocol and manuscript. Coordination of the protocol development.

Funding This work was supported by The European Commission and the Consumers, Health, Agriculture and Food Executive Agency (CHAFEA). Grant agreements number: SGA 770411, SGA 811558 and SGA 847103.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs

Carlos Martin Saborido http://orcid.org/0000-0002-3969-6768 Alberto M Borobia http://orcid.org/0000-0002-8584-3263

REFERENCES

- 1 International Registry in Organ Donation and Transplantation. Pediatric transplants in European countries from 2008 to 2012. Available: http://www.irodat.org/2014
- 2 Passweg JR, Baldomero H, Peters C, et al. Hematopoietic SCT in Europe: data and trends in 2012 with special consideration of pediatric transplantation. Bone Marrow Transplant 2014;49:744–50.
- 3 Gómez MP, Pérez B, Manyalich M. International Registry in Organ Donation and Transplantation--2013. *Transplant Proc* 2014;46:1044–8.
- 4 Young GS, Mintzer LL, Seacord D, et al. Symptoms of posttraumatic stress disorder in parents of transplant recipients: incidence, severity, and related factors. *Pediatrics* 2003;111:e725–31.
- 5 Dharnidharka VR, Lamb KE, Zheng J, et al. Lack of significant improvements in long-term allograft survival in pediatric solid organ transplantation: a US national registry analysis. *Pediatr Transplant* 2015;19:477–83.
- 6 Or-Geva N, Reisner Y. The evolution of T-cell depletion in haploidentical stem-cell transplantation. *Br J Haematol* 2016;172:667–84.
- 7 Bertaina A, Roncarolo MG, Engineering G. Graft engineering and adoptive immunotherapy: new approaches to promote immune tolerance after hematopoietic stem cell transplantation. *Front Immunol* 2019;10:1342.
- 8 Héon-Klin V. European reference networks for rare diseases: what is the conceptual framework? Orphanet J Rare Dis 2017;12:137.
- 9 Jara P, Baker A, Baumann U, *et al.* Cross-cutting view of current challenges in paediatric solid organ and haematopoietic stem cell transplantation in Europe: the European reference network TransplantChild, 2019.
- 10 Swerdlow SH. WHO classification of tumours of haematopoietic and lymphoid tissues: international agency for research on cancer, 2017.
- 11 World Health Organization. International clinical trials registry platform (ICTRP) search portal apps. Available: who.int/trialsearch
- 12 Covidence systematic review software (veritas health innovation, Melbourne, Australia), 2017. Available: www.covidence.org
- 13 Higgins J, Altman D, Sterne J. Assessing risk of bias in included studies. In: Handbook for systematic reviews of interventions version 510, 2011.
- 14 Cochrane Effective Practice and Organisation of Care (EPOC). EPOC resources for review authors, 2017.
- 15 Jüni P, Loke Y, Pigott T, et al. Risk of bias in non-randomised studies of interventions (ROBINS-I): detailed guidance, 2016.