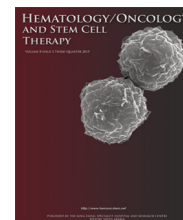




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Worldwide Network for Blood and Marrow Transplantation (WBMT) recommendations for establishing a hematopoietic stem cell transplantation program in countries with limited resources (Part II): Clinical, technical and socio-economic considerations ☆

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Abstract

The development of hematopoietic stem cell transplantation (HSCT) programs can face significant challenges in most developing countries because such endeavors must compete with other government health care priorities, including the delivery of basic services. While this may be a limiting factor, these countries should prioritize development of the needed expertise to offer state of the art treatments including transplantation, by providing financial, technological, legal, ethical and other needed support. This would prove beneficial in providing successful programs customized to the needs of their population, and potentially provide long-term cost-savings by circumventing the need for their citizens to seek care abroad. Costs of establishing HSCT program and the costs of the HSCT procedure itself can be substantial barriers in developing countries. Additionally, socioeconomic factors intrinsic to specific countries can influence access to HSCT, patient eligibility for HSCT and timely utilization of HSCT center capabilities. This report describes recommendations from the Worldwide Network for Blood and Marrow Transplantation (WBMT) for establishing HSCT programs with a specific focus on developing countries, and identifies challenges and opportunities for providing this specialized procedure in the resource constrained setting.

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Introduction

The establishment of hematopoietic stem cell transplantation (HSCT) programs in developing countries can enhance and improve tertiary care health services. There are various positive attributes that favor the establishment of such a

high-profile venture; however, there are also significant obstacles to be addressed.

Since the obvious issue in most economies is cost distribution and budget allocation for the populations' health-care, public health measures take precedence over the non-communicable chronic diseases. However, over time, there has been increasing focus on chronic diseases particularly cancers as these have become leading cause of mortality in both developing and developed nations. Thus there has been an exponential growth of both prevalence and inci-

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dence of the diseases which can be cured by HSCT including sickle cell anemia, thalassemia, leukemia, myeloma, lymphoma, immunodeficiencies and metabolic disorders. As a result, many new HSCT centers have been opening in the developing nations.

In most developing countries, a HSCT program has to compete for allocation of limited funds with other priorities for basic health care services such as food, sanitation, immunization, population control and prevention of communicable diseases. Developing countries should also have the expertise to offer 'state-of-the art' treatments, including HSCT which can provide treatment locally at a much lower cost than abroad.

The most important step would be to provide financial, technological, legal, ethical and other support for local individuals and institutions to proactively establish new HSCT program. The goal is to develop a customized local experience tailored to each developing country and also to allow local dissemination of this experience as it evolves [1].

While establishing a HSCT program in a developing country, one should take into consideration several difficulties. Financial, technologic, logistic, social, and the availability of skilled manpower are all potential difficulties. Given the exponential growth in both the numbers of HSCT worldwide and the establishment of new HSCT centers in the high and low income countries, the Worldwide Network for Blood and Marrow Transplantation (WBMT) has recognized the need to provide guidance to institutions and individuals who are considering start of a new HSCT center. Part I of this report describes the absolute minimum, minimum, preferred, and ideal requirements for the establishment of a new HSCT program. This part II of the series describes the clinical, technical and financial considerations for establishing a HSCT program in the resource constrained setting (typical for developing countries).

Financial issues and cost of establishing a transplantation program

HSCT remains a highly specialized, complex, resource intense and costly medical procedure. A 2009 report from the Agency for Healthcare Research and Quality (AHRQ) in the United States (US) showed that HSCT was among the top ten procedures with the greatest increase in hospital costs from 2004 to 2007. Total US national costs of HSCT hospitalization increased from \$694 million to \$1.3 billion over this time period [2].

Thus establishment of a dedicated center for this costly procedure requires a comprehensive understanding of economic indicators and challenges. There are four main economic evaluations that provide information to guide decision making on the basis of the value for money: cost minimization, cost benefit, cost effectiveness, and cost utility.

Cost minimization is commonly practiced in HSCT whenever lower cost, equally effective treatment is chosen over more expensive treatments. Cost benefit analysis is rarely used in procedures like transplant because it requires assignment of monetary costs to measure clinical benefits which are difficult to assign in this complex setting with potential for long-term cure for a proportion of recipients.

Cost utility analysis is a specific type of cost effectiveness analysis where outcomes are adjusted to consider health related quality of life, so that a cure without treatment sequelae is considered more valuable than a cure resulting continuing health disabilities [3].

In this paper we will emphasize HSCT interventions that focus primarily on cost-effectiveness or cost-utility. To develop a cost containment program, proof of both clinical and economic effectiveness is preferred before widespread adoption of new technologies [4].

It is critical to identify the exact drivers of cost before considering initiation of a HSCT program. Little available data to evaluate the exact drivers of HSCT costs in developing countries. A recent study of establishment of a cancer center in a developing country (Rwanda) indicated that \$556,105 US dollars was the necessary start-up funding to implement the cancer program [5]. The annual operating cost of the cancer program was found to be \$957,203 US\$. Radiotherapy, labor, and chemotherapy were the most significant cost drivers, however radiotherapy required sending patients out of country because there were no radiation units in Rwanda. Labor accounted for 21%, whereas chemotherapy, supportive medications, and consumables accounted for 15% of the costs. While the radiation therapy is not routinely performed for HSCT, it is necessary part of certain preparative regimens and thus establishment of a radiation therapy unit is likely to significantly increase the costs.

The high costs of HSCT can be presumably attributed to various factors as discussed below (Fig. 1).

Patient related factors

When designing a national program for HSCT in a developing country, few patient related factors can be assessed for cost reduction. Although there is no consistent correlation between costs and patient age, sex, performance status, or disease risk, in some more recent studies, advanced risk disease was a significant predictor of higher costs [6–10].

In view of the limited resources in developing countries, health authorities should allocate available resources to the best priorities where low cost inputs yield high dividends. However, there are no clear recommendations and each country needs to adopt the policies that satisfy its population needs.

Considering the young median age in many developing countries, it would be prudent to initially make HSCT available to younger patients with curable diagnoses and longer lifespan benefit. Subsequently, expanding eligibility for HSCT to older and advanced disease subjects may be appropriate as the program's experience develops.

Transplant center experience

Cost reduction and clinical outcomes have been shown to improve with increasing institutional experience [11]. However, this economic advantage may be offset as the complexity of treated patients increases and more aggressive supportive interventions are applied, resulting in a plateau in the improvement curve [11–13]. Growing local expertise

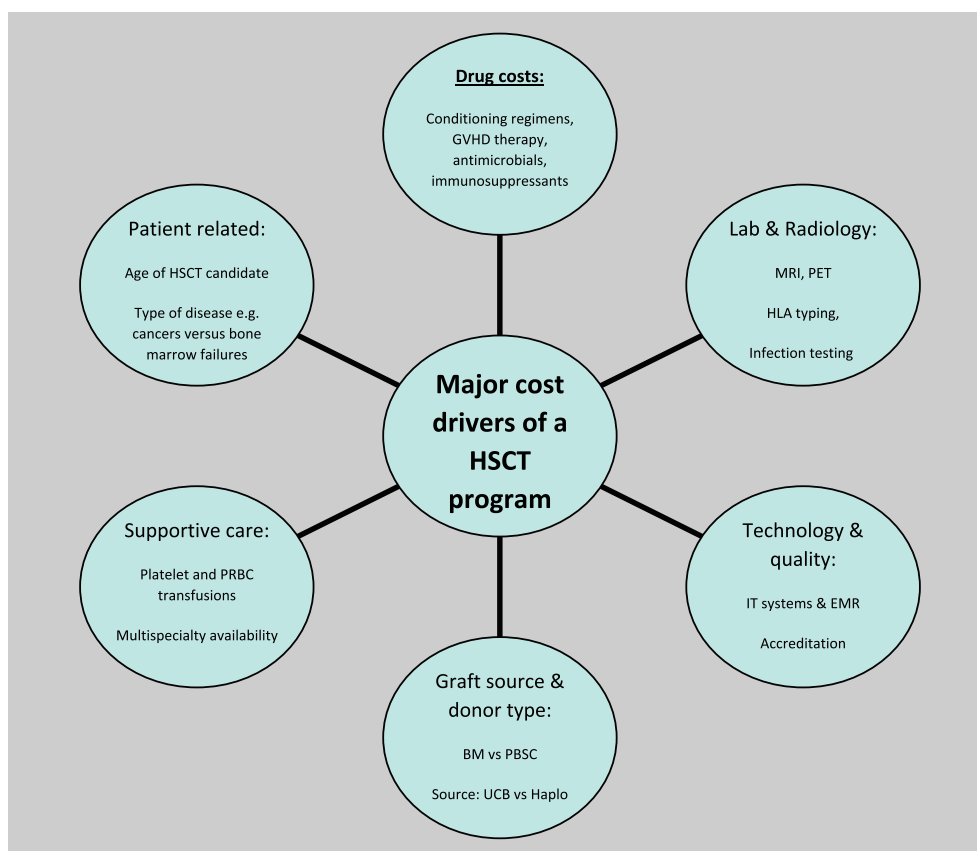


Fig. 1 Major determinants of costs in establishment of an HSCT program. HSCT: hematopoietic stem cell transplant; MRI: Magnetic resonance imaging; PET: positron emission tomogram; HLA: human leukocyte antigen; IT: information technology; EMR: electronic medical records; BM: bone marrow; PBSC: peripheral blood stem cells; PRBC: packed red blood cells; GVHD: graft-versus-host-disease; UCB: umbilical cord blood; haplo: haploidentical; RD: related donor; URD: unrelated donor.

and adopting cost effective practices can limit total costs and improve transplant outcomes.

Human resources and continuous training

Availability of well-trained staff at different steps of transplantation with continuous training and to advance their knowledge is a cornerstone of any successful transplant program. Migration of health care professionals from developing to developed countries deprives the developing world of valuable and essential human resources [14]. Countries should strengthen health system requirements, including physical infrastructure and skilled human resources to meet the multidisciplinary requirements of HSCT aiming for high quality and safety as fundamental principles. International cooperation and twinning with other institutions in developed countries could facilitate exchange of expertise across the globe. Adequate attention for neutropenic and hygienic precautions and any other measures to reduce infection should be considered.

Donor selection and HLA typing

With the advance in immunogenetics and transplantation immunology, particularly in the structure and function of

the HLA system in the 1990s, new and efficient technologies for HLA typing emerged and progressed [15,16].

According to the guidelines of World Marrow Donor Association (WMDA) and European Federation for Immunogenetics (EFI), high-resolution HLA typing should be performed both for HSCT recipients and donors. HLA typing should also include the HLA-C locus due to the recognized role of this locus in graft rejection [17,18].

The technology for HLA typing has evolved from the serological level to the cellular level, and recently to the molecular level. Serotyping was the mainstream method for HLA typing and played a critical role in organ transplantation before the 1990s. However, most HLA antisera are polyclonal with lower specificity and variable sensitivity. Therefore, molecular methods to type HLA at the DNA level have replaced serologic and cellular typing.

Commonly used DNA based HLA typing methods include PCR based sequence specific primers (PCR-SSP), and PCR based restriction fragment length polymorphism (PCR-RFLP), single-strand conformation polymorphism (PCR-SSCP), sequence-specific oligonucleotide (PCR-SSO) and single nucleotide polymorphism (PCR-SNP). PCR-SSP genotyping was a commonly used method for HLA typing in clinical laboratories worldwide. PCR-SSP and PCR-SSO methods have a high cost and prolonged operation time, therefore are rarely used for HLA typing at present.

PCR-SNP is a simple and fast method with high resolution and will become more commonly used as the technology continues to improve. At present, PCR-sequence-based typing (PCR-SBT) technology has significant advantages over other HLA typing methods in terms of accuracy, efficiency and automation. In addition, the operational costs have been greatly reduced [15]. It is recommended that new programs in developing countries with limited resources should start by performing matched sibling transplantation, where high resolution typing may not be necessary and some risks are reduced.

Outsourcing HLA typing can be a cost-effective alternative in developing countries where laboratories with immunogenetic capabilities and expertise are not yet available. Many companies throughout the developed countries offer molecular-based HLA typing at very competitive prices, particularly for bulk contracts.

Conditioning intensity

Both the intensity and duration of conditioning affect the cost of HSCT. Large studies confirmed that the costs associated with reduced intensity regimens are lower, with fewer median hospital days within the first year of the transplant compared with high-dose or myeloablative regimens [8].

Myeloablative allogeneic HSCT is not only associated with a higher frequency and severity of short-term toxicities, but also late complications such as a higher likelihood of infertility, growth retardation in children and new primary malignancies. This may also increase on the use of blood products, risk of infections, transplant-related mortality, and length of hospital stay. Despite these advantages, lower-intensity regimens must be adapted for important patient and disease related variables as a recent multicenter trial showed a clear advantage in reducing relapse of AML using myeloablative regimens in younger fit patients [19].

Several recent studies had suggested that intermediate intensity regimens with a 20–30% reduction in dose intensity could reduce toxicity without causing significant increases in the risk of relapse or overall worse transplantation outcomes [20–22].

The cost and limited availability of radiation therapy in many developing countries should not be a major obstacle as non-radiation based conditioning regimens are available for nearly all diseases or conditions in which HSCT is indicated.

Blood product support

In adult recipients of autologous HSCT, two randomized trials have demonstrated similar rates of bleeding when therapeutic rather than prophylactic strategy for platelet transfusion was used [23,24]. Both American Society of Clinical Oncology and British Society of Haematology recommend that therapeutic platelet transfusion strategy could be used in autologous HSCT setting which will result in less platelet usage and substantial cost savings [25,26]. In allogeneic HSCT, a randomized study subgroup analysis found similar rates of bleeding when low dose of platelet (1.1×10^{11}) was used compared to medium (2.2×10^{11}) or

high dose (4.4×10^{11}). This led to a decreased number of platelets transfused per patient at doses between 1.1×10^{11} and 4.4×10^{11} platelets per m^2 with similar bleeding events [27]. Irradiated blood products should be utilized according to international guidelines.

Performing autologous stem cell transplant without stem cell cryopreservation

Cryopreservation of stem cells needs a relatively advanced stem cell processing laboratory with mechanical, controlled rate freezers. Several reports have described the feasibility of non-cryopreserved G-CSF mobilized whole blood or autologous bone marrow (with or without prior administration of G-CSF). Stem cell graft containing blood units or bone marrow can be briefly stored in a standard blood bank refrigerator at +4 °C until infusion [28–30].

The outcomes of autologous HSCT for multiple myeloma using non-cryopreserved stem cells and without G-CSF support has recently been described by several centers [31–34]. This technique depends on abbreviated conditioning, with one day of high dose melphalan for myeloma or short duration conditioning for lymphoma patients. This technique avoids the need for costly cryopreservation technology and also avoids the possible side effects described with infusion of dimethyl sulfoxide (DMSO) which is required for cryopreservation. These autologous transplantation techniques were reported to yield early engraftment and reduced hospital stay with significant cost savings. Outcomes were comparable to conventional conditioning with cryopreserved stem cells in multiple myeloma patients [31–34]. Two recent studies of non-cryopreserved autografts from developing countries utilizing post-HSCT G-CSF also indicate comparable engraftment rates to cryopreserved autografts [35,36].

Thus, for a new HSCT center, it may not be necessary to have mechanical freezers in place for autograft cryopreservation, as safety and efficacy of utilizing non-cryopreserved stem cells is evident.

Graft source

Peripheral blood stem cells (PBSC) are known to offer more rapid neutrophil and platelet recovery compared to bone marrow grafts with an early cost reduction of approximately 30% compared to bone marrow in some studies [37–39]. The use of PBSC can lead to specific resource saving in hospitalization, platelet transfusions and use of growth factors [40,41].

Unlike autologous transplantation, chronic GVHD is a serious late complication of allogeneic HSCT and results in serious morbidity and mortality. Most studies report a higher incidence of chronic GVHD with the use of allogeneic PBSCs, which may potentially offset the early cost savings. Appropriate selection of cases and developing well-informed indications for the use of PBSCs could reflect favorably on procedural costs and transplant outcomes [42].

In a recent study by the Center for International Blood and Marrow Transplant Research (CIBMTR), the use of PBSCs resulted in an acceptable alternative for transplanting patients with aplastic anemia in developing countries, as

PBSC grafts were associated with faster engraftment, lower frequency of infections, and a lower likelihood of graft rejection in heavily pretransfused patients [43].

However, in autologous HSCT there is strong evidence of clinical benefit and cost savings using PBSCs which has been consistently reported [44–47].

Alternative donors and graft manipulation:

The use of alternative donors, specifically HLA-compatible unrelated donors (URD), has emerged as a significant driver of costs, even beyond the costs of stem cell procurement [8,48,49]. Among the various sources of alternative donors, myeloablative umbilical cord blood (UCB) transplantation is associated with the highest costs, followed by matched URD. Accordingly, these donor sources should not be considered a priority in developing countries for a new HSCT program.

The preferred and most cost effective alternate donor transplantation modality in developing countries may be a related (family-member) haploidentical transplantation using post-transplant cyclophosphamide (PTCy) for GVHD prevention. The posttransplant course, however, might require more experience as conventional, URD HSCT.

Alternatives to PTCy for haploidentical transplantation use different methods of T-cell depletion (TCD) of the donor graft or other cellular manipulation which are complex and require advanced and costly stem cell processing technology [50].

Cost of supportive care medications:

Pharmacy costs range from 8% to 39% of the total expenditures in HSCT. Hematopoietic growth factors, GVHD prophylactic drugs and antimicrobials are the major contributors to pharmacy costs [51–53]. Several generic forms are now available for fluconazole and more recently for voriconazole as well [54]. This could help offset some costs, provided that these alternative products demonstrate similar efficacy. Pharmacy costs are expected to continuously rise given the changes in HSCT practice with increasing use of newer immunosuppressive regimens and the higher cost of new anti-infective agents [52]. The long-term excess pharmacy costs for patients with chronic GVHD who may require prolonged immunosuppressive treatments are unpredictable and may be large [52].

A biosimilar drug is a similar copy of an approved injectable original biologic substance, which may be available after the original patent protection has expired [55]. Since drugs are produced by cultured cells, small biological differences between original and biosimilars may exist. However, the use of well-established biosimilars should be considered for cost containment and for improved availability of drugs needed for HSCT provided that they are demonstrably as safe and efficacious as the originator product. If properly evaluated and clinical effectiveness is proven these biosimilars, their generally reduced costs may contribute to the long-term financial sustainability of HSCT programs [55–57]. Several biosimilars of G-CSF are less expensive alternatives to the original brand product. The European Medicines Agency (EMA) has recently approved several

biosimilar versions after the patent of the original G-CSF brand expired in Europe in 2006 [55].

Several G-CSF biosimilars have been evaluated in the setting of stem cell mobilization for autologous HSCT. Results show similar mobilization yields with comparable safety profiles as the originator G-CSF. Moreover, both myeloid and platelet recovery times are similar to the originator G-CSF product [56–62]. This non-inferiority model could be extrapolated to other medications, ultimately leading to significant cost saving. Highly reputable pharmaceutical companies are already involved in the manufacturing process of several biosimilar medications essential for HSCT [63]. Table 1 presents several currently approved biosimilars which are used in the HSCT arena. The utilization of these biosimilars should be explored in developing countries when local approvals are in place.

However, the major problems encountered beyond the costs of certain drugs are reliable availability. The experience in different countries and continents underlines the need to check the availability and approval of the essential drugs to perform HSCT. In some countries cyclosporine is only available orally but not intravenously, Busulfan may not be available at all and the import of the drug is sometimes very difficult. The WBMT prepared a list for essential drugs, which should be available or for a successful program. Licensing of drugs in a country may depend on the demand and some drugs needed for HSCT may be used only for HSCT. Sometimes availability of drug needed for HSCT will also improve the treatment of the underlying disease before HSCT. Close interaction with the health authorities of the country is recommended to guide informed policies for specific drug availabilities.

Post transplantation factors

Several post-transplant factors may greatly increase costs. Prolonged hospitalization and late complications are the most significant drivers of costs. Designing programs for post-transplant care including home health services and outpatient follow up systems allowing safe follow up at either their own homes or at a hostel where a well-trained and qualified nurse can monitor patients who need less aggressive intervention, have been found to reduce post-transplant costs [64].

Socioeconomic and other factors

In many developing countries, many acute leukemia patients die before referral to a national or regional HSCT center. This indirectly leads to a relatively larger proportion of HSCT being done for non-neoplastic indications such as bone marrow failure and hemoglobinopathies, diseases more permissive of delays until HSCT. The time from diagnosis to HSCT is likely to be longer in developing countries with the resulting unintended consequences of having sicker candidates present for HSCT due to advanced disease, poor performance status, more infections or transfusion alloimmunization. The consequences of delay may be higher costs of HSCT and poorer outcomes. Efforts to shorten the time from diagnosis to HSCT should be considered a priority in developing countries. Increasing public awareness and

Table 1 List of some Biosimilars approved in the United States and the European Union pertaining to HSCT*.

| Generic/molecule | Biosimilar | Year approved | Use in HSCT |
|------------------|------------------|---------------------------|---|
| Filgrastim | Tevagrastim | 2008 (EMA) | Mobilization of peripheral stem cells for autologous HSCT |
| | Ratiograstim | 2008 (EMA) | |
| | Filgrastim Hexal | 2009 (EMA) | |
| | Zarzio | 2009 (EMA) | |
| | Accofil | 2014 (EMA) | |
| | Zarxio | 2015 (US-FDA) | |
| Rituximab | Truxima | 2017 (EMA) | Treatment of chronic GVHD |
| | Rixathon | 2017 (EMA) | |
| | Ritemvia | 2017 (EMA) | |
| Infliximab | Inflectra | 2013 (EMA); 2016 (US-FDA) | Treatment of acute GVHD |
| | Flixabi | 2016 (EMA) | |
| Etanercept | Benepali | 2016 (EMA) | Treatment of acute GVHD |
| | Erelzi | 2016 (US-FDA); 2017 (EMA) | Treatment of BOS Treatment of IPS |
| Enoxaparin | Inhixa | 2016 (EMA) | DVT prophylaxis |
| | Thorinane | 2016 (EMA) | DVT treatment |

EMA: European Medicines Agency; US-FDA: United States Food and Drug Administration; GVHD: Graft-versus-host-disease; BOS: Bronchiolitis obliterans syndrome; IPS: Idiopathic pulmonary syndrome; DVT: Deep venous thrombosis; HSCT: Hematopoietic stem cell transplantation.

*The table list only some of the approved biosimilars and not intended to be inclusive of all approved biosimilars. WBMT is working on a separate publication that will have a complete list of approved biosimilars.

patient education about essential hygienic and infection control measures as well as utilization of social services may also help educate patients and caregivers about recommendations that will increase HSCT success in developing countries.

The Human Development Index (HDI) is used by the United Nations Organization to evaluate a country's socioeconomic achievements based on three parameters: longevity, knowledge, and standard of living [65]. The number of transplants performed per unit population, as well as early and long-term outcomes are directly related to the HDI [66–70].

Information technology (IT) and quality benchmarks:

The most effective way to improve HSCT outcomes is to establish and maintain good quality programs in transplant centers. Established databases to define benchmarks for error reduction and improvement of outcomes. It is desirable for each HSCT center to have an internal database with experienced data managers and staff who can maintain the database and report the data to global registries (e.g. EBMT, CIBMTR or others). Developments in artificial intelligence (AI) for some aspects of tertiary care centers' management is predicted to lower costs. These may include machine learning algorithms in medical billing, supply chain management, scheduling efficiencies, virtual radiology (for image interpretation), and prevention of re-admissions [71–77]. Since many AI companies are currently originating in developing countries, it may be valuable to explore the

application of AI systems at HSCT startup with the goal of cost-reduction.

Telemedicine in developing countries

Available techniques today allow intensive cooperation with experienced centers. Pilot programs are currently active across the world. This technique is particularly valuable where a very experienced HSCT program director is not available. Important guidelines for success involve training of the local senior physicians, suitable facilities and laboratory capabilities in place and regular communication with outside consultants.

Conclusions

Establishment of a HSCT center in countries with limited resources is a multistep endeavor requiring many financial, social, technical and human resources and involvement of physicians, health authorities, politicians, nurses and scientific societies. The main obstacle in some countries remains constrained resources and inexperience which may lead to high operating and maintenance costs, but may also complicate initial organization of a program. The WBMT has outlined the major drivers of costs for a HSCT program and presents general recommendations to help limit initial program costs. New cost-effectiveness studies from developing countries for each aspect of HSCT (conditioning type, GVHD management, IT systems implementation, graft source and donor choice, laboratory testing, drug costs [and biosimilar use], blood bank utilization [defined thresholds for PRBC

and platelet transfusion] may be of particular value in improving the safety and affordability of HSCT.

Declaration of Competing Interest

None of the authors declare any relevant conflict of interest.

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