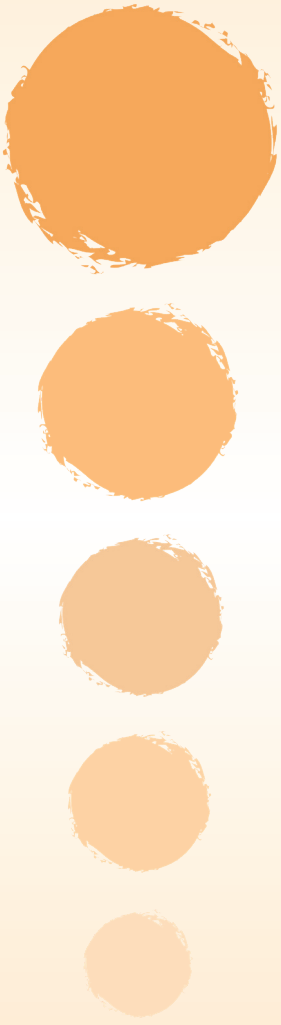
Patient-centered value-based healthcare in long-term follow-up after pediatric stem cell transplantation for nonmalignant diseases

Bense, J.E.



Chapter 1

General introduction

PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR NONMALIGNANT DISEASES

Allogeneic pediatric hematopoietic stem cell transplantation (HSCT) is an intensive, curative treatment for an increasing number of patients with nonmalignant diseases (1). HSCT is a high intensity treatment, in which conditioning regimens are required for achieving positive HSCT outcome (2). Conditioning regimens consists primarily of a combination of chemotherapy and immunosuppressants. Due to chemotherapy and immunosuppressants, children have (transiently) impaired immunity and are at risk for (severe) complications, such as organ toxicity and infections. In the setting of allogeneic HSCT there is a risk of graft versus host disease (GVHD), which itself, but also the treatment, could result in severe complications (1). Immune reconstitution takes several months or, in rare cases, even years, during which supportive care and restrictions due to impaired immunity are gradually phased out.

In the setting of nonmalignant diseases, the indications for HSCT include inborn errors of immunity (IEI), hemoglobinopathies (HB), and inherited and acquired bone marrow failure (BMF) disorders (3, 4). Some of these diseases are (acutely) life-threatening, while others are characterized by a chronic, progressive, and disabling life-shortening course and decreased quality of life. HSCT is aimed at curing hematologic and immunologic deficiencies. However, some nonmalignant diseases involve multiple organ systems. The non-hematologic or non-immunologic related deficiencies are still present, or could arise, after HSCT, as it would in non-transplanted patients, even if the hematopoietic system is fully replaced and become of health donor origin (5). The possible pre-existing disease manifestations could affect the HSCT procedure itself (e.g., drug choice in the presence of pre-existing renal impairment in sickle cell disease), as well as the post-transplant follow-up.

In the last decades advances in conditioning regimens, donor selection, and prophylaxis and treatment of infections and GvHD have resulted in improved survival (4, 6). With these advances, an increasing number of patients are being transplanted, or being considered for HSCT, while until recently they would receive conservative, non-curative therapy. Consequently, the long-term physical and psychosocial outcomes of HSCT are becoming increasingly important.

LATE EFFECTS: DEVELOPMENTS & SCREENING GUIDELINES

After pediatric HSCT late effects can arise, due to the HSCT procedure itself or due to the underlying disease (5). Knowledge of late effects is required to adjust treatment modalities to prevent or limit late effects, and to offer supportive care. To gain a better understanding of late effects, a screening follow-up program is in place at the

Leiden University Medical Center (LUMC). Patients transplanted in childhood for a nonmalignant disease enter this program from two years after HSCT onwards. Since late effects can also occur many years after pediatric HSCT, the follow-up program continues throughout adulthood. The Late Effects Comprehensive Care & Follow-up (LEEF) program annually screens patients for physical and mental health.

At the start of the LUMC follow-up program, the national screening guidelines of late effects after childhood cancer were used (7). However, HSCT for nonmalignant diseases differs substantially from HSCT for malignant diseases with respect to applied conditioning regimens. Further, patients differ in comorbidity, health status, and health related quality of life (HRQoL) pre-HSCT. Moreover, the underlying disease itself can be a predisposing factor for the occurrence (of severity) of late effects after HSCT. To provide adequate care, screening guidelines for pediatric HSCT for nonmalignant diseases are necessary. Currently, international guidelines are mostly expert-opinion-based rather than evidence-based, and are predominantly aimed at late effects of childhood cancer (7-9).

To establish an evidence-based screening guideline for pediatric HSCT for nonmalignant diseases research is essential. Current late effects research is mainly focused on clinical outcomes such as survival, immune reconstitution, chronic GvHD, growth, endocrine and gonadal dysfunction. However, to properly determine the late effects after this intensive treatment, study of patients' overall well-being is essential too, including HRQoL and psychosocial outcomes.

LATE EFFECTS COMPREHENSIVE CARE & FOLLOW-UP (LEEF) PROGRAM: PROVIDING OPTIMAL CARE

In addition to screening for late effects and looking at overall well-being, the Late Effects Comprehensive Care & Follow-up program is also aimed at providing optimal care, which is adjusted to patients' needs throughout life. Whether optimal care is provided should not solely be up to the healthcare professional (HCP), but should also be defined by the patient. Patient involvement in the development and evaluation of the LEEF program is therefore essential. Patients' healthcare perspectives and what is of importance to them, is fundamental to evaluate the value of the provided care.

VALUE-BASED HEALTHCARE

In recent years, the healthcare system has gradually moved towards a system of value-based healthcare (VBHC). With VBHC Porter and Teisberg seek to create value in healthcare by achieving the best possible outcomes that matter to people at the lowest cost (10). However, the implementation strategies of VBHC has faced

persistent challenges (11). Therefore, Porter and Lee created a strategic agenda and described six VBHC components: (1) organize into integrated practice units (IPUs), (2) measure outcomes and costs for every patient, (3) move to bundled payment for care cycles, (4) integrate care delivery across separate facilities, (5) expand excellent services across geography, and (6) build an enabling information technology platform (12).

While the relevance and necessity of VBHC have become increasingly evident in healthcare, the implementation of VBHC has proven to be a challenge (11, 13). Firstly, the definition of VBHC turns out to be open to interpretation and the strategic value agenda by Porter and Lee is incomplete (14-18). Van der Nat et al (2022) suggested to add four components to the existing VBHC components: (1) set up value-based quality improvement, (2) integrate value in patient communication, (3) invest in a culture of value delivery (education), and (4) build learning platforms for healthcare professionals (Figure 1) (19). Secondly, shared decision making (SDM) is often seen as part of the VBHC principles (14, 20). SDM is not emphasized in Porter's definition since the model is aimed at the patient group level and outcomes are used for benchmarking (10, 12). As stated by van der Nat et al (2022), when outcomes, such as clinical outcomes and PROMs, become a part of the conversation between the healthcare professional and patient, SDM and VBHC intersect (19). The authors assert, 'Experts in both fields advocate the use of PROMs and clinical outcomes in shared-decision making as an opportunity to strengthen value-based healthcare' (19). Thirdly, there is ambiguity regarding the inclusion of patient experiences in the VBHC principles. Teisberg et al (2020) stated not to see patient experiences as value, since VBHC focuses primarily on improving health outcomes, and perceives patient experiences as a result of the delivered care (21). A different point of view is presented by Chatterjee et al (2015), who showed better clinical process and outcomes measures through higher patient satisfaction scores (22). In addition, in the setting of VBHC, the Netherlands Federation of University Medical Centers (NFU) defined health outcomes as clinical outcomes (e.g. hormonal function, graft function, kidney function), patient-reported outcomes (e.g. physical function, sleep disturbance, cognitive function), and patient-reported experiences (23).

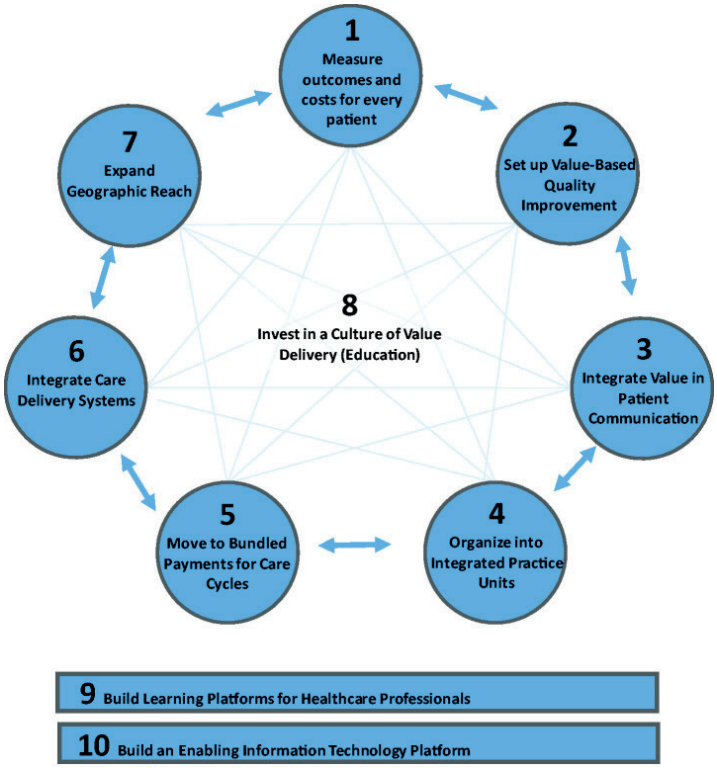


Figure 1. VBHC components: extended version by van der Nat et al (2022) (19)

Although there is no consensus on the definition of and implementation strategies for VBHC, it is evident that VBHC principles are increasingly being applied in current healthcare. With the aim of providing optimal care, the VBHC principles were implemented at the Late Effects Comprehensive Care & Follow-up (LEEF) program after pediatric HSCT for nonmalignant diseases. In our view, with an emphasis on the patient perspective, VBHC posits a combination of improved health outcomes through better processes of care, enhanced incorporation of patient experience, and optimal use of effort and costs (Figure 2).

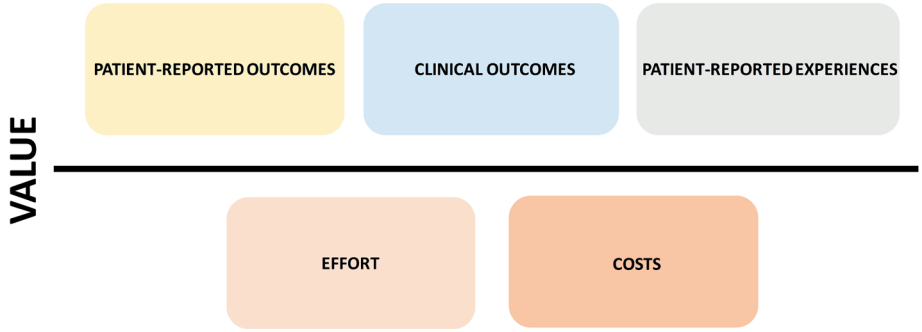


Figure 2. VBHC at the Late Effects Comprehensive Care & Follow-up (LEEF) program after pediatric HSCT for nonmalignant diseases

GAPS OF KNOWLEDGE

In 2018, the first steps towards a long-term follow-up program after pediatric HSCT for nonmalignant diseases at the LUMC had been taken which was based on guidelines and experiences of follow-up after childhood cancer (7). Currently, international screening programs and consensus on long-term follow-up after pediatric HSCT for nonmalignant diseases, including follow-up continuing into adulthood, are lacking. There is limited research in the field of late effects of pediatric HSCT for nonmalignant diseases, research predominantly has focused on late effects of childhood cancer (8, 9). However, knowledge on late effects is essential to adjust the screening guidelines for providing optimal care.

VBHC has predominantly been implemented in care paths aimed at managing acute or chronic diseases, with the primary goal of symptom control. Lessons learned from these care paths have been adapted to similar care paths. However, there is a lack of knowledge of VBHC implementation in care paths where the focus solely lies on screening, where active disease and symptoms are lacking. Additionally, there is no VBHC implementation experience in care paths involving multiple age categories, including children, adolescents, and adults.

When initiating VBHC in comprehensive care follow-up programs after pediatric HSCT for nonmalignant diseases, the need for accurately assessing the patient's overall well-being becomes more pressing. By integrating research into the VBHC initiation, the gap of knowledge on late effects and overall well-being in patients after this type of HSCT is addressed, while providing care of value.

AIM AND OUTLINE OF THIS THESIS

The first aim of this thesis was to evaluate the Late Effects Comprehensive Care & Follow-up (LEEF) program after pediatric stem cell transplantation for nonmalignant diseases at the LUMC, regarding various late effects and health-related quality of life. The second aim was to implement and evaluate aspects of value-based healthcare at the LEEF program.

Part I of this thesis focuses on the long-term clinical outcomes of pediatric HSCT for nonmalignant diseases. At the beginning of this thesis a screening guideline for late effects of pediatric HSCT for nonmalignant diseases was developed and is described in **Chapter 2.** Integrated in this guideline are the endocrine late effects, which are described in **Chapter 3.**

Part II of this thesis focuses on patient-reported outcomes and patient-reported experiences in pediatric HSCT for nonmalignant diseases. **Chapter 4** describes the long-term psychosocial impact of this high-intensive treatment. Additionally, the long-term parental distress of parents of children transplanted is addressed in **Chapter 5**. Lastly, **Chapter 6** describes the long-term patient-reported outcomes of pediatric HSCT for nonmalignant diseases.

Part III of this thesis focuses on the implementation and evaluation of VBHC at the Late Effects Comprehensive Care & Follow-up (LEEF) program after pediatric HSCT for nonmalignant diseases. **Chapter 7** describes the value of value of using patient-reported outcomes for health screening during long-term follow-up after stem cell transplantation in children with nonmalignant diseases. Finally, **Chapter 8** addresses the lessons learned from the VBHC implementation at the LEEF program.

REFERENCES

1. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med. 2006;354(17):1813-26.
2. Shaw P, Shizuru J, Hoenig M, Veys P. Conditioning Perspectives for Primary Immunodeficiency Stem Cell Transplants. Front Pediatr. 2019;7:434.
3. Duarte RF, Labopin M, Bader P, Basak GW, Bonini C, Chabannon C, et al. Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. Bone Marrow Transplant. 2019;54(10):1525-52.
4. Passweg JR, Baldomero H, Basak GW, Chabannon C, Corbacioglu S, Duarte R, et al. The EBMT activity survey report 2017: a focus on allogeneic HCT for nonmalignant indications and on the use of non-HCT cell therapies. Bone Marrow Transplant. 2019;54(10):1575-85.
5. Dietz AC, Duncan CN, Alter BP, Bresters D, Cowan MJ, Notarangelo L, et al. The Second Pediatric Blood and Marrow Transplant Consortium International Consensus Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation: Defining the Unique Late Effects of Children Undergoing Hematopoietic Cell Transplantation for Immune Deficiencies, Inherited Marrow Failure Disorders, and Hemoglobinopathies. Biol Blood Marrow Transplant. 2017;23(1):24-9.
6. Passweg JR, Baldomero H, Chabannon C, Basak GW, de la Cámara R, Corbacioglu S, et al. Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years. Bone Marrow Transplant. 2021;56(7):1651-64.
7. Taakgroep LATER van de Stichting Kinderoncologie Nederland (SKION). Richtlijn follow-up na kinderkanker: meer dan 5 jaar na diagnose 2009 [1:[Available from: https://www.skion.nl/workspace/uploads/richtlijn_follow-up_na_kinderkanker_deel_1_boekje_met_aanbevelingen_1.pdf.
8. van Kalsbeek RJ, van der Pal HJH, Kremer LCM, Bardi E, Brown MC, Effeney R, et al. European PanCareFollowUp Recommendations for surveillance of late effects of childhood, adolescent, and young adult cancer. Eur J Cancer. 2021;154:316-28.
9. Long-term follow-up guidelines: International Guideline Harmonization Group for Late Effects of Childhood Cancer; [Available from: https://www.ighg.org/guidelines/topics/.
10. Porter ME, Teisberg EO. Redefining Health Care: Creating value-based competition on results. 6 ed. Boston: Mass: Harvard Business Review Press; 2006.
11. van Staalduinen DJ, van den Bekerom P, Groeneveld S, Kidanemariam M, Stiggelbout AM, van den Akker-van Marle ME. The implementation of value-based healthcare: a scoping review. BMC Health Serv Res. 2022;22(1):270.
12. Porter ME, Lee TH. The Strategy That Will Fix Health Care. Harvard Business Review. 2013:1-37.
13. Depla AL, Pluut B, Lamain-de Ruiter M, Kersten AW, Evers IM, Franx A, et al. PROMs and PREMs in routine perinatal care: mixed methods evaluation of their implementation into integrated obstetric care networks. J Patient Rep Outcomes. 2023;7(1):26.

14. Lansdaal D, van Nassau F, van der Steen M, Bruijne M, Smeulers M. Lessons learned on the experienced facilitators and barriers of implementing a tailored VBHC model in a Dutch university hospital from a perspective of physicians and nurses. BMJ Open. 2022;12(1):e051764.

15. Lewis S. Value-based healthcare: is it the way forward? Future Healthc J. 2022;9(3):211-5.

16. Heijsters F, van Breda FGF, van Nassau F, van der Steen MKJ, Ter Wee PM, Mullender MG, et al. A pragmatic approach for implementation of value-based healthcare in Amsterdam UMC, the Netherlands. BMC Health Serv Res. 2022;22(1):550.

17. Groenewoud AS, Westert GP, Kremer JAM. Value based competition in health care's ethical drawbacks and the need for a values-driven approach. BMC Health Serv Res. 2019;19(1):256.

18. van Engen V, Bonfrer I, Ahaus K, Buljac-Samardzic M. Value-Based Healthcare From the Perspective of the Healthcare Professional: A Systematic Literature Review. Front Public Health. 2021;9:800702.

19. van der Nat PB. The new strategic agenda for value transformation. Health Serv Manage Res. 2022;35(3):189-93.

20. Steinmann G, Delnoij D, van de Bovenkamp H, Groote R, Ahaus K. Expert consensus on moving towards a value-based healthcare system in the Netherlands: a Delphi study. BMJ Open. 2021;11(4):e043367.

21. Teisberg E, Wallace S, O'Hara S. Defining and Implementing Value-Based Health Care: A Strategic Framework. Acad Med. 2020;95(5):682-5.

22. Chatterjee P, Tsai TC, Jha AK. Delivering value by focusing on patient experience. Am J Manag Care. 2015;21(10):735-7.

23. NFU. Waardegedreven Zorg position paper. [Available from: https://nfukwaliteit.nl/pdf/NFU-Position_Paper_Waardegedreven_Zorg.pdf.