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"The development of a core outcome set for clinical trials examining the effects of rehabilitative interventions in patients with hematological malignancies undergoing allogeneic stem cell transplantation"

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Declaration

"On my own responsibility and being aware of the possibility of sanctions by the Department Assembly, I declare responsibly that for the writing of my Doctoral Thesis I did not use the whole or part of another author's work or the ideas and concepts of another author without mentioning the source of origin (book, newspaper or magazine article, website, etc.). In addition, I declare that I checked the possibility of plagiarism of the final version of the Doctoral Dissertation through the Turnitin electronic platform and submitted the relevant analysis and its results in electronic and paper form to the Department Secretariat."

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List of Publications

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2. Vollenweider R, **Manettas AI,** Häni N, de Bruin ED, Knols RH. Passive motion of the lower extremities in sedated and ventilated patients in the ICU - a systematic review of early effects and replicability of Interventions. PLoS One. 2022 May 12;17(5):e0267255. doi: 10.1371/journal.pone.0267255. PMID: 35552550; PMCID: PMC9098053.

Preface

The process of completing this thesis has been a rewarding and intellectually enriching journey, marked by both challenges and valuable collaborations. From the initial development of the research question, through the comprehensive scoping review, and culminating in the Delphi consensus process, this work required sustained effort, coordination, and the engagement of experts from diverse fields.

I would like to express my sincere gratitude to my supervisors Prof.Dr. Tsaklis, Prof.Dr. Jamurtas and Dr. Mokkink, whose guidance and expertise were instrumental at every stage of the research and writing process. Their constructive feedback and unwavering support greatly enhanced the quality of this thesis.

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I am also deeply appreciative of the panelists who participated in the Delphi study and took the time to share their knowledge and experience. This work would not have been possible without their thoughtful engagement and willingness to reach consensus on complex methodological issues.

Completing this thesis has broadened my scientific perspective and deepened my appreciation for collaborative research. I remain grateful to everyone who supported and inspired me along the way.

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Summary

This doctoral thesis addresses the challenges of outcome heterogeneity and measurement inconsistency in research on rehabilitative interventions for patients with hematological malignancies undergoing allogeneic hematopoietic stem cell transplantation (HSCT). These patients experience complex physical and psychosocial sequelae requiring multidisciplinary rehabilitation, yet progress in the field is limited by wide variability in the outcomes measured, the instruments used to assess them, and the timing of assessments, factors which compromise the comparability, clinical interpretability and synthesis of clinical research.

To systematically address this problem, the thesis employs the following approach. First, a comprehensive scoping review was conducted, mapping all outcomes, measurement instruments, and time points reported in relevant rehabilitation intervention trials in patients undergoing HSCT. The review revealed significant heterogeneity and demonstrated that inconsistent terminology and measurement practices hinder evidence synthesis and clinical translation.

Based on the evidence mapped in the scoping review, a two-round Delphi study was performed with international experts and clinicians in rehabilitation after HSCT and allogeneic HSCT. The Delphi process sought consensus on a clinical core outcome set and related measurement guidelines for use in future clinical trials. Consensus was achieved for two main settings (hospital and non-hospital), standardizing the assessment of two primary outcomes (strength using handgrip dynamometry and the 30-second sit-to-stand test and exercise capacity using the six-minute walk test)) at clearly defined time points. The guidelines were designed to apply broadly to both allogeneic and autologous HSCT populations, addressing the need for harmonization across varying treatment settings and phases of care.

This thesis is the first to develop a consensus-derived core outcome and measurement guideline specific to HSCT rehabilitation trials, providing structured recommendations on "what to measure," "how to measure," and "when to measure." The adoption of these guidelines in future research is expected to reduce outcome-reporting bias and research waste, facilitate reliable meta-analysis, and ultimately improve clinical care for HSCT recipients. Limitations include the exclusion of direct patient-reported outcomes due to the focus on clinician- and performance-based assessment, and a modest expert participation rate in the Delphi rounds. Future work should prioritize patient involvement for the development of comprehensive core outcome sets.

Keywords

COS, core outcome set, HSCT, hematopoietic stem cell transplantation, rehabilitation

Περίληψη

Η παρούσα διδακτορική διατριβή εξετάζει τις προκλήσεις που απορρέουν από την ετερογένεια των αποτελεσμάτων και την ασυνέπεια των μετρήσεων στην έρευνα για τις αποκαταστασιακές παρεμβάσεις σε ασθενείς με αιματολογικές κακοήθειες που υποβάλλονται σε αλλογενή μεταμόσχευση αιμοποιητικών βλαστοκυττάρων (HSCT). Οι ασθενείς αυτοί παρουσιάζουν πολύπλοκες σωματικές και ψυχοκοινωνικές επιπτώσεις, οι οποίες απαιτούν πολυεπιστημονική αποκατάσταση, ωστόσο, η πρόοδος στον συγκεκριμένο τομέα παρεμποδίζεται από τη μεγάλη ποικιλία των μετρούμενων αποτελεσμάτων, των εργαλείων αξιολόγησης που χρησιμοποιούνται και του χρονισμού των αξιολογήσεων, παράγοντες που περιορίζουν τη συγκρισιμότητα, την κλινική ερμηνευσιμότητα και τη σύνθεση των ερευνητικών δεδομένων.

Για τη συστηματική αντιμετώπιση του προβλήματος αυτού, η διατριβή υιοθετεί την εξής μεθοδολογική προσέγγιση. Αρχικά διενεργήθηκε μια εκτενής χαρτογραφική ανασκόπηση, η οποία χαρτογράφησε όλες τις εκβάσεις, τα εργαλεία μέτρησης και τα χρονικά σημεία αξιολόγησης που αναφέρονται σε σχετικές κλινικές δοκιμές αποκαταστασιακών παρεμβάσεων σε ασθενείς μετά από HSCT. Η ανασκόπηση αποκάλυψε σημαντική ετερογένεια και απέδειξε ότι η ασυνεπής ορολογία και οι διαφοροποιημένες πρακτικές μέτρησης δυσχεραίνουν τη σύνθεση των δεδομένων και τη μεταφορά των αποτελεσμάτων στην κλινική πράξη.

Με βάση τα δεδομένα που χαρτογραφήθηκαν στη scoping review, πραγματοποιήθηκε μια δίκυκλη μελέτη τύπου Delphi με τη συμμετοχή διεθνών ειδικών και κλινικών επαγγελματιών στον τομέα της αποκατάστασης μετά από HSCT και αλλογενή HSCT. Η διαδικασία Delphi αποσκοπούσε στην επίτευξη συναίνεσης σχετικά με ένα βασικό σύνολο κλινικών εκβάσεων και συναφείς οδηγίες μέτρησης για χρήση σε μελλοντικές κλινικές δοκιμές. Επιτεύχθηκε συναίνεση για δύο κύρια πλαίσια (ενδονοσοκομειακό και εξωνοσοκομειακό), με τυποποίηση της αξιολόγησης δύο πρωτευόντων εκβάσεων — της μυϊκής δύναμης (μέσω δυναμομετρίας χειρός και της δοκιμασίας 30 δευτερολέπτων καθίσματος-ανόρθωσης) και της ικανότητας

άσκησης (μέσω της δοκιμασίας βαδίσματος έξι λεπτών), σε σαφώς καθορισμένα χρονικά σημεία. Οι οδηγίες σχεδιάστηκαν ώστε να εφαρμόζονται ευρέως τόσο σε πληθυσμούς με αλλογενή όσο και σε αυτόλογη HSCT, καλύπτοντας την ανάγκη για εναρμόνιση μεταξύ διαφορετικών θεραπευτικών πλαισίων και φάσεων φροντίδας.

Η διατριβή αυτή είναι η πρώτη που αναπτύσσει ένα σύνολο βασικών εκβάσεων και κατευθυντήριων οδηγιών μέτρησης βασισμένων σε διεθνή συναίνεση, ειδικά για τις κλινικές δοκιμές αποκατάστασης μετά από HSCT, παρέχοντας δομημένες συστάσεις σχετικά με το «τι πρέπει να μετράται», «πώς να μετράται» και «πότε να μετράται». Η υιοθέτηση αυτών των οδηγιών σε μελλοντικές έρευνες αναμένεται να μειώσει την προκατάληψη στην αναφορά εκβάσεων και τη σπατάλη ερευνητικών πόρων, να διευκολύνει την αξιόπιστη μετα-ανάλυση και τελικά να βελτιώσει την κλινική φροντίδα των ληπτών HSCT. Οι περιορισμοί περιλαμβάνουν τον αποκλεισμό άμεσων εκβάσεων που αναφέρονται από τους ασθενείς, λόγω της εστίασης σε αξιολογήσεις από κλινικούς και βασισμένες στην απόδοση, καθώς και τον σχετικά περιορισμένο αριθμό εμπειρογνωμόνων που συμμετείχαν στις γύρες Delphi. Μελλοντικές εργασίες θα πρέπει να δώσουν προτεραιότητα στη συμμετοχή των ασθενών για την ανάπτυξη πιο περιεκτικών βασικών συνόλων εκβάσεων.

Λέξεις-κλειδιά

COS, βασικό σύνολο εκβάσεων, HSCT, μεταμόσχευση αιμοποιητικών βλαστοκυττάρων, αποκατάσταση

Introduction

Allogeneic HSCT represents the most effective treatment and often the only curative option for patients with diverse hematological malignancies. While this procedure substantially improves survival prospects, it is accompanied by considerable morbidity. Among the most critical complications is graft-versus-host disease (GvHD), which requires long-term immunosuppressive therapy (IST). Although IST can mitigate GvHD, it also predisposes patients to infections, toxicities, and a marked reduction in quality of life. Compared with autologous HSCT, allogeneic recipients face unique vulnerabilities, including higher mortality and profound loss of physical vitality, rendering rehabilitation both more challenging and more urgently needed. Multidisciplinary rehabilitation programs have shown potential to improve physical capacity, alleviate treatment sequelae, and enhance survival outcome in these patients. Nevertheless, their feasibility and safety remain closely tied to transplantation-related complications, immunosuppression, and psychosocial challenges.

Despite the increasing implementation of rehabilitation interventions for patients after allogeneic HSCT, one of the greatest obstacles to progress lies in the heterogeneity of clinical research in this field. Substantial diversity exists not only in patient selection and intervention content but also, and most critically, in the outcome domains assessed and the measurement instruments applied. This inconsistency complicates the interpretation of individual trials, hampers or even prevents secondary synthesis, and undermines the development of evidence-based clinical guidelines. According to the Cochrane framework, such heterogeneity stems from both clinical diversity (differences in populations, interventions, outcomes and settings) and methodological diversity (variability in study design and risk of bias). Existing trials in the rehabilitation of HSCT patients exemplify these issues, with outcome selection often guided by local priorities instead of standardized frameworks, resulting in a patchwork of evidence with limited comparability. While international initiatives such as the Harmony Alliance are developing core outcome sets (COS) for several hematological neoplasms, patients undergoing allogeneic HSCT remain insufficiently represented, even though they

constitute a distinct subgroup with predictable complications such as GvHD, infection risk, and physical deconditioning. The absence of standardized outcome definitions and measurement protocols perpetuates research waste and restricts the applicability of study findings to clinical and guideline development.

The primary aim of this thesis is to address this research gap by developing a consensus-based clinical Core Outcome Set (COS) incorporated in measurement guidelines for rehabilitation trials in patients with hematological malignancies treated with allogeneic HSCT. Specifically, the work seeks to define which clinical outcomes are the minimum that should be measured ("what") in any new trial, the most appropriate instruments to assess them ("with what"), and the optimal time-points of assessment ("when"). By doing so, the thesis contributes to reducing heterogeneity in clinical outcome selection and enhancing the comparability of clinical trials, thereby advancing the evidence base for rehabilitation in this complex population.

To achieve this objective, a two-step methodological approach was employed. First, a scoping review systematically mapped the outcomes, assessment tools, and measurement schedules reported in current rehabilitation research involving AlloHSCT populations. Using established methodological frameworks (PRISMA-ScR), this review synthesized the available evidence, revealed inconsistencies, and identified domains of variability. Building on this evidence base, a Delphi consensus study was then conducted, involving international, multidisciplinary experts in HSCT and oncological rehabilitation. Over two rounds, experts evaluated candidate outcomes, proposed instruments, and recommended measurement time-points. Together, this two-step procedure ensured that the proposed measurement guidelines were both empirically grounded and internationally validated. This thesis is structured into three interrelated parts:

Part A, "Theoretical Foundations" provides the necessary background, including the principles of hematopoiesis, the indications and complications of stem cell transplantation and

the current state of research in rehabilitation for HSCT. It also introduces the theoretical concept of core outcome sets and their proposed role in reducing heterogeneity.

Part B, “Core Research” presents the studies forming the heart of this work: the scoping review and the Delphi Study. These chapters establish the magnitude of outcome variability and propose a standardized measurement framework for future research.

Part C, “Discussion and Conclusions” integrates the findings from prior sections, critically examines methodological and practical challenges, highlights the implications for clinical and scientific practice, and formulates recommendations for ongoing and future efforts in HSCT rehabilitation research.

Through this integrated structure, the thesis develops a coherent progression from foundational context to empirical innovation, to critical reflection, offering a systematic response to one of the most persistent barriers in advancing rehabilitation research for allogeneic HSCT

CHAPTER 1: Theoretical Foundations

1.1 Blood and Hematopoiesis

Blood is a complex, regenerative tissue formed from hematopoietic stem cells (HSCs), which reside in the bone marrow and continually give rise to all mature blood cells throughout life. Understanding the developmental stages, differentiation pathways, and the role of immature precursors, known as "blasts", is crucial for grasping both physiological hematopoiesis and the pathobiology of hematological malignancies.

Hematopoietic stem cells (HSCs) are multipotent, self-renewing cells located primarily in the bone marrow [1]. HSCs emerge during embryogenesis from specialized hemogenic endothelium in the aorta-gonad-mesonephros region and migrate to the fetal liver for expansion before establishing residency in the bone marrow [2]. They differentiate into three primary lineages, each giving rise to distinct blast populations:

1. Myeloid lineage: HSCs first form common myeloid progenitors (CMPs), which further differentiate into blasts committed to granulocytes (neutrophils, eosinophils, basophils), monocytes (precursors of macrophages), megakaryocytes (for platelets), and erythrocytes (red blood cells) [3].
2. Lymphoid lineage: HSCs produce common lymphoid progenitors (CLPs), which become lymphoblasts that differentiate into B lymphocytes (antibody production), T lymphocytes (cellular immunity), and natural killer cells (innate cytotoxicity) [3].
3. Erythroid lineage: Arising from the myeloid pathway, erythroid blasts mature into erythrocytes, responsible for oxygen transport via hemoglobin [3].

"Blast" cells are immature precursors in the differentiation hierarchy which gradually undergo sequential maturation. Under normal circumstances, only mature cells populate

peripheral blood. The appearance of excess blasts in blood, a hallmark of acute leukemias, signals malignant clonal proliferation and differentiation arrest [4].

1.2 Hematological Malignancies

Hematological malignancies often result from genetic mutations or chromosomal translocations that cause differentiation arrest and uncontrolled proliferation of blasts [5]. Examples include:

- Acute myeloid (AML) and lymphoblastic leukemias (ALL): Characterized by accumulation of myeloblasts due to blocked maturation or by lymphoblast expansion.
- Myeloid and lymphoid leukemias: Involve aberrant proliferation of more mature progenitors but may progress to an acute "blast phase" [6].
- Myelodysplastic Syndromes (MDS) and Myeloproliferative Neoplasms (MPN)
- Lymphomas: Divided into Hodgkin and non-Hodgkin.
- Plasma cell neoplasms: Multiple myeloma and Plasmacytoma [5].

Blast crises cause cytopenia and tissue infiltration, manifesting as anemia, infection, and bleeding. Progression from HSCs to blasts, and then to mature cells, is hijacked, leaving the marrow packed with non-functional precursors [7].

1.3 Hematopoietic Stem Cell Transplantation

HSCT is a cornerstone of therapy for hematological malignancies. This intensive procedure replaces diseased or dysfunctional hematopoietic systems with healthy stem cells, facilitating cure or sustained disease control [8]. HSCT use has expanded dramatically over recent decades. From 2000 to 2021, the annual number of transplants reported by the European Society for Blood and Marrow Transplantation (EBMT) centers doubled, exceeding

45,000 procedures in 2019 [9]. Globally, more than 1.5 million HSCTs have been performed [10].

The two principal HSCT forms (autologous and allogeneic) differ fundamentally in terms of clinical application, risk profile, and epidemiology. In Europe in 2021, 46% of transplants were allogeneic, and 54% autologous [11]. In the US, a similar split is observed, with considerable variation according to disease and patient population [12].

Autologous HSCT employs self-derived stem cells, mainly for multiple myeloma, relapsed lymphomas, and some solid tumors, leveraging high-dose chemotherapy [13]. Outcomes depend on chemosensitivity [14]. There is no immunological graft-versus-tumor (GVT) effect and virtually no risk of GvHD. Non-relapse mortality is much lower (<5%), though relapse remains more common overall [15]. Autologous HSCT is rarely curative outside of specific diseases and is being superseded by novel therapies in some indications [16,14].

Allogeneic HSCT is the foundation of curative therapy for high-risk hematological malignancies [17]. Epidemiological monitoring demonstrates expanding access, improved safety, and ongoing innovation. Optimal outcomes depend on integrated risk assessment, multidisciplinary care, and continual alignment of practice with emerging evidence [18]. The field is defined by rapid evolution: new donor sources, reduced intensity and haploidentical conditioning, personalized risk stratification, and enhanced survivorship models. International registries and harmonized accreditation standards continue to improve practice and outcomes [19, 20].

Allogeneic HSCT is performed using stem cells drawn from a matched sibling, a matched unrelated donor, or a mismatched/haploidentical donor. It is a standard of care for patients with adverse or intermediate-risk AML in first or subsequent complete remission, high-risk ALL including those with measurable residual disease or adverse cytogenetics, advanced-phase chronic myeloid leukemia (CML), higher-risk MDS, advanced myelofibrosis, select cases of chronic lymphocytic leukemia (CLL), and aggressive lymphomas after either relapse or CAR-

T cell therapy failure [17]. Risk stratification for allogeneic HSCT incorporates disease-related markers, measurable residual disease status, patient comorbidities and age, organ function as measured by the HCT-Comorbidity Index, previous therapy responses, and overall relapse risk [21].

The choice of donor has progressed beyond the historical focus on matched sibling donors, which now account for less than 30% of allogeneic HSCTs. Advances in histocompatibility matching and supportive care have made outcomes such as overall survival, disease free survival and non-relapse mortality for matched unrelated donors comparable to those from siblings. When neither is available, alternative donors, including haploidentical relatives mismatched by one HLA haplotype or umbilical cord blood, are increasingly used, especially in the absence of a fully matched donor [22]. Peripheral blood stem cells are preferred for most transplants (>70%), though bone marrow or cord blood may be selected for pediatric or certain adult indications [23].

Five-year overall survival after allogeneic HSCT varies from 30–80%, highest when transplantation is done in first complete remission and lowest for patients with active or refractory disease [24,25]. Relapse remains the leading cause of treatment failure, while non-relapse mortality relates to infection, organ toxicity, and GvHD [26]. Improvements in supportive care and comorbidity management have successfully halved transplant-related mortality during the past two decades, even among older adults [27]. According to the 2021 EBMT report, over 27,000 allogeneic and 32,000 autologous transplants took place in Europe, with AML the most common indication for allogeneic procedures (>30%), followed by ALL (17%), lymphomas, MDS, and myelofibrosis. The median age of recipients continues to rise, and more than 20% of HSCTs are now in patients older than 60 [11]. Notably, the use of haploidentical donors has increased substantially, now accounting for 25–30% of allogeneic HSCTs in Europe [28].

The GVT effect is a pivotal therapeutic mechanism in allogeneic HSCT for hematological malignancies. It refers to the beneficial immunological response whereby donor-derived

immune cells recognize and attack residual malignant cells in the recipient, thereby reducing the risk of relapse and contributing to long-term remission [29]. The GVT effect hinges predominantly on donor T lymphocytes, although other cell types such as natural killer (NK) and natural killer T (NKT) cells may also play important roles, particularly in newer allogeneic cell-based immunotherapies [30].

Importantly, the GVT effect is inseparable from GvHD, which occurs when donor immune cells also target recipient healthy tissues. While some degree of GvHD is often associated with a stronger GVT effect and reduced relapse rates, severe GvHD carries significant morbidity and mortality, highlighting the need for a delicate balance between anti-tumor immunity and the risk of alloreactivity [31].

The choice of preparative chemotherapy regimen, referred to as conditioning intensity, for allogeneic HSCT, either myeloablative conditioning (MAC) or reduced intensity conditioning (RIC), determines the risk of early side effects, chances of disease relapse, long-term survival, and which patients are eligible for transplant [32].

MAC regimens are designed to eradicate both malignant cells and the recipient's hematopoiesis through administration of high-dose chemotherapy and/or total body irradiation, thus enabling robust donor engraftment and exerting powerful anti-leukemic effects. Classic regimens frequently employ agents such as busulfan, cyclophosphamide, and total body irradiation, whereas newer protocols now incorporate drugs like thiotepa to further improve disease control and overall survival [33,34,35]. The intensity of these regimens leads to profound and prolonged cytopenias, which in turn increase the risk for mucositis, gastrointestinal, hepatic, and infectious complications, as well as a greater incidence of organ toxicity and GvHD. Consequently, transplant-related mortality in the early post-transplant phase is typically higher with myeloablative approaches [36].

Historically, MAC has been the preferred choice for patients with high-risk or aggressive leukemias, primarily due to lower relapse rates associated with extensive cytoreduction and

enhanced graft-versus-leukemia effects [37]. Myeloablative conditioning remains the standard for fit adults younger than 50–60 years with adequate organ function and acute leukemia in remission [36,37].

For older adults or those with significant comorbidities, previous myelodysplasia, or secondary leukemias, RIC regimens have become increasingly favored and they have expanded the eligibility for HSCT by employing lower doses of chemotherapy and/or radiation, often in combinations such as fludarabine, lower-dose busulfan, and melphalan, to decrease regimen-related toxicity. These regimens offer a better safety profile, reduced early organ toxicity, and are more suitable for patients with compromised performance status [32]. RIC has shown comparable overall survival, disease free survival and non-relapse mortality to MAC in select patients with secondary acute myeloid leukemia (AML), and for individuals with non-malignant diseases or indolent lymphomas, therefore, it is now often preferred due to its favorable tolerability and lower risk profile [38].

RIC regimens result in less severe myelosuppression and organ toxicity, as well as marked reductions in early transplant-related mortality, but these benefits are counterbalanced by a higher risk of disease relapse, particularly in younger patients or those with unfavorable molecular markers. However, non-relapse mortality is substantially lower with RIC, and the immune-mediated GVT effect remains intact and may even be augmented by post-transplant immune strategies such as donor lymphocyte infusions [39].

Patients receiving RIC typically experience shorter hospitalizations, fewer early complications, faster recovery of function, and improved immediate quality of life compared to those treated with MAC [39]. Despite these early benefits, both approaches entail lasting risks, especially chronic GvHD, infections, and secondary cancers, necessitating continued, multidisciplinary survivorship care [40,41]. Current research remains highly focused on optimizing conditioning strategies, balancing disease control with minimization of toxicity, and developing maintenance and immune-augmenting approaches to further improve long-term results [42].

Although high-dose chemotherapy followed by HSCT provides curative potential, it is associated with a profound myelosuppressive burden that results in severe and prolonged reductions in peripheral blood cell counts, leading to extended periods of pancytopenia.

Cytopenias are an inevitable and clinically significant consequence of HSCT, exposing patients to heightened risks of life-threatening infections, bleeding episodes, and profound declines in their overall quality of life [43].

Following the conditioning phase, stem cells are infused with the aim of restoring bone marrow function. During the intervening period before engraftment is achieved, patients experience severe and prolonged cytopenias. The depth and duration of these low counts depend on factors such as infused cell dose, individual age, marrow reserve, and intensity of the preparative regimen [44]. The underlying mechanisms stem from the direct effects of chemotherapeutic agents on hematopoietic stem and progenitor cells (HSPCs) within the bone marrow microenvironment. Cytotoxic agents induce apoptosis and senescence in progenitor populations and disrupt the supportive stromal niche, resulting in both immediate and sustained impairment of blood cell production [44].

Neutropenia is a direct consequence of loss of neutrophil precursors. Absolute neutrophil counts often drop below 500 cells/μl, with a concomitant risk of bacterial and fungal infections. Febrile neutropenia is frequently observed, necessitating empirical antimicrobial therapy and isolation [44]. Chemotherapy-induced thrombocytopenia manifests as spontaneous bruising, mucosal bleeding, and the threat of major hemorrhagic events, particularly when platelet counts fall below 10,000/μl. Platelet recovery is usually slower than neutrophil recovery post-transplant, and platelet transfusions are routine [44]. Anemia surfaces as reduced hemoglobin synthesis due to marrow suppression, drug effects, and occasionally, immune-mediated destruction. Symptoms include fatigue, dyspnea, and impaired physical functioning. Red cell transfusions are necessary until sustained marrow recovery is achieved [44].

To address these challenges, standard supportive care regimens incorporate myeloid growth factors, such as G-CSF, to speed neutrophil recovery, even though bone pain commonly occurs as a side effect [45]. Platelet and red blood cell transfusions remain essential for managing thrombocytopenia and anemia. Those with pre-existing bone marrow impairment, resulting from prior treatment, older age, or marrow infiltration, usually face deeper and more prolonged cytopenias. Allogeneic transplant recipients, especially those with GvHD, may have further delays in engraftment and hematopoietic recovery [44].

While allogeneic HSCT remains a curative option for many malignant and non-malignant diseases, it comes at the cost of acute, subacute, and late complications that can affect virtually every organ system, with profound clinical consequences for recipients. Profound and prolonged immunosuppression, combined with damage to mucosal barriers and the frequent use of indwelling vascular access, places transplant patients at exceptionally high risk for serious infections, notably within the first few months following HSCT. Neutropenic fever emerges as the most frequent early infectious complication, while invasive fungal infections and viral reactivations, such as cytomegalovirus and Epstein-Barr virus, can still be fatal despite aggressive prophylactic strategies. Hospitalization for severe infectious complications remains one of the primary causes of non-relapse mortality in this population.

Another potentially life-threatening complication, particularly after myeloablative conditioning, is sinusoidal obstructive syndrome (also known as veno-occlusive disease). This disorder stems from endothelial injury within the hepatic sinusoids, manifesting as jaundice, hepatomegaly, ascites, and, in severe cases, multi-organ dysfunction. Advances in risk assessment and therapies such as defibrotide have improved outcomes, but veno-occlusive disease continues to present a significant challenge [41].

Early organ injury after transplantation can affect the lungs (with complications like diffuse alveolar hemorrhage and idiopathic pneumonia), kidneys, and heart. These injuries may result from the toxic effects of conditioning regimens, infections, or immune-mediated processes and often necessitate admission to intensive care.

Long-term survivors continue to face risks associated with inadequate or delayed immune reconstitution, which predisposes to recurrent infections. Even years after transplantation, the risk persists for encapsulated bacterial pneumonias, herpesvirus reactivations, and opportunistic infections, especially among those with ongoing immunosuppression. Chronic organ dysfunction develops as a result of cumulative exposures to chemotherapy, radiotherapy, and immunosuppressive medications, with frequent endocrinopathies, such as thyroid dysfunction, impaired glucose metabolism, premature ovarian failure, and infertility, documented among survivors [46].

Cardiac and vascular complications also accumulate over time, with an increased risk for premature atherosclerosis, hypertension, and cerebrovascular events, particularly in those treated with total body irradiation. Chronic renal disease and pulmonary complications, including bronchiolitis obliterans and fibrotic syndromes, pose substantial morbidity and erode quality of life, sometimes with an incidence of chronic kidney disease exceeding 20% several years post-transplant [47].

Another major concern is the markedly elevated risk of secondary malignancies. Survivors face a two- to fourfold greater cumulative risk for developing solid tumors or hematologic cancers compared to the general population, with the risk rising over time and driven by prior exposures to radiation, chemotherapy, and chronic immunosuppression [48].

Psychosocial and quality-of-life issues are pervasive in the transplant survivor population. Persistent fatigue, cognitive difficulties, emotional distress, and social dysfunction are frequently reported, especially among those with complicated post-transplant courses or lingering sequelae. These challenges underscore the importance of holistic care and monitoring throughout the survivorship continuum [49].

GvHD represents the major long-term challenge following allogeneic HSCT. It is mediated by donor T cells mounting an immune response against host tissues and is traditionally classified into acute GvHD, which occurs within the first 100 days after transplantation, and

chronic GvHD, which typically manifests after three months but may exhibit overlapping features of both forms [50].

Acute GvHD primarily targets the skin, liver, and gastrointestinal tract, with severe cases potentially leading to life-threatening organ failure. Chronic GvHD, by contrast, presents as a multisystem autoimmune-like syndrome. It can involve the skin, eyes, oropharynx, liver, lungs, gastrointestinal tract, and musculoskeletal system, leading to wide-ranging morbidity [51].

The incidence of acute GvHD is estimated at 30–50%, while chronic GVHD affects up to 40% of patients. Risk factors include use of unrelated or mismatched donors, peripheral blood stem cells, and advanced recipient age [52]. Despite advances, chronic GvHD remains the leading cause of late non-relapse mortality and morbidity among survivors of allogeneic [53].

GvHD presents with a diverse range of clinical manifestations depending on the organs involved, making diagnosis and management complex. The skin can show sclerotic or lichenoid rashes and changes in pigmentation, often reflecting chronic inflammation and immune attack. Ocular involvement typically results in severe dryness and keratoconjunctivitis sicca, leading to discomfort and increased risk for infection. Ulceration and lichen planus-like lesions frequently develop in the oral mucosa, contributing to pain and impaired nutrition. The liver may be affected, manifesting as hyperbilirubinemia and impaired hepatic function, which sometimes results in jaundice and abnormal liver enzymes. Pulmonary complications, such as bronchiolitis obliterans syndrome, cause progressive airflow limitation and can significantly impact respiratory health. Musculoskeletal presentations include fasciitis and joint contractures, resulting in stiffness and decreased mobility. The hematological and immunological systems may manifest cytopenias alongside persistent immune dysfunction, further increasing the risk for infections and impairing overall health [54,55].

Chronic GvHD significantly compromises quality of life. Standard management relies on prolonged immunosuppression, which itself increases susceptibility to infections and secondary malignancies. Progress in supportive care, early detection of GvHD complications,

and novel immunomodulatory treatments has improved certain outcomes, but the disease remains the primary obstacle to successful long-term recovery [56].

1.4 Rehabilitative Interventions for HSCT

Rehabilitation is increasingly recognized as a comprehensive and multimodal health strategy aimed at optimizing functioning and reducing disability across a wide spectrum of health conditions, injuries, and impairments [57].

It is relevant to individuals of any age and can be delivered at all stages of illness, from acute care to long-term survivorship. Contemporary conceptualizations, such as the definition proposed by the Cochrane Rehabilitation initiative, frame rehabilitation as a person-centered and collaborative process directed at enhancing an individual's capacity, including body structures, functions, activities, and participation, as well as their actual performance within specific environmental and personal contexts [58]. The overarching goal is to optimize functioning for those currently experiencing, or at heightened risk of, disability. Structured in alignment with the PICO (Population, Intervention, Comparison, Outcome) framework, this definition highlights that effective rehabilitation must necessarily be multimodal, individualized, and dynamically tailored to evolving health needs and personal goals [59].

While advances in transplantation techniques and supportive care have significantly improved survival rates, HSCT remains associated with profound and multifaceted challenges. Patients frequently experience prolonged physical deconditioning, fatigue, and a marked reduction in quality of life [60]. Rehabilitation, delivered across the entire continuum of care, has therefore emerged as an essential strategy for optimizing outcomes in this vulnerable population [61]. Individuals with hematological malignancies undergoing HSCT are particularly susceptible to severe functional decline. Conditioning chemotherapy regimens, total body irradiation, and subsequent immunosuppressive therapies initiate a cascade of detrimental effects, including cytopenias, muscle wasting, neuropathy, mucositis, and cardiorespiratory

compromise. The trajectory is further complicated by GvHD, infections, and metabolic disturbances, all of which may significantly restrict mobility and independence.

Following transplantation, patients often contend with reduced muscle strength and endurance, diminished exercise tolerance, poor balance, and limitations in activities of daily living [60]. Fatigue, depression, anxiety, and fear of relapse create further barriers [62]. Over the long term, complications such as osteoporosis and metabolic syndrome exacerbate survivorship challenges [63,64]. These impairments are strongly associated with diminished quality of life, lower return-to-work rates, and increased healthcare utilization [65,66]. Within this context, rehabilitation provides not only the means of regaining function but also psychosocial support and long-term resilience [61].

Successful rehabilitation hinges on close multidisciplinary collaboration and active patient involvement. Teams often include physiatrists, physical therapists, occupational therapists, nurses, psychologists, and social workers, working in concert to provide comprehensive care [57]. In HSCT, integration with disciplines such as nutrition, pharmacy, psychology, and nursing is particularly critical. Rehabilitation is not limited to a single phase but must span the continuum of HSCT care [57].

Prehabilitation includes exercise and education prior to admission, to strengthen resilience, counter pre-transplant decline, and improve survival and recovery trajectories. Better pre-transplant fitness, such as six-minute walk performance ≥400 m, is associated with lower non-relapse mortality and faster regain of independence [67].

Inpatient rehabilitation occurs during hospitalization and focuses on mobilization, maintenance of muscle mass, prevention of immobility-related complications (delirium, thrombosis, pressure ulcers), and support for severely immunocompromised patients [68]. Safety protocols adjust activity intensity based on cytopenias and anemia thresholds. For instance, <10,000/μL platelets requires restriction to ADLs, while >20,000/μL may allow cautious resistance training [69].

Post-acute and long-term rehabilitation after hospital discharge targets restored functional independence, reintegration, and management of long-term sequelae such as osteoporosis, metabolic syndrome, and chronic GvHD. Outpatient physiotherapy and long-term follow-up improve exercise tolerance, counter fatigue, and promote psychosocial well-being [70,71,61]. Evidence from trials and meta-analyses confirm improvements in physical function, reduced fatigue, enhanced QOL, and improved return-to-work rates [72,73].

1.5 Heterogeneity in trials on rehabilitation for HSCT

Heterogeneity is particularly pronounced in cancer rehabilitation research, where trials face wide variation in patient populations, cancer stages, interventions, and outcomes. Oncology rehabilitation trials must accommodate different tumor types, comorbidities, and prior treatments, limiting direct comparability across studies [74]. This creates obstacles for meta-analysis, diluting signals of benefit and slowing translation to practice.

For HSCT, systematic reviews consistently observe major heterogeneity across intervention types, timing and duration of intervention, patient characteristics, and outcome measures. Such diversity often complicates pooling of results, increases uncertainty, and limits applicability to clinical practice, highlighting the urgent need for standardization in design and reporting [72].

Heterogeneity in meta-analysis refers to the variability that inevitably arises when synthesizing results from different studies, as no two trials are ever exactly alike. Distinguishing between the various forms of heterogeneity is fundamental to interpreting findings and assessing the validity of pooled estimates. In the literature, three main types are commonly described: clinical heterogeneity, methodological heterogeneity, and statistical heterogeneity [75]. Clinical heterogeneity refers to genuine differences in populations, treatments or outcome. Methodological heterogeneity refers to variability introduced by differences in study design (including outcome measurement selection) and risk of bias.

Statistical heterogeneity refers to variation in the measured effects across studies that exceeds what would be expected by chance alone. It is the quantitative manifestation of diversity and reflects the combined influence of both clinical and methodological sources. Understanding the interplay between these three forms is essential for the thoughtful and rigorous use of meta-analysis in evidence synthesis [76].

Clinical heterogeneity, often termed clinical diversity, captures differences in populations, interventions and outcomes among included trials [77]. These variations reflect real-world complexity and make clinical heterogeneity a central consideration in evidence synthesis. Clinical heterogeneity arises in dimensions such as patient age, comorbidities, disease severity, healthcare systems, intervention protocols (dose, duration, delivery, co-interventions, adherence), outcomes' definitions, or clinical context (acute vs. chronic care, country, or health system) [78]. Importantly, such variability will only translate into heterogeneity in effect sizes if it modifies the intervention effect, i.e., when subgroups or settings truly respond differently, resulting in a genuine difference in the "true" effect across studies.

Not all observed differences necessarily threaten validity. In some cases, clinical heterogeneity can enhance applicability and generalizability when interpreted judiciously [78]. Formal approaches, such as the Clinical Diversity in Meta-analysis (CDIM) tool, have been developed to systematically assess and map clinical diversity [78]. Systematic mapping supports deliberation on external validity and applicability to specific patient groups or healthcare contexts.

Clinical heterogeneity directly challenges both the internal and external validity of pooled estimates. Pooling dissimilar studies may generate results that are not meaningful for any real-world population or intervention. Sometimes, high clinical diversity precludes useful pooling, necessitating reliance on narrative synthesis or structured subgroup analyses. Broad inclusion criteria may exacerbate diversity in pragmatic reviews, whereas overly narrow criteria improve homogeneity at the expense of generalizability. Judicious management of clinical diversity across the review process is thus essential.

Methodological heterogeneity refers to variability introduced by differences in study design and risk of bias. Examples include inconsistencies in randomization, allocation concealment, blinding, measurement instrument selection or attrition handling. Unlike clinical heterogeneity, methodological heterogeneity reflects how differences in trial conduct may distort estimates of intervention effects. An example is when studies perform measurements at different time points, which can lead to variations in how intervention effects are observed and compared.

Statistical heterogeneity that arises solely from methodological differences suggests that discrepancies are due to bias, not true differences in treatment effect. For example, poorly blinded studies might systematically overestimate benefits compared to rigorously designed trials. Recognizing methodological heterogeneity is therefore critical for evaluating the credibility of meta-analysis results [79].

Statistical heterogeneity is observed as variation in the measured effects across studies that exceeds what would be expected by chance alone. It is the quantitative manifestation of diversity and reflects the combined influence of both clinical and methodological sources [80]. Heterogeneity statistics such as Cochran's Q or the I^2 metric are commonly employed to measure this form [81]. Importantly, statistical heterogeneity represents inconsistency of observed treatment effects but does not automatically reveal whether differences are due to true clinical variation, systematic bias, or random error. Misinterpreting statistical heterogeneity without acknowledging underlying causes can lead to inappropriate conclusions and misguided recommendations [80].

1.6 Core Outcome Sets

The lack of standardization in both outcome selection and the measurement instruments used represents a fundamental contributor to clinical and methodological heterogeneity in HSCT rehabilitation trials and a key barrier to comparability. Trials for similar conditions often employ different measurement tools, leading to inconsistencies that hinder data synthesis and

interpretation. Core Outcome Sets (COS) and accompanying measurement sets directly address this challenge. COS are standardized collections of *outcomes* that represent the minimum to be measured and reported in all clinical trials for a specific condition or intervention [82]. Standardization is achieved by providing a consensus-based list of outcomes that at least should be measured, along with explicit recommendations for validated and appropriate *measurement instruments* (i.e. the measurement set), in any future rehabilitation trial in patients with hematologic malignancies treated with HSCT. Developed through consensus among relevant stakeholders, COS aim to resolve one of the major challenges in health research: The inconsistency and incomparability of outcomes across studies, which undermines the ability to synthesize evidence, draw meaningful conclusions, and translate findings into practice or policy [83].

Historically, clinical trials have selected and defined outcomes based on local priorities, feasibility, or available measures. This has resulted in a proliferation of unique or poorly defined outcomes for the same conditions. In oncology, for example, one review reported over 25,000 unique outcomes, many referenced only once or twice across trials [83]. This creates major barriers: Evidence synthesis becomes difficult or invalid due to incomparable or missing outcome data. Selective outcome reporting based on statistical significance introduces reporting bias, potentially distorting evidence bases [84].

Patients, clinicians, and policymakers often find that research does not address outcomes most relevant to their needs and decisions. The lack of outcome standardization leads to wasted research efforts and the possibility that harmful interventions may be approved on incomplete or selectively reported outcomes [84]. COS were established to counteract these deficiencies through:

1. Harmonizing outcome selection to reduce avoidable research waste
2. Enhancing transparency, comparability, and stakeholder relevance
3. Supporting systematic reviews, meta-analyses, and guideline development [82].

There are three types of COS:

1. Clinical outcome sets focus on health indicators such as disease control, survival, adverse events, or functional outcomes measured from a clinical perspective.
2. Patient-reported outcome sets capture quality of life, symptom experience, and psychosocial well-being, measured from the patient perspective, increasingly recognized as essential for regulatory and clinical evaluation [85].
3. Composite or multi-domain sets integrate clinical, patient-reported, biomarker, and economic indicators, such as survival, health-related quality of life, toxicity, and resource use in cancer research [82].

COS are developed using rigorous and transparent methodologies that engage patients, clinicians, researchers, regulators, and policymakers. These processes typically include systematic reviews to identify outcomes and measurement tools, followed by consensus-building methods such as the Delphi technique, nominal group discussions, or patient focus groups [86].

By harmonizing study endpoints, COS facilitate better comparability across trials, which strengthens meta-analyses, systematic reviews, and the reliability of clinical guidelines [84]. This accelerates translation of evidence into policy and practice. COS also ensure that research addresses outcomes important to patients and caregivers, promoting alignment of research with real-world decision needs and supporting person-centered care [87]. Regulatory agencies and guideline developers increasingly mandate COS to be evaluated as trial endpoints for licensing, reimbursement, and implementation standards. By ensuring consistent collection of key outcomes, COS reduce selective outcome reporting and thereby strengthen the transparency and credibility of biomedical research. The value of COS is widely recognized, and many journals and funders require their use or a clear justification for deviation [84]. Current efforts include extending COS across additional diseases, pediatric and rare populations, and aligning standards internationally. Sustained investment in stakeholder

engagement, methodological refinement, and international collaboration ensure COS remain relevant, feasible, and impactful for evolving research and healthcare landscapes.

1.7 References

1. Aiuti A, Scala S, Chabannon C. Biological properties of hematopoietic stem cells: scientific basis for hematopoietic cell transplantation. In: Sureda A, Corbacioglu S, Greco R, et al., editors. *The EBMT Handbook: Hematopoietic Cell Transplantation and Cellular Therapies*[Internet]. 8th ed. Cham (CH): Springer; 2024 Apr 11. Chapter 7. Available from: https://www.ncbi.nlm.nih.gov/books/NBK608248/ doi:10.1007/978-3-031-44080-9_7

2. Ng AP, Alexander WS. Haematopoietic stem cells: past, present and future. *Cell Death Discov.* 2017 Feb 6;3:17002. doi:10.1038/cddiscovery.2017.2. PMID: 28180000; PMCID: PMC52927

3. Seita J, Weissman IL. Hematopoietic stem cell: self-renewal versus differentiation. *Wiley Interdiscip Rev Syst Biol Med.* 2010 Nov–Dec;2(6):640–653. doi:10.1002/wsbm.86. PMID: 20890962; PMCID: PMC2950323.

4. Yoder MC. Blood cell progenitors: insights into the properties of stem cells. *Anat Rec A Discov Mol Cell Evol Biol.* 2004 Jan;276(1):66–74. doi:10.1002/ar.a.10133. PMID: 14699635.

5. Taylor J, Xiao W, Abdel-Wahab O. Diagnosis and classification of hematologic malignancies on the basis of genetics. *Blood.* 2017 Jul 27;130(4):410–423. doi:10.1182/blood-2017-02-734541. Epub 2017 Jun 9. PMID: 28600336; PMCID: PMC5533199.

6. Chennamadhavuni A, Iyengar V, Mukkamalla SKR, et al. Leukemia [Updated 2023 Jan 17]. In:StatPearls[Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560490/

7. Chennamadhavuni A, Iyengar V, Mukkamalla SKR, et al. Leukemia [Updated 2023 Jan 17]. In:*StatPearls*[Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560490/

8. Plackoska V, Shaban D, Nijnik A. Hematologic dysfunction in cancer: mechanisms, effects on antitumor immunity, and roles in disease progression.*Front Immunol.*2022 Dec 6;13:1041010. doi:10.3389/fimmu.2022.1041010. PMID: 36561751; PMCID: PMC9763314.

9. Khaddour K, Hana CK, Mewawalla P. Hematopoietic stem cell transplantation. In:*StatPearls*[Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. 2023 May 6 [updated 2025 Jan–]. PMID: 30725636.

10. Passweg JR, Baldomero H, Ciceri F, de la Cámara R, Glass B, Greco R, Hazenberg MD, Kalwak K, McLornan DP, Neven B, Perić Z, Risitano AM, Ruggeri A, Snowden JA, Sureda A. Hematopoietic cell transplantation and cellular therapies in Europe 2022: CAR-T activity and trends.*Bone Marrow Transplant.*2022;57:1256–1272.

11. Niederwieser D, Baldomero H, Bazuaye N, Bupp C, Chaudhri N, Corbacioglu S, Elhaddad A, Frutos C, Galeano S, Hamad N, Hamidieh AA, Hashmi S, Ho A, Horowitz MM, Iida M, Jaimovich G, Karduss A, Kodera Y, Kröger N, Péffault de Latour R, Lee JW, Martínez-Rolón J, Pasquini MC, Passweg J, Paulson K, Seber A, Snowden JA, Srivastava A, Szer J, Weisdorf D, Worel N, Koh MBC, Aljurf M,

Greinix H, Atsuta Y, Saber W. One and a half million hematopoietic stem cell transplants: continuous and differential improvement in worldwide access with the use of non-identical family donors. *Haematologica*. 2022 May 1;107(5):1045-1053. doi: 10.3324/haematol.2021.279189. PMID: 34382386; PMCID: PMC9052915.

12. Passweg JR, Baldomero H, Ciceri F, Corbacioglu S, de la Cámara R, Dolstra H, Glass B, Greco R, McLornan DP, Neven B, de Latour RP, Perić Z, Ruggeri A, Snowden JA, Sureda A. . Hematopoietic cell transplantation and cellular therapies in Europe 2021. The second year of the SARS-CoV-2 pandemic. A Report from the EBMT Activity Survey. *Bone Marrow Transplant* **58**, 647–658 (2023). https://doi.org/10.1038/s41409-023-01943-3

13. D'Souza A, Fretham C, Lee SJ, Arora M, Brunner J, Chhabra S, Devine S, Eapen M, Hamadani M, Hari P, Pasquini MC, Perez W, Phelan RA, Riches ML, Rizzo JD, Saber W, Shaw BE, Spellman SR, Steinert P, Weisdorf DJ, Horowitz MM. Current Use of and Trends in Hematopoietic Cell Transplantation in the United States. Biol Blood Marrow Transplant. 2020 Aug;26(8):e177-e182. doi: 10.1016/j.bbmt.2020.04.013. Epub 2020 May 11. Erratum in: Transplant Cell Ther. 2022 Oct;28(10):715-716. doi: 10.1016/j.jtct.2021.02.006. PMID: 32438042; PMCID: PMC7404814.

14. Gorin NC. Autologous stem cell transplantation in hematological malignancies. Springer Semin Immunopathol. 2004 Nov;26(1-2):3-30. doi: 10.1007/s00281-004-0172-4. Epub 2004 Oct 7. PMID: 15480668.

15. Bal S, Costa LJ, Sauter C, Litovich C, Hamadani M. Outcomes of Autologous Hematopoietic Cell Transplantation in Diffuse Large B Cell Lymphoma Refractory to Firstline Chemoimmunotherapy. Transplant Cell Ther. 2021 Jan;27(1):55.e1-

55.e7. doi: 10.1016/j.bbmt.2020.09.004. Epub 2020 Sep 17. PMID: 32949754; PMCID: PMC7965782.

16. Champlin R. Selection of Autologous or Allogeneic Transplantation. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003. Available from: https://www.ncbi.nlm.nih.gov/books/NBK12844/

17. Simnett SJ, Stewart LA, Sweetenham J, et al. Autologous stem cell transplantation for malignancy: a systematic review of the literature. 2000. In: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. York (UK): Centre for Reviews and Dissemination (UK); 1995-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK68426/

18. Carreras E, Dufour C, Mohty M, Kröger N, editors. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies [Internet]. 7th ed. Cham (CH): Springer; 2019. PMID: 32091673.

19. Mohamed Ahmed AB, Elagab EA, Abdalla Ahmed EA, Hassan Mahgoub NE, Dawod Faky FS, Shamina NA, Subahi N. Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation in Adult Acute Myeloid Leukemia: A Systematic Review. Cureus. 2025 Sep 17;17(9):e92549. doi: 10.7759/cureus.92549. PMID: 41111822; PMCID: PMC12533790.

20. Inoue Y, Cioccio J, Mineishi S, Minagawa K. Evolution of Allogeneic Stem Cell Transplantation: Main Focus on AML. Cells. 2025 Apr 10;14(8):572. doi: 10.3390/cells14080572. PMID: 40277898; PMCID: PMC12026247.

21. Snowden JA, Sánchez-Ortega I, Corbacioglu S, Basak GW, Chabannon C, de la Camara R, Dolstra H, Duarte RF, Glass B, Greco R, Lankester AC, Mohty M, Neven B, de Latour RP, Pedrazzoli P, Peric Z, Yakoub-Agha I, Sureda A, Kröger N; European Society for Blood and Marrow Transplantation (EBMT). Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. Bone Marrow Transplant. 2022 Aug;57(8):1217-1239. doi: 10.1038/s41409-022-01691-w. Epub 2022 May 19. PMID: 35589997; PMCID: PMC9119216.

22. Pabst T, Bacher U. Risk stratification systems for allogeneic haematopoietic stem-cell transplantation. *Lancet Haematol.* 2021 Mar;8(3):e166-e167. doi:10.1016/S2352-3026(20)30403-8.

23. Jimenez AMJ, Spellman SR, Politikos I, McCurdy SR, Devine SM, Al Malki MM, Bolon Y-T, Lee SJ, Dehn J, Pidala J, Maiers M, Askar M, Malmberg C, Auletta JJ, Stefanski H, Broglie L, Qayed M, Horwitz M, Wilder JS, Gooptu M, Mehta RS, Fernandez-Viña M, Shaw BE, Shaffer BC. Allogeneic hematopoietic cell donor selection: contemporary guidelines from the NMDP/CIBMTR. *Transplant Cell Ther.* 2025 Jul 5:S2666-6367(25)01290-4. doi:10.1016/j.jtct.2025.07.004

24. Anasetti C, Logan BR, Lee SJ, Waller EK, Weisdorf DJ, Wingard JR, Cutler CS, Westervelt P, Woolfrey A, Couban S, Ehninger G, Johnston L, Maziarz RT, Pulsipher MA, Porter DL, Mineishi S, McCarty JM, Khan SP, Anderlini P, Bensinger WI, Leitman SF, Rowley SD, Bredeson C, Carter SL, Horowitz MM, Confer DL; Blood and Marrow Transplant Clinical Trials Network. Peripheral-blood stem cells versus bone marrow from unrelated donors. N Engl J Med. 2012 Oct 18;367(16):1487-96. doi: 10.1056/NEJMoa1203517. PMID: 23075175; PMCID: PMC3816375.

25. Nangia U, Majhail NS, Simhadri PK, Chandramohan D, and Baratam P, Overall survival in hematopoietic stem cell transplant patients with hematologic malignancies: accounting for the unobserved risk factors. *J Clin Oncol.* 2025;43(16_suppl):e18553. doi:10.1200/JCO.2025.43.16_suppl.e18553.

26. Tatari, M., Kasaeian, A., Mousavian, AH. *et al.* Prognostic factors for survival after allogeneic transplantation in acute myeloid leukemia in Iran using censored quantile regression model. *Sci Rep* **15**, 9055 (2025). https://doi.org/10.1038/s41598-025-92107-4

27. Antier C, Jullien M, Tessoulin B, Loirat M, Peterlin P, Garnier A, Le Bourgeois A, Chevallier P, Guillaume T. Late Relapse after Allogeneic Stem Cell Transplantation in Patients Treated for Acute Myeloid Leukemia: Relapse Incidence, Characteristics, Role of Conditioning Regimen, and Outcome. Cancers (Basel). 2024 Apr 5;16(7):1419. doi: 10.3390/cancers16071419. PMID: 38611097; PMCID: PMC11011193.

28. Larue M, Labopin M, Schroeder T, Pavletic S, Badoglio M, de la Camara R, et al. Long-term outcome of 2-year survivors after allogeneic hematopoietic cell transplantation for acute leukemia. *HemaSphere.* 2024;8(10):e70026. doi:10.1002/hem3.70026

29. Passweg JR, Baldomero H, Bader P, Bonini C, Duarte RF, Dufour C, Gennery A, Kröger N, Kuball J, Lanza F, Montoto S, Nagler A, Snowden JA, Styczynski J, Mohty M. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. Bone Marrow Transplant. 2017 Jun;52(6):811-817. doi: 10.1038/bmt.2017.34. Epub 2017 Mar 13. PMID: 28287639; PMCID: PMC5467246.

30. Martin PJ, Weisdorf D, Storer B. Graft-versus-tumor effect. In: Waller E, editor. *Reference Module in Biomedical Sciences*. Amsterdam: Elsevier; 2005. Available from:https://www.sciencedirect.com/science/chapter/referencework/abs/pii/B0122275551000940

31. Ringdén O, Karlsson H, Olsson R, Omazic B, Uhlin M. The allogeneic graft-versus-cancer effect. Br J Haematol. 2009 Dec;147(5):614-33. doi: 10.1111/j.1365-2141.2009.07886.x. Epub 2009 Sep 4. PMID: 19735262.

32. Storb R, Gyurkocza B, Storer BE, Sorror ML, Blume K, Niederwieser D, Chauncey TR, Pulsipher MA, Petersen FB, Sahebi F, Agura ED, Hari P, Bruno B, McSweeney PA, Maris MB, Maziarz RT, Langston AA, Bethge W, Vindeløv L, Franke GN, Laport GG, Yeager AM, Hübel K, Deeg HJ, Georges GE, Flowers ME, Martin PJ, Mielcarek M, Woolfrey AE, Maloney DG, Sandmaier BM. Graft-versus-host disease and graft-versus-tumor effects after allogeneic hematopoietic cell transplantation. J Clin Oncol. 2013 Apr 20;31(12):1530-8. doi: 10.1200/JCO.2012.45.0247. Epub 2013 Mar 11. PMID: 23478054; PMCID: PMC3625710.

33. Atilla E, Ataca Atilla P, Demirer T. A Review of Myeloablative vs Reduced Intensity/Non-Myeloablative Regimens in Allogeneic Hematopoietic Stem Cell Transplantations. Balkan Med J. 2017 Jan;34(1):1-9. doi: 10.4274/balkanmedj.2017.0055. Epub 2017 Jan 5. PMID: 28251017; PMCID: PMC5322516.

34. Connor MP, Loren AW, Hexner EO, Martin ME, Gill SI, Luger SM, Mangan JK, Perl AE, McCurdy SR, Pratz KW, Timlin C, Freyer CW, Carulli A, Catania C, Smith J, Hollander L, Zebrowski AM, Stadtmauer EA, Porter DL, Frey NV. Clofarabine

and Busulfan Myeloablative Conditioning in Allogeneic Hematopoietic Cell Transplantation for Patients With Active Myeloid Malignancies. Transplant Cell Ther. 2023 Feb;29(2):113-118. doi: 10.1016/j.jtct.2022.10.027. Epub 2022 Nov 4. PMID: 36336258.

35. Maahs L, Avila AM, Koshy M, Sweiss K, Ahn KH, Chen Z, Uzoka C, Galvez C, Sanchez M, Rubinstein P, Quigley J, Zucchetti E, Mahmud N, Aydogan B, Patel P, Rondelli D. Intensified conditioning with high-dose total marrow irradiation and myeloablative chemotherapy reduces risk of relapse without increasing toxicity in allogeneic hematopoietic stem cell transplant for high-risk myeloid malignancies: a phase II study. Haematologica. 2025 Jun 19. doi: 10.3324/haematol.2025.287457. Epub ahead of print. PMID: 40534485.

36. Arita K, Kondo T, Sugita J, Shigematsu A, Shiratori S, Wakasa K, Yasumoto A, Ibata M, Shono Y, Kikuchi M, Goto H, Takeda Y, Takahata M, Kato N, Nishio M, Ota S, Tanaka J, Imamura M. Sequential chemotherapy and myeloablative allogeneic hematopoietic stem cell transplantation for refractory acute lymphoblastic leukemia. Int J Hematol. 2011 Sep;94(3):291-295. doi: 10.1007/s12185-011-0919-3. Epub 2011 Aug 31. PMID: 21879292.

37. Scott BL, Pasquini MC, Fei M, Fraser R, Wu J, Devine SM, Porter DL, Maziarz RT, Warlick E, Fernandez HF, Soiffer RJ, Alyea E, Hamadani M, Bashey A, Giralt S, Geller NL, Leifer E, Hourigan CS, Gui G, Mendizabal A, Horowitz MM, Deeg HJ, Horwitz ME. Myeloablative versus Reduced-Intensity Conditioning for Hematopoietic Cell Transplantation in Acute Myelogenous Leukemia and Myelodysplastic Syndromes-Long-Term Follow-Up of the BMT CTN 0901 Clinical Trial. Transplant Cell Ther. 2021 Jun;27(6):483.e1-483.e6. doi:

10.1016/j.jtct.2021.02.031. Epub 2021 Feb 26. PMID: 33775615; PMCID: PMC8217373.

38. Scott BL, Pasquini MC, Logan BR, Wu J, Devine SM, Porter DL, Maziarz RT, Warlick ED, Fernandez HF, Alyea EP, Hamadani M, Bashey A, Giralt S, Geller NL, Leifer E, Le-Rademacher J, Mendizabal AM, Horowitz MM, Deeg HJ, Horwitz ME. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. J Clin Oncol. 2017;35(11):1154-1161. doi:10.1200/JCO.2016.70.7091.

39. Russell NH, Hills RK, Thomas A, Thomas I, Kjeldsen L, Dennis M, Craddock C, Freeman S, Clark RE, Burnett AK. Outcomes of older patients aged 60 to 70 years undergoing reduced intensity transplant for acute myeloblastic leukemia: results of the NCRI acute myeloid leukemia 16 trial. Haematologica. 2022 Jul 1;107(7):1518-1527. doi: 10.3324/haematol.2021.279010. PMID: 34647442; PMCID: PMC9244837.

40. Niederwieser C, Iacobelli S, Franke GN, Koster L, van Os M, Platzbecker U, Hübel K, Scheid C, Müller LP, Stelljes M, Morozova E, Passweg J, Onida F, Dreger P, Saccardi R, Ladetto M, Salmenniemi U, Bethge W, Poiré X, Kobbe G, McLornan DP, Robin M, Kröger N. Reduced intensity versus myeloablative conditioning for MDS: long-term results of an EBMT phase III study (RICMAC). Bone Marrow Transplant. 2024 Aug;59(8):1084-1091. doi: 10.1038/s41409-024-02282-7. Epub 2024 Apr 25. PMID: 38664589; PMCID: PMC11296945.

41. Savani BN, Griffith ML, Jagasia S, Lee SJ. How I treat late effects in adults after allogeneic stem cell transplantation. Blood. 2011 Mar 17;117(11):3002-9. doi:

10.1182/blood-2010-10-263095. Epub 2010 Dec 30. PMID: 21193694; PMCID: PMC3062306.

42. Arnaout K, Patel N, Jain M, El-Amm J, Amro F, Tabbara IA. Complications of allogeneic hematopoietic stem cell transplantation. Cancer Invest. 2014 Aug;32(7):349-62. doi: 10.3109/07357907.2014.919301. Epub 2014 Jun 5. PMID: 24902046.

43. Sureda A, Corbacioglu S, Greco R, Kröger N, Carreras E, editors. *The EBMT Handbook: Hematopoietic Cell Transplantation and Cellular Therapies* [Internet]. 8th ed. Cham (CH): Springer; 2024. doi:10.1007/978-3-031-44080-9. Available from: https://www.ncbi.nlm.nih.gov/books/NBK608238/

44. Gao A, Zhang L, Zhong D. Chemotherapy-induced thrombocytopenia: literature review. Discov Oncol. 2023 Jan 25;14(1):10. doi: 10.1007/s12672-023-00616-3. PMID: 36695938; PMCID: PMC9877263.

45. Kurtin S. Myeloid toxicity of cancer treatment. J Adv Pract Oncol. 2012 Jul;3(4):209-24. PMID: 25031949; PMCID: PMC4093344.

46. Blayney DW, Schwartzberg L. Chemotherapy-induced neutropenia and emerging agents for prevention and treatment: a review. *Cancer Treat Rev.* 2022;109:102427. doi:10.1016/j.ctrv.2022.102427.

47. Mohty B, Mohty M. Long-term complications and side effects after allogeneic hematopoietic stem cell transplantation: an update. Blood Cancer J. 2011 Apr;1(4):e16. doi: 10.1038/bcj.2011.14. Epub 2011 Apr 29. PMID: 22829137; PMCID: PMC3255242.

48. Mohty, B., Mohty, M. Long-term complications and side effects after allogeneic hematopoietic stem cell transplantation: an update. *Blood Cancer Journal* **1**, e16 (2011). https://doi.org/10.1038/bcj.2011.14

49. Epperla N, Russell NH, Bhatt N, Regan S, Aljurf M, Kröger N, Miklos DB, Murthy H, Peric Z, Warsch J, Grigg A, Shah BN, Oran B, Baird JS; ASTCT/CIBMTR/EBMT POLICY GROUP. Clinical practice recommendations for transplantation and cellular therapies in diffuse large B-cell lymphoma. *Transpl Cell Ther.* 2023;9(5):S2666-6367(23)01361-1. doi:10.1016/S2666-6367(23)01361-1.

50. Kurosawa S, Yamaguchi T, Mori T, Kanamori H, Onishi Y, Emi N, Fujisawa S, Kohno A, Nakaseko C, Saito B, Kondo T, Hino M, Nawa Y, Kato S, Hashimoto A, Fukuda T. Patient-reported quality of life after allogeneic hematopoietic cell transplantation or chemotherapy for acute leukemia. Bone Marrow Transplant. 2015 Sep;50(9):1241-9. doi: 10.1038/bmt.2015.137. Epub 2015 Jun 15. PMID: 26076127.

51. Justiz Vaillant AA, Modi P, Mohammadi O. Graft-Versus-Host Disease. [Updated 2024 Jun 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538235/

52. Höller E, Greinix H, Zeiser R. Acute graft-versus-host disease. In: Sureda A, Corbacioglu S, Greco R, et al., editors. *The EBMT Handbook: Hematopoietic Cell Transplantation and Cellular Therapies* [Internet]. 8th ed. Cham (CH): Springer; 2024 Apr 11. Chapter 43. doi:10.1007/978-3-031-44080-9_43. Available from: https://www.ncbi.nlm.nih.gov/books/NBK608233/

53. Di Francesco A, Raiola AM, Dominietto A, Di Grazia C, Gualandi F, Van Lint MT, Bregante S, Chiusolo P, Laurenti L, Sora F, Giammarco S, Metafuni E, Fresa A, Sica S, Angelucci E, Bacigalupo A. Acute graft versus host disease 1976-2020: reduced incidence and predictive factors. Front Med (Lausanne). 2024 Jan 24;10:1320692. doi: 10.3389/fmed.2023.1320692. PMID: 38327272; PMCID: PMC10847269.

54. Lee CJ, Wang T, Chen K, Arora M, Brazauskas R, Spellman SR, Kitko C, MacMillan ML, Pidala JA, Badawy SM, Bhatt N, Bhatt VR, DeFilipp Z, Diaz MA, Farhadfar N, Gadalla S, Hashmi S, Hematti P, Hossain NM, Inamoto Y, Lekakis LJ, Sharma A, Solomon S, Lee SJ, Couriel DR. Severity of Chronic Graft-versus-Host Disease and Late Effects Following Allogeneic Hematopoietic Cell Transplantation for Adults with Hematologic Malignancy. Transplant Cell Ther. 2024 Jan;30(1):97.e1-97.e14. doi: 10.1016/j.jtct.2023.10.010. Epub 2023 Oct 14. PMID: 37844687; PMCID: PMC10842798.

55. MacDonald KP, Hill GR, Blazar BR. Chronic graft-versus-host disease: biological insights from preclinical and clinical studies. Blood. 2017 Jan 5;129(1):13-21. doi: 10.1182/blood-2016-06-686618. Epub 2016 Nov 7. PMID: 27821504; PMCID: PMC5216261.

56. Ratanatharathorn V, Ayash L, Lazarus HM, Fu J, Uberti JP. Chronic graft-versus-host disease: clinical manifestation and therapy. Bone Marrow Transplant. 2001 Jul;28(2):121-9. doi: 10.1038/sj.bmt.1703111. PMID: 11509929.

57. Gruber I, Koelbl O, Herr W, Holler E, Edinger M, Wolff D. Impact of chronic graft-versus-host disease on quality of life and cognitive function of long-term transplant survivors after allogeneic hematopoietic stem cell transplantation with total body

irradiation. Radiat Oncol. 2022 Nov 29;17(1):195. doi: 10.1186/s13014-022-02161-9. PMID: 36447269; PMCID: PMC9706937.

58. Wade DT. What is rehabilitation? An empirical investigation leading to an evidence-based description. Clin Rehabil. 2020 May;34(5):571-583. doi: 10.1177/0269215520905112. Epub 2020 Feb 10. PMID: 32037876; PMCID: PMC7350200.

59. Negrini S, Borg K, Cusick A, Ferriero G, Frontera WR, Gross DP, Heinemann A, Machalicek W, Moore AP, Nudo RJ, Pérennou D, Stam H, Kiekens C. Global statements to produce and implement evidence in the post-COVID-era provide a path forward for rehabilitation - A joint initiative of Cochrane Rehabilitation and the leading journals in the field. J Rehabil Med. 2022 Nov 1;54:jrm00345. doi: 10.2340/jrm.v54.4858. PMID: 36317496; PMCID: PMC9639464.

60. Battel I, Arienti C, Levack W, Kiekens C, Negrini S. The new rehabilitation definition for research purposes could improve rehabilitation description in Cochrane Systematic Reviews. Cochrane Evid Synth Methods. 2024 Sep 12;2(9):e70000. doi: 10.1002/cesm.70000. PMID: 40474874; PMCID: PMC11795883.

61. Fu JB, Morishita S. Inpatient Rehabilitation of Hematopoietic Stem Cell Transplant Patients: Managing Challenging Impairments and Medical Fragility. Am J Phys Med Rehabil. 2024 Mar 1;103(3S Suppl 1):S46-S51. doi: 10.1097/PHM.0000000000002408. PMID: 38364030; PMCID: PMC10878715.

62. Steinberg A, Asher A, Bailey C, Fu JB. The role of physical rehabilitation in stem cell transplantation patients. Support Care Cancer. 2015 Aug;23(8):2447-60. doi:

10.1007/s00520-015-2744-3. Epub 2015 May 14. PMID: 25971213; PMCID: PMC4703401.

63. Noyan S, Gündogdu F, Bozdağ SC. The level of fatigue, insomnia, depression, anxiety, stress, and the relationship between these symptoms following allogeneic hematopoietic stem cell transplantation: a cross-sectional study. Support Care Cancer. 2023 Mar 29;31(4):244. doi: 10.1007/s00520-023-07703-9. PMID: 36977784.

64. Hautmann AH, Elad S, Lawitschka A, Greinix H, Bertz H, Halter J, Faraci M, Hofbauer LC, Lee S, Wolff D, Holler E. Metabolic bone diseases in patients after allogeneic hematopoietic stem cell transplantation: report from the Consensus Conference on Clinical Practice in chronic graft-versus-host disease. Transpl Int. 2011 Sep;24(9):867-79. doi: 10.1111/j.1432-2277.2011.01264.x. Epub 2011 May 9. PMID: 21557780.

65. Harvanová Ľ, Petríková L, Bojtárová E, Žiaková B, Martišová M, Lábska V, Hrubiško M, Bátorová A, Mladosievičová B. Metabolic syndrome in long-term survivors after allogeneic hematopoietic stem cell transplantation. Klin Onkol. 2022 Spring;35(2):132-138. English. doi: 10.48095/ccko2022132. PMID: 35459338.

66. Filgueira L, Steinberg A, Mendonca R, Lim SH. Returning to employment following allogeneic hematopoietic stem cell transplant: A major problem among survivors. EJHaem. 2023 Oct 9;4(4):1132-1142. doi: 10.1002/jha2.788. PMID: 38024592; PMCID: PMC10660407.

67. Avenoso D, Davidson JA, Larvin H, Brewer HR, Rice CT, Ecsy K, Sil A, Skinner L, Hudson RDA. Healthcare Resource Utilization and Associated Costs in Patients

With Chronic Graft-Versus-Host Disease Post-Allogeneic Hematopoietic Stem Cell Transplantation in England. Transplant Cell Ther. 2024 Dec;30(12):1207.e1-1207.e11. doi: 10.1016/j.jtct.2024.10.002. Epub 2024 Oct 9. PMID: 39389467.

68. Jones LW, Devlin SM, Maloy MA, Wood WA, Tuohy S, Espiritu N, Aquino J, Kendig T, Michalski MG, Gyurkocza B, Schaffer WL, Ali B, Giralt S, Jakubowski AA. Prognostic Importance of Pretransplant Functional Capacity After Allogeneic Hematopoietic Cell Transplantation. Oncologist. 2015 Nov;20(11):1290-7. doi: 10.1634/theoncologist.2015-0200. Epub 2015 Oct 7. PMID: 26446235; PMCID: PMC4718429.

69. Inoue J, Ono R, Okamura A, Matsui T, Takekoshi H, Miwa M, Kurosaka M, Saura R, Shimada T. The impact of early rehabilitation on the duration of hospitalization in patients after allogeneic hematopoietic stem cell transplantation. Transplant Proc. 2010 Sep;42(7):2740-4. doi: 10.1016/j.transproceed.2010.05.153. PMID: 20832579.

70. Houston JL, Boyd KP, Gittings PM, Cavalheri V. What are safe hemoglobin, neutrophil and platelet counts for people with hematological malignancies to participate in exercise and activities of daily living: a scoping review. Support Care Cancer. 2025 Jun 21;33(7):605. doi: 10.1007/s00520-025-09612-5. PMID: 40542825; PMCID: PMC12182480.

71. Persoon S, Kersten MJ, van der Weiden K, Buffart LM, Nollet F, Brug J, Chinapaw MJ. Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: a systematic review and meta-analysis. Cancer Treat Rev. 2013 Oct;39(6):682-90. doi: 10.1016/j.ctrv.2013.01.001. Epub 2013 Feb 26. PMID: 23485478.

72. van Haren IE, Timmerman H, Potting CM, Blijlevens NM, Staal JB, Nijhuis-van der Sanden MW. Physical exercise for patients undergoing hematopoietic stem cell transplantation: systematic review and meta-analyses of randomized controlled trials. Phys Ther. 2013 Apr;93(4):514-28. doi: 10.2522/ptj.20120181. Epub 2012 Dec 6. PMID: 23224217.

73. Persoon S, Kersten MJ, van der Weiden K, Buffart LM, Nollet F, Brug J, Chinapaw MJ. Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: a systematic review and meta-analysis. Cancer Treat Rev. 2013 Oct;39(6):682-90. doi: 10.1016/j.ctrv.2013.01.001. Epub 2013 Feb 26. PMID: 23485478.

74. van Haren IE, Timmerman H, Potting CM, Blijlevens NM, Staal JB, Nijhuis-van der Sanden MW. Physical exercise for patients undergoing hematopoietic stem cell transplantation: systematic review and meta-analyses of randomized controlled trials. Phys Ther. 2013 Apr;93(4):514-28. doi: 10.2522/ptj.20120181 Add to Citavi project by DOI. Epub 2012 Dec 6. PMID: 23224217 Add to Citavi project by Pubmed ID.

75. Hirsch BR, Califf RM, Cheng SK, Tasneem A, Horton J, Chiswell K, Schulman KA, Dilts DM, Abernethy AP. Characteristics of oncology clinical trials: insights from a systematic analysis of ClinicalTrials.gov. JAMA Intern Med. 2013 Jun 10;173(11):972-9. doi: 10.1001/jamainternmed.2013.627. Erratum in: JAMA Intern Med. 2013 Sep 9;173(16):1560. PMID: 23699837.

76. Deeks JJ, Higgins JPT, Altman DG, McKenzie JE, Veroniki AA (eds). *Chapter 10: Analysing data and undertaking meta-analyses*. In: Higgins JPT, Thomas J,

Chandler J, Cumpston M, Li T, Page MJ, Welch VA (eds). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.5 [Internet]. London: The Cochrane Collaboration; 2024. Available from: https://www.cochrane.org/authors/handbooks-and-manuals/handbook/current/chapter-10#section-10-10-1

77. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. Chapter 10: Analysing data and undertaking meta-analyses. In: *Cochrane Handbook for Systematic Reviews of Interventions* version 6.5 [Internet]. London: The Cochrane Collaboration; 2024. Available from: https://www.cochrane.org/authors/handbooks-and-manuals/handbook/current/chapter-10#section-10-10

78. Tugwell P, Tovey D, et al. Should we formalise the assessment of clinical heterogeneity/diversity in systematic reviews. J Clin Epidemiol. 2021;135:A4–A5. doi: 10.1016/j.jclinepi.2021.02.004.

79. Barbateskovic M, Koster TM, Eck RJ, Maagaard M, Afshari A, Blokzijl F, Cronhjort M, Dieperink W, Fabritius ML, Feinberg J, French C, Gareb B, Geisler A, Granholm A, Hiemstra B, Hu R, Imberger G, Jensen BT, Jonsson AB, Karam O, Kong Z, Korang SK, Koster G, Lai B, Liang N, Lundstrøm LH, Marker S, Meyhoff TS, Nielsen EE, Nørskov AK, Munch MW, Risom EC, Rygård SL, Safi S, Sethi N, Sjövall F, Lauridsen SV, van Bakelen N, Volbeda M, van der Horst ICC, Gluud C, Perner A, Møller MH, Keus E, Wetterslev J. A new tool to assess Clinical Diversity In Meta-analyses (CDIM) of interventions. J Clin Epidemiol. 2021 Jul;135:29-41. doi: 10.1016/j.jclinepi.2021.01.023. Epub 2021 Feb 6. PMID: 33561529.

80. Pitre T, Kirsh S, Jassal T, Anderson M, Padoan A, Xiang A, Mah J, Zeraatkar D. The impact of blinding on trial results: A systematic review and meta-analysis. Cochrane Evid Synth Methods. 2023 Jun 20;1(4):e12015. doi: 10.1002/cesm.12015. PMID: 40475370; PMCID: PMC11795910.

81. Choi GJ, Kang H. Heterogeneity in meta-analyses: an unavoidable challenge worth exploring. Korean J Anesthesiol. 2025 Aug;78(4):301-314. doi: 10.4097/kja.25001. Epub 2025 Feb 14. PMID: 39956636; PMCID: PMC12326561.

82. Yang K, Lin E, Xu W, Zhu L, Tong T. An Alternative Measure for Quantifying the Heterogeneity in Meta-Analysis. Stat Med. 2025 May;44(10-12):e70089. doi: 10.1002/sim.70089. PMID: 40405379; PMCID: PMC12099030.

83. Kirkham JJ, Williamson P. Core outcome sets in medical research. BMJ Med. 2022 Oct 17;1(1):e000284. doi: 10.1136/bmjmed-2022-000284. PMID: 36936568; PMCID: PMC9951367.

84. Lawlor A, MacLennan S, Bogaerts J, Litiere S, Golfinopoulos V, Lehmann J, Szturz P, Williamson P, Van Hemelrijck M. Core outcome sets in cancer clinical trials: current status and future opportunities-an EORTC perspective. Trials. 2025 Apr 9;26(1):129. doi: 10.1186/s13063-025-08812-y. PMID: 40205620; PMCID: PMC11983956.

85. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, Clarke M, Gargon E, Gorst S, Harman N, Kirkham JJ, McNair A, Prinsen CAC, Schmitt J, Terwee CB, Young B. The COMET Handbook: version 1.0. Trials. 2017 Jun 20;18(Suppl 3):280. doi: 10.1186/s13063-017-1978-4. PMID: 28681707; PMCID: PMC5499094.

86. Ciani O, Salcher-Konrad M, Meregaglia M, Smith K, Gorst SL, Dodd S, Williamson PR, Fattore G. Patient-reported outcome measures in core outcome sets targeted overlapping domains but through different instruments. J Clin Epidemiol. 2021 Aug;136:26-36. doi: 10.1016/j.jclinepi.2021.03.003. Epub 2021 Mar 6. PMID: 33689837.

87. Kirkham JJ, Davis K, Altman DG, Blazeby JM, Clarke M, Tunis S, Williamson PR. Core Outcome Set-STAndards for Development: The COS-STAD recommendations. PLoS Med. 2017 Nov 16;14(11):e1002447. doi: 10.1371/journal.pmed.1002447. PMID: 29145404; PMCID: PMC5689835.

88. Dodd S, Gorst SL, Young A, Lucas SW, Williamson PR. Patient participation impacts outcome domain selection in core outcome sets for research: an updated systematic review. J Clin Epidemiol. 2023 Jun;158:127-133. doi: 10.1016/j.jclinepi.2023.03.022. Epub 2023 Apr 11. PMID: 37054902

CHAPTER 2: Scoping Review

This chapter corresponds to the following peer-reviewed publication:

A Scoping Review on Outcomes and Outcome Measurement Instruments in Rehabilitative Interventions for Patients with Hematological Malignancies Treated with Allogeneic Stem Cell Transplantation

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Author Contributions

A.I.M.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, writing—original draft; P.T.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, writing—original draft; D.K.: data curation, formal analysis, investigation, validation; L.B.M.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, writing—original draft. All authors have read and agreed to the published version of the manuscript.

Abstract

Rationale: Allogeneic hematopoietic stem cell transplantation (HSCT) is associated with increased treatment-related mortality, loss of physical vitality, and impaired quality of life. Future research will investigate the effects of multidisciplinary rehabilitative interventions in alleviating these problems. Nevertheless, published studies in this field show considerable heterogeneity in selected outcomes and the outcome measurement instruments used. The purpose of this scoping review is to provide an overview of the outcomes and outcome measurement instruments used in studies examining the effects of rehabilitative interventions for patients treated with allogeneic HSCT. Methods: We conducted a scoping review that included randomized controlled trials, pilot studies, and feasibility studies published up to 28 February 2022. Results: We included *n* = 39 studies, in which *n* = 84 different outcomes were used 227 times and *n* = 125 different instruments were used for the measurements. Conclusions: Research in the field of rehabilitation for patients with hematological malignancies treated with allogeneic HSCT is hampered by the excess outcomes used, the inconsistent outcome terminology, and the inconsistent use of measurement instruments in terms of setting and timing. Researchers in this field should reach a consensus with regard to the use of a common terminology for the outcomes of interest and a homogeneity when selecting measurement instruments and measurement timing methods.

Keywords: allogeneic stem cell transplantation, outcomes, outcome measurement instruments, rehabilitation, hematological malignancies

2.1 Introduction

2.1.1 Rationale

Allogeneic hematopoietic stem cell transplantation (HSCT) improves the survival rate of patients with hematological malignancies and offers the best chance for cure in a wide range of patients [1,2]. Graft versus Host disease (GvHD) is the most recognized post-allogeneic

HSCT complication [3]. Immunosuppressive therapy (IST) is used to treat or prevent both GvHD and further organ damage once GvHD occurs. GvHD and IST are the two factors most commonly associated with impaired quality of life in these patients [4], distinguishing these patients from those undergoing autologous HSCT. In addition to impaired quality of life, patients treated with allogeneic HSCT for hematological malignancies may have increased treatment-related mortality and loss of physical vitality [5].

Rehabilitation is a complex problem-solving process that is delivered by multidisciplinary teams in inpatient or outpatient settings that aims to improve the patient's quality of life and degree of social integration [6]. Rehabilitative interventions for patients undergoing allogeneic HSCT can improve physical vitality and quality of life as well as decrease mortality [7]. Moreover, early rehabilitation reduces the duration of hospitalization for allogeneic HSCT [8].

Rehabilitative interventions for allogeneic HSCT patients can be challenging with regard to the feasibility of their many phases of treatment. Prior to transplantation, problems related to blood count may not allow the patient to participate in certain rehabilitative interventions. During hospitalization, symptom burden, infections, blood count limitations, or severe fatigue may further prevent the use rehabilitative interventions. Post-hospitalization, GvHD symptoms, blood count fluctuations, or even psychosocial factors may affect the feasibility of rehabilitative interventions. Researchers have long been aware of the importance of the feasibility of rehabilitative interventions among allogeneic HSCT patients [9] and they argue that feasibility and safety should be assessed prior to the development of rehabilitative programs [10].

Future research in this field will investigate the effects of multidisciplinary rehabilitative interventions in a variety of settings. Research in this field has already shown considerable heterogeneity in selected outcomes and in the outcome measurement instruments used [11,12]. Synthesizing, comparing, and interpreting the results from different studies can be challenging when they refer to different outcomes and are measured by different instruments.

2.1.2 Objectives

The purpose of this scoping review is to provide an overview of the outcomes and outcome measurement instruments used in studies examining the effects of rehabilitative interventions for patients treated with allogeneic HSCT, thus enabling a better understanding of the sources of heterogeneity.

2.2 Methods

This scoping review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews statement PRISMA ScR (www.prisma-statement.org, (accessed on 28 February 2022)).

2.2.1 Data Sources and Study Selection

The search strategy was developed in collaboration with a librarian to retrieve articles of interest from the MEDLINE, EMBASE, and Cochrane databases in February 2022. Searches were performed with the following terms: (1. xp Hematopoietic Stem Cell Transplantation/ or (transplant* adj5 (“stem cell*” or “hematopoietic cell*” or “haematopoietic cell*”)).ti,ab. 2. exp Rehabilitation/ or exp Physical Therapy Modalities/ or exp Exercise/ or exp Exercise Therapy/ or (rehabilitation* or rehabilitative or exercise* or physiotherap* or readaption* or readaptation* or readjustment* or kinesiotherap* or kinesitherap* or training* or (physical adj3 (therap* or treatment*))).ti,ab. 3. (1 and 2) 4. 3 not (animals not humans).sh.). To be included, publications had to be randomized controlled trials, pilot studies, or feasibility studies; published in English or in German; and had to investigate the effects of a rehabilitative intervention shortly before, during, or after allogeneic stem cell transplantation in adult patients with hematological malignancies. After removing duplicates, the titles and abstracts were screened by two reviewers (AM and DK) against the agreed upon inclusion and exclusion criteria. Studies with no obvious relevance to the research questions were removed. Final inclusion was performed

after retrieving and screening the full texts, while disagreements between reviewers were resolved by consensus.

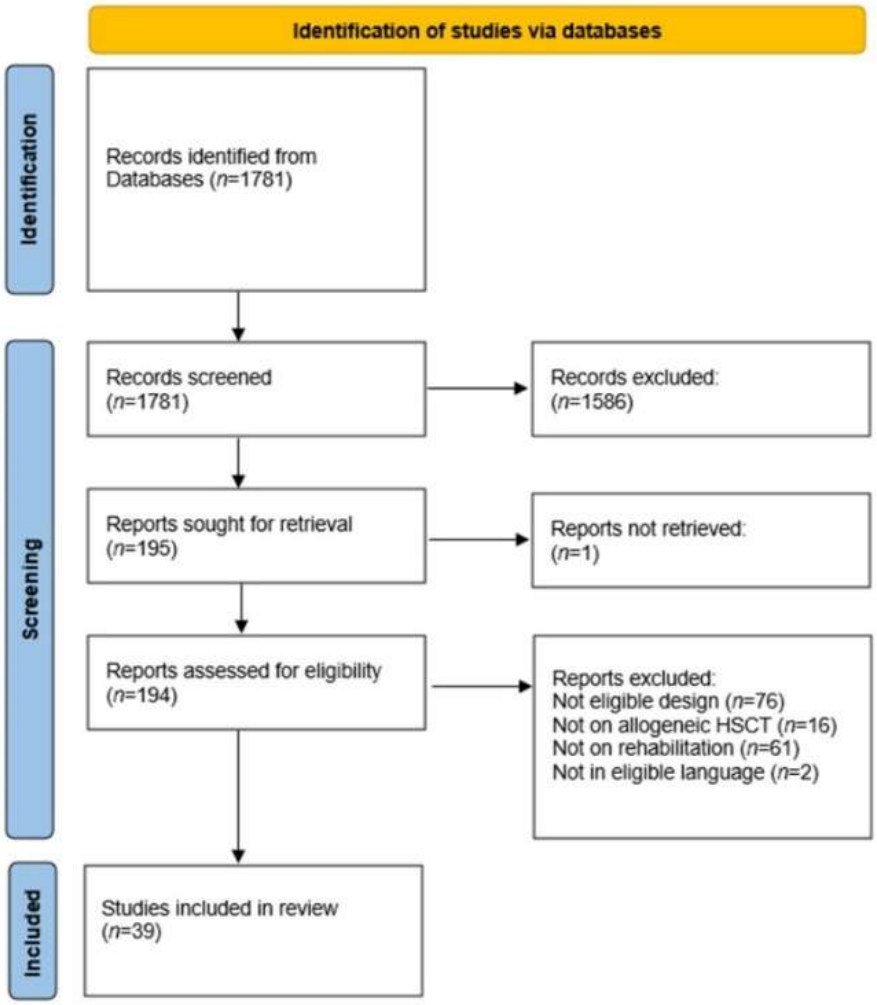
2.2.2 Data Extraction, Data Synthesis and Analysis

The following data were extracted from each article by the lead author: population, intervention, setting, year of publication, country where the research was conducted, outcomes used, outcome measurement instruments used, and timing of measurements. The outcomes and outcome instruments were extracted and classified based on the exact way the authors used them, regardless of the conformity of their terminology with the literature. For example, “aerobic capacity”, “peak aerobic capacity”, and “functional aerobic capacity” were considered and classified as three different outcomes. The extracted outcomes were not classified as primary or secondary, as this information could not be consistently retrieved from the studies. Furthermore, we classified them according to their measurement core area (Life Impact or Pathophysiological Manifestation) based on the conceptual framework of Boers et al. [13]. According to this framework, outcomes, including the symptoms, signs, events, and biomarkers, that describe how health conditions manifest themselves by abnormal physiology are classified as “Pathophysiological Manifestation” outcomes. Outcomes describing how patients feel, function, or survive are classified as “Life Impact” outcomes. Boers et al. [13] label adverse events separately in their framework in recognition of the prominent role of feasibility in outcome measurements. In this scoping review, we used a third core area to classify all of the feasibility concepts separately. Based on the descriptions of El Kotob et al. [14] and Thabane et al. [15], outcomes describing the feasibility with regard to the safety, processes, resources, and management of a study were classified as “Feasibility” outcomes. Furthermore, the timing of outcome measurements was extracted to show the time-point of the measurements in relation to the day of transplantation and the number of measurements in hierarchical order. We classified the timing of the measurements according to hospital or non-hospital settings.

2.3. Results

Our search yielded a total of n = 1781 publications after duplicates were removed (**Figure 1**).

Figure 1. *Scoping Review study selection flowchart.*



Of these, we assessed n = 195 for eligibility based on the full text. A total of n = 39 studies of the following types met the inclusion criteria [16 - 54]: n = 24 randomized clinical trials, n = 9 pilot studies, and n = 6 feasibility studies (**Table 1**). In these 39 studies, n = 84 different outcomes were used 227 times and were measured using n = 125 different instruments **(Table 2)**.

Table 1. *Scoping Review study characteristics*

Study Characteristics	
Included Studies	*N* = 39(YY%)
Study Design	
RCTs	24 (62%)
Feasibility Studies	9 (23%)
Pilot Studies	6 (15%)
Population	
Allogeneic stem cell transplantation	14 (36%)
Allogeneic and autologous stem cell transplantation	25 (64%)
Setting	
Hospital	22 (56%)
Outpatient post HSCT	11 (28%)
Outpatient pre HSCT	3 (8%)
Throughout	2 (5%)
Inpatient post HSCT	1 (3%)
Intervention	
Psychological Interventions	5 (13%)
Exercise Training	17 (44%)
Respiratory Training	3 (8%)
Physical Modalities	2 (5%)
Relaxation Techniques	2 (5%)
Other	10 (25%)
Language	
English	39 (100%)
Country	
USA	13 (34%)
Germany	9 (23%)
Canada	4 (10%)
Brazil	4 (10%)
Switzerland	2 (5%)
Other	7 (18%)

Table 2. *Scoping Review outcomes and outcome measurement instruments.*

CORE AREA «FEASIBILITY»					
Allogeneic					
Outcomes	Instruments	Design	Phase	Intervention	Reference
Feasibility(16,17) *N* = 2	Adherence(16) Adverse Events(16) Program completion from 50% of the patients(17) Recruitment(16)	Feasibility Pilot Study(17)	Hospital(17)	Exercise(16,17)	Santa mina et al., 2020 Schuler et al., 2016
HSCT					
Outcomes	Instruments	Design	Phase	Intervention	Reference
Feasibility(18-25)(27) *N* = 7	Adherence (18-21)25,27	Feasibility(18-20) Pilot Study(21),(25)	Hospital(18-20) Outpatient post(21) Outpatient pre (25)	Electric Muscle Stimulation(18) Healing touch(19) Inspiratory muscle training(20) Home based aerobic exercise(6) Exercise Training and Nutritional Support(25)	Bewarder et al., 2019 Lu et al., 2016 De almeida et al., 2020 Wilson et al., 2005 Rupnik et al., 2020
	Attrition(20,21)25,27	Feasibility(20) Pilot Study(21),(25)	Hospital(20) Outpatient post(21) Outpatient pre (25)	Inspiratory muscle training(20) Home based aerobic exercise(21) Exercise Training and Nutritional Support(25)	De almeida et al., 2020 Wilson et al., 2005 Rupnik et al., 2020
	Retention(19, 22)	Feasibility(19, 22)	Hospital(19) Outpatient post(22)	Healing touch(19) Yoga(22)	Lu et al., 2016 Baydoun et al., 2020
	Acceptability(21), 25	Pilot Study(21),25	Outpatient post(21) Outpatient pre(25)	Home based aerobic exercise(21) Exercise Training and Nutritional Support(25)	Wilson et al., 2005 Rupnik et al., 2020
	Accrual Acceptance(22)	Feasibility(22)	Outpatient post(22)	Yoga(22)	Baydoun et al., 2020

	Adverse Events(22)	Feasibility(22)	Outpatient post(22)	Yoga(22)	Baydoun et al., 2020
	N/A(23)	RCT(23)	Hospital(23)	Exergaming (23)	Schumacher et al., 2018
	Protocol Adherence(22)	Feasibility(22)	Outpatient post(22)	Yoga(22)	Baydoun et al., 2020
	Rate of participant enrolment(24)	Pilot Study(24)	Outpatient post(24)	Positive Psychology Intervention(24)	Amonoo et al., 2020
	Rate of session completion(24)	Pilot Study(24)	Outpatient post(24)	Positive Psychology Intervention(24)	Amonoo et al., 2020
	Recruitment(19)27	Feasibility(19)	Hospital(19)	Healing touch(19)	Lu et al., 2016
	Recruitment Rate(20)	Feasibility(20)	Hospital(20)	Inspiratory muscle training(20)	De almeida et al., 2020
Safety(18,20,21)25 *N* = 4	Adverse Events(18,20,21) The WHO bleeding Scale(18)	Feasibility(18,20) Pilot Study(21)	Hospital(18,20) Outpatient post(21)	Electric Muscle Stimulation(18) Inspiratory muscle training(20) Home based aerobic exercise(21)	Bewarder et al., 2019 De almeida et al., 2020 Wilson et al., 2005
Acceptability(24) *N* = 1	Rating of ease and utility(24)	Pilot Study(24)	Outpatient post(24)	Positive Psychology Intervention(24)	Amonoo et al., 2020
Adherence(26) *N* = 1	Exercise Sessions completed as proportion of the prescribed exercises(26)	RCT(26)	Throughout(26)	Exercise Training(26)	Peters et al., 2018
Attrition(26) *N* = 1	N/A(26)	RCT(26)	Throughout(26)	Exercise Training(26)	Peters et al., 2018
Compliance(26) *N* = 1	Exercise Sessions completed(26)	RCT(26)	Throughout(26)	Exercise Training(26)	Peters et al., 2018
Progression after initial prescription(26) *N* = 1	Added sets, repetitions or exercises(26)	RCT(26)	Throughout(26)	Exercise Training(26)	Peters et al., 2018
Adverse Events(27)					Fioritto et al., 2021
CORE AREA LIFE IMPACT					
Allogeneic					
Outcomes	Instruments	Design	Phase	Intervention	Reference

Fatigue(16, 17, 28-33) *N* = 8	Brief Fatigue Inventory(28, 29)	Pilot Study(28) RCT(29)	Outpatient post(28, 29)	Individualized Exercise Program(28) Supervised exercise program(29)	Carlson et al., 2006 Shleton et al., 2008
	FACT-F(16, 28)	Feasibility(16) Pilot Study(28)	Hospital(16) Outpatient post(28)	Exercise(16) Individualized Exercise Program(28)	Santa mina et al., 2020 Carlson et al., 2006
	Multidimensional Fatigue Inventory(16, 30)	Feasibility(16) RCT(30)	Hospital(16, 30)	Exercise(16) Whole Body Vibration Training(30)	Santa mina et al., 2020 Pahl et al., 2020
	EORTC QLQ FA-13(17)	Pilot Study(17)	Hospital(17)	Exercise(17)	Schuler et al., 2016
	FACT-An Anemia Scale(31)	RCT(31)	Hospital(31)	Multimodal Intervention(31)	Jarden et al., 2009
	Fatigue Impact Scale (FIS)(32)	RCT(32)	Inpatient post(32)	Inspiratory muscle training(32)	Bargi et al., 2015
	Piper Fatigue Scale(33)	RCT(33)	Hospital(33)	Relaxation Breathing Exercise(33)	Kim et al., 2005
Depression(16, 17, 28, 32, 33) *N* = 5	Hospital Anxiety And Depression Scale(17)	Pilot Study(17)	Hospital(17)	Exercise(17)	Schuler et al., 2016
	Montgomery-Âsberg Depression Rating Scale (MADRS)(32)	RCT(32)	Inpatient post(32)	Inspiratory muscle training(32)	Bargi et al., 2015
	Structured Clinical Interview(28)	Pilot Study(28)	Outpatient post(28)	Individualized Exercise Program(28)	Carlson et al., 2006
	The Beck Depression Inventory(33)	RCT(33)	Hospital(33)	Relaxation Breathing Exercise(33)	Kim et al., 2005
	The Center for Epidemiological Studies Depression Scale (CES-D)(28)	Pilot Study(28)	Outpatient post(28)	Individualized Exercise Program(28)	Carlson et al., 2006

	The Patient Health Questionnaire 9 (PHQ-9)(16)	Feasibility(16)	Hospital(16)	Exercise(16)	Santa mina et al., 2020
Quality of Life(17, 30, 32, 34, 35) *N* = 5	EORTC QLQ-C30(17, 30, 32, 34)	Pilot Study(17) RCT(30, 32, 34)	Hospital(17, 30, 34) Inpatient post(32)	Exercise(17) Inspiratory muscle training(32) Exercise Training(34) Whole Body Vibration Training(30)	Schuler et al., 2016 Bargi et al., 2015 Baumann et al., 2011 Pahl et al., 2020
	FACT-BMT(35)	Feasibility(35)	Outpatient post(35)	Telehealth Psychoeducational support(35)	Lounsbery et al., 2010
Health related Quality of Life(16, 31, 36, 37) *N* = 4	EORTC QLQ-C30(16, 31, 36, 37)	Feasibility(16) RCT(31, 36, 37)	Hospital(16, 31, 36) Throughout(37)	Exercise(16) Multimodal Intervention(31) Whole Body Vibration Training(36) Self administered exercise(37)	Santa mina et al., 2020 Kaeding et al., 2018 Wiskemann et al., 2011
Anxiety(16, 33, 38) *N* = 3	Generalized Anxiety Disorder GAD7(16)	Feasibility(16)	Hospital(16)	Exercise(16)	Santa mina et al., 2020
	The State-Trait Anxiety Inventory(33)	RCT(33)	Hospital(33)	Relaxation Breathing Exercise(33)	Kim et al., 2005
	Visual Analog Scale(38)	RCT(38)	Hospital(38)	Music Therapy(38)	Doro et al., 2017
Mood(28, 38) *N* = 2	Profile of Mood States (POMS)(28)	Pilot Study(28)	Outpatient post(28)	Individualized Exercise Program(28)	Carlson et al., 2006
	Visual Analog Scale(38)	RCT(38)	Hospital(38)	Music Therapy(38)	Doro et al., 2017
Distress(37) *N* = 1	The National Comprehensive Cancer Network Distress Thermometer(37)	RCT(37)	Throughout(37)	Self administered exercise(37)	Wiskemann et al., 2011

Perception of Personal Benefits(35) *N* = 1	Post Traumatic growth inventory(35)	Feasibility(35)	Outpatient post(35)	Telehealth Psychoeducational support(35)	Lounsbery et al., 2010
Physical Activity(30) *N* = 1	Freiburg Questionnaire on physical activity(30)	RCT(30)	Hospital(30)	Whole Body Vibration Training(30)	Pahl et al., 2020
Physical Well Being(37) *N* = 1	Hospital Anxiety And Depression Scale(37)	RCT(37)	Throughout(37)	Self administered exercise(37)	Wiskemann et al., 2011
Psychological Well Being(31) *N* = 1	Hospital Anxiety And Depression Scale(31)	RCT(31)	Hospital(31)	Multimodal Intervention(31)	Jarden et al., 2009
Self efficacy for exercise(16) *N* = 1	Exercise Self Efficacy Scale(16)	Feasibility(16)	Hospital(16)	Exercise(16)	Santa mina et al., 2020
Spirituality and Meaning Making(35) *N* = 1	FACT-SP(35)	Feasibility(35)	Outpatient post(35)	Telehealth Psychoeducational support(35)	Lounsbery et al., 2010
Subjective Distress(35) *N* = 1	Impact of Event Scale Revised(35)	Feasibility(35)	Outpatient post(35)	Telehealth Psychoeducational support(35)	Lounsbery et al., 2010
HSCT					
Outcomes	Instruments	Design	Phase	Intervention	Reference
Fatigue(21,22, 39-43) *N* = 7	Brief Fatigue Inventory(39)	RCT(39)	Hospital(39)	Relaxation Techniques(39)	Jafari et al., 2018
	Chalder Fatigue Scale(40)	RCT(40)	Hospital(40)	Strength Training(40)	Hacker et al., 2017
	EORTC QLQ-C30(40)	RCT(40)	Hospital(40)	Strength Training(40)	Hacker et al., 2017
	FACT-An Anaemia Scale(41)	RCT(41)	Outpatient post(41)	Outpatient physical exercise(41)	Knols et al., 2011
	Fatigue Symptom Inventory(21)	Pilot Study(21)	Outpatient post(21)	Home based aerobic exercise(21)	Wilson et al., 2005
	Multidimensional Fatigue Inventory(22)	Feasibility(22)	Outpatient post(22)	Yoga(22)	Baydoun et al., 2020
	SF36(42)	RCT(42)	Outpatient post(42)	Exercise_Relaxation_Information(42)	Bird et al., 2010

	The Fatigue Questionnaire (FQ)(43)	Feasibility(43)	Outpatient post(43)	Mindfulness based Intervention(43)	Grossman et al., 2015
Depression(19, 23, 43-46) *N* = 6	Hospital Anxiety And Depression Scale(23, 44-46)	RCT(23, 44-46)	Hospital(23, 44-46)	Exergaming(23)	Schumacher et al., 2018
				Media Art(44)	Mc Cabe et al., 2013
				Palliative Care(45)	El Jawahri et al., 2017
				Problem Solving Training(46)	Balck et al., 2019
	The Centre for Epidemiological Studies Depression Scale (CES-D)(19, 43)	Feasibility(19, 43)	Hospital(19)	Healing touch(19)	Lu e al 2016
			Outpatient post(43)	Mindfulness based Intervention(43)	Grossman et al., 2015
Anxiety(23, 43-46) *N* = 5	Hospital Anxiety And Depression Scale(23, 44, 46)	RCT(23, 44-46)	Hospital(23, 44-46)	Exergaming(23)	Schumacher et al., 2018
				Media Art(44)	Mc Cabe et al., 2013
				Palliative Care(45)	El Jawahri et al., 2017
				Problem Solving Training(46)	Balck et al., 2019
	The Spielberger Trait Anxiety Scale (STAI)(43)	Feasibility(43)	Outpatient post(43)	Mindfulness based Intervention(43)	Grossman et al., 2015
Quality of Life (19, 34, 40, 42, 45) *N* = 5	EORTC QLQ-C30(34, 40)	RCT(34, 40)	Hospital(34, 40)	Exercise Therapy(34)	Baumann et al., 2010
				Strength Training(40)	Hacker et al., 2017
	FACT-BMT(19, 45)	Feasibility(19)	Hospital(19)	Healing touch(19)	Lu e al 2016
		RCT(45)	Hospital(45)	Palliative Care(45)	El Jawahri et al., 2017
	The Graham and Longman QoL Questionnaire(42)	RCT(42)	Outpatient post(42)	Exercise_Relaxation_Information(42)	Bird et al., 2010

Health related Quality of Life(21, 23,25,27 41, 43, 47) *N* = 7	EORTC QLQ-C30(41, 25,27)	RCT(41) Pilot (25) Feasibility (27)	Outpatient post(41) Outpatient pre (25)	Outpatient physical exercise(41) Exercise Training and Nutritional Support (25) Individualized Exercise Training (27)	Knols et al., 2011 Rupnik et al., 2020 Fioritto et al., 2021
	FACT(43)	Feasibility(43)	Outpatient post(43)	Mindfulness based Intervention(43)	Grossman et al., 2015
	FACT-BMT(23,47)	RCT(23,47)	Hospital(23,47)	Exergaming(23) Multidirectional Walking (47)	Schumacher et al., 2018 Potiaumpai et al., 2020
	Profile of Health Related Quality of Life in Chronic Disorders(43)	Feasibility(43)	Outpatient post (43)	Mindfulness based Intervention(43)	Grossman et al., 2015
	SF36(21, 23)	Pilot Study(21)	Outpatient post(21)	Home based aerobic exercise(21)	Wilson et al., 2005
		RCT(23)	Hospital(23)	Exergaming(23)	Schumacher et al., 2018
Physical Activity(40, 41) 3	Accelerometry(40)	RCT(40)	Hospital(40)	Strength Training(40)	Hacker et al., 2017
	International Physical Activity Questionnaire(41)	RCT(41)	Outpatient post(41)	Outpatient physical exercise(41)	Knols et al., 2011
	The Godin leisure time exercise questionnaire(40)	RCT(40)	Hospital(40)	Strength Training(40)	Hacker et al., 2017
Distress(19, 44) *N* = 2	Profile of Mood States (POMS)(19)	Feasibility(19)	Hospital(19)	Healing touch(19)	Lu e al 2016
	The Distress Thermometer(44)	RCT(44)	Hospital(44)	Media Art(44)	Mc Cabe et al., 2013

Post traumatic Stress Disorder Symptoms(45, 48) *N* = 2	Clinician administered PTSD Scale for DSM IV(48)	RCT(48)	Outpatient post(48)	Cognitive Behavioural Therapy(48)	DuHamel et al., 2010
	PCL-C(45, 48)	RCT(45, 48)	Hospital(45)	Palliative Care(45)	El Jawahri et al., 2017
			Outpatient post(33)	Cognitive Behavioural Therapy(48)	DuHamel et al., 2010
Psychological distress(46, 48) *N* = 2	Brief Symptom Inventory(48)	RCT(48)	Outpatient post(48)	Cognitive Behavioural Therapy(48)	DuHamel et al., 2010
	SCL-K-9(46)	RCT(46)	Hospital(46)	Problem Solving Training(46)	Balck et al., 2019
Bodily Pain(42)	SF36(42)	RCT(42)	Outpatient post(42)	Exercise_Relaxation_Information(42)	Bird et al., 2010
Coping(46) *N* = 1	The Brief COPE(46)	RCT(46)	Hospital(46)	Problem Solving Training(46)	Balck et al., 2019
Extend of the pain(46) *N* = 1	The Questions Of Pain(46)	RCT(46)	Hospital(46)	Problem Solving Training(46)	Balck et al., 2019
General Distress(46) *N* = 1	The National Comprehensive Cancer Network Distress Thermometer(46)	RCT(46)	Hospital(46)	Problem Solving Training(46)	Balck et al., 2019
General distress and depressive symptoms(49)	Brief Symptom Inventory(49)	RCT(49)	Outpatient post(49)	Telephone administered cognitive behavioural therapy(49)	Applebaum et al., 2012
General Mental Health(42) *N* = 1	SF36(42)	RCT(42)	Outpatient post(42)	Exercise_Relaxation_Information(42)	Bird et al., 2010
Illness Related PTSD Symptoms(49)	PCL-C(49)	RCT(49)	Outpatient post(49)	Telephone administered cognitive behavioural therapy(49)	Applebaum et al., 2012

Mental Well Being(50)	Cancer and Treatment Distress(50)	RCT(50)	Outpatient pre(50)	Exercise and Stress Management(50)	Jacobsen et al., 2014
	Pittsburgh Sleep Quality Index(35)	RCT(35)	Outpatient pre(35)	Exercise and Stress Management(35)	Jacobsen et al., 2014
Physical Fitness(8)	Human Activity Profile (8)	RCT(8)	Hospital(8)	Exergaming (8)	Schumacher et al., 2018
Physical Functioning(27)	SF36(27)	RCT(27)	Outpatient post(27)	Exercise_Relaxation_Information(27)	Bird et al., 2010
Physical Well Being(35)	SF36(35)	RCT(35)	Outpatient pre(35)	Exercise and Stress Management(35)	Jacobsen et al., 2014
Problem Solving Ability(46) *N* = 1	The Social Problem Solving Inventory-Revised (SPSI-R)(46)	RCT(46)	Hospital(46)	Problem Solving Training(46)	Balck et al., 2019
Psychological health(42)	General Health Questionnaire (42)	RCT(42)	Outpatient post(42)	Exercise_Relaxation_Information(42)	Bird et al., 2010
Psychological Performance(18)	EORTC QLQ-C30(18)	Feasibility(18)	Hospital(18)	Electric Muscle Stimulation(18)	Bewarder et al., 2019
	Multidimensional Fatigue Inventory(18)	Feasibility(18)	Hospital(18)	Electric Muscle Stimulation(18)	Bewarder et al., 2019
Quantified Walking Activity(41)	Accelerometry(41)	RCT(41)	Outpatient post(41)	Outpatient physical exercise(41)	Knols et al., 2011
Role Limitation(42)	SF36(42)	RCT(42)	Outpatient post(42)	Exercise_Relaxation_Information(42)	Bird et al., 2010
Self Reported Physical Function(41)	EORTC QLQ-C30(41)	RCT(41)	Outpatient post(41)	Outpatient physical exercise(41)	Knols et al., 2011
Social Functioning(42)	SF36(42)	RCT(42)	Outpatient post(42)	Exercise_Relaxation_Information(42)	Bird et al., 2010
Social support(46) *N* = 1	N/A	RCT(46)	Hospital(46)	Problem Solving Training(46)	Balck et al., 2019
Symptom Burden(45) *N* = 1	Edmonton Symptom Assessment Scale(45)	RCT(45)	Hospital(45)	Palliative Care(45)	El Jawahri et al., 2017
Therapeutic alliance(49)	Working Alliance Inventory Short Form (49)	RCT(49)	Outpatient post(49)	Telephone administered cognitive	Applebaum et al., 2012

				behavioural therapy(49)	
Vitality(42)	SF36(42)	RCT(42)	Outpatient post(42)	Exercise_Relaxation_Information(42)	Bird et al., 2010

CORE AREA PATHOPHYSIOLOGY					
Allogeneic					
Outcomes	Instruments	Design	Phase	Intervention	Reference
Endurance(17, 51) *N* = 2	Bicycle ergometer(17)	Pilot Study(17)	Hospital(17)	Exercise(17)	Schuler et al., 2016
	The 6 Minutes Walk Test(17)	Pilot Study(17)	Hospital(17)	Exercise(17)	Schuler et al., 2016
	The WHO Scheme(51)	RCT(51)	Hospital(51)	Exercise Training(51)	Baumann et al., 2011
Functional Performance(30, 31) *N* = 2	2 min stair climb test(31)	RCT(31)	Hospital(31)	Multimodal Intervention(31)	Jarden et al., 2009
	Chairing test on force plate(30)	RCT(30)	Hospital(30)	Whole Body Vibration Training(30)	Pahl et al., 2020
	Maximum Counter movement jump(30)	RCT(30)	Hospital(30)	Whole Body Vibration Training(30)	Pahl et al., 2020
Handgrip Strength(16, 32) *N* = 2	Hand Grip Dynamometer(16, 32)	Feasibility(16) RCT(32)	Hospital(16) Inpatient post(32)	Exercise(16) Inspiratory muscle training(32)	Santa mina et al., 2020 Bargi et al., 2015
Physical Performance(28, 29) *N* = 2	50-foot walk test(29)	RCT(29)	Outpatient post(29)	Supervised exercise program(29)	Shleton et al., 2008
	Blood Lactate Concentrate(28)	Pilot Study(28)	Outpatient post(28)	Individualized Exercise Program(28)	Carlson et al., 2006
	Cardiac Output(28)	Pilot Study(28)	Outpatient post(28)	Individualized Exercise Program(28)	Carlson et al., 2006
	Forward reach(29)	RCT(29)	Outpatient post(29)	Supervised exercise program(29)	Shleton et al., 2008
	Oxygen Uptake (VO2)(28)	Pilot Study(28)	Outpatient post(28)	Individualized Exercise Program(28)	Carlson et al., 2006

	Power Output(28)	Pilot Study(28)	Outpatient post(28)	Individualized Exercise Program(28)	Carlson et al., 2006
	Rating of Perceived Exertion (RPE)(28)	Pilot Study(28)	Outpatient post(28)	Individualized Exercise Program(28)	Carlson et al., 2006
	Respiratory Exchange Ratio(28)	Pilot Study(28)	Outpatient post(28)	Individualized Exercise Program(28)	Carlson et al., 2006
	Stroke Volume(28)	Pilot Study(28)	Outpatient post(28)	Individualized Exercise Program(28)	Carlson et al., 2006
	The 6 Minutes Walk Test(29)	RCT(29)	Outpatient post(29)	Supervised exercise program(29)	Shleton et al., 2008
	Timed repeated sit to stand(29)	RCT(29)	Outpatient post(29)	Supervised exercise program(29)	Shleton et al., 2008
	Uniped stance time(29)	RCT(29)	Outpatient post(29)	Supervised exercise program(29)	Shleton et al., 2008
	Ventilatory Threshold (28)	Pilot Study(28)	Outpatient post(28)	Individualized Exercise Program(28)	Carlson et al., 2006
Pulmonary Function(32, 51) *N* = 2	Spirometry(32,51)	RCT(32, 51)	Hospital(51) Inpatient post(32)	Exercise Training(51) Inspiratory muscle training(32)	Baumann et al., 2011 Bargi et al., 2015
Aerobic endurance performance capacity(36)	The 6 Minutes Walk Test(36)	RCT(36)	Hospital(36)	Whole Body Vibration Training(36)	Kaeding et al., 2018
Body Composition(30)	Displacement Plethysmography(30)	RCT(30)	Hospital(30)	Whole Body Vibration Training(30)	Pahl et al., 2020
Body Mass Index(16)	Bioimpendance Analysis(16)	Feasibility(16)	Hospital(16)	Exercise(16)	Santa mina et al., 2020
Cardiorespiratory Fitness(30)	Cardiopulmonary Exercise Testing(30)	RCT(30)	Hospital(30)	Whole Body Vibration Training(30)	Pahl et al., 2020
Functional Aerobic Capacity(16)	30 Second Sit to Stand Test(16)	Feasibility(16)	Hospital(16)	Exercise(16)	Santa mina et al., 2020
	The 6 Minutes Walk Test(16)	Feasibility(16)	Hospital(16)	Exercise(16)	Santa mina et al., 2020
Functional Status(52)	Karnofsky Performance Status Scale(52)	RCT(52)	Hospital(52)	Walking Regimen(52)	DeFor et al., 2007

Isokinetic Leg Performance(36)	Biodex System(36)	RCT(36)	Hospital(36)	Whole Body Vibration Training(36)	Kaeding et al., 2018
Knee Extension Strength(17)	External resistor(17)	Pilot Study(17)	Hospital(17)	Exercise(17)	Schuler et al., 2016
Leucocyte count(33)	Total and differental Counts of white blood cells(33)	RCT(33)	Hospital(33)	Relaxation Breathing Exercise(33)	Kim et al., 2005
Maximal Exercise Capacity(32)	The Modified Incremental Shuttle Walking Test (MISWT)(32)	RCT(32)	Inpatient post(32)	Inspiratory muscle training(32)	Bargi et al., 2015
Muscle Strength(31)	Isotonic muscular strength(31)	RCT(31)	Hospital(31)	Multimodal Intervention(31)	Jarden et al., 2009
	Maximal isometric voluntary strength(31)	RCT(31)	Hospital(31)	Multimodal Intervention(31)	Jarden et al., 2009
Pain(38)	Visual Analog Scale(38)	RCT(38)	Hospital(38)	Music Therapy(38)	Doro et al., 2017
Peak aerobic capacity(16)	Cardiopulmonary Exercise Testing(16)	Feasibility(16)	Hospital(16)	Exercise(16)	Santa mina et al., 2020
Peak Oxygen Consumption(30)	Cardiopulmonary Exercise Testing(30)	RCT(30)	Hospital(30)	Whole Body Vibration Training(30)	Pahl et al., 2020
Peripheral Muscle Strength(32)	Hand-Held Dynamometer(32)	RCT(32)	Inpatient post(32)	Inspiratory muscle training(32)	Bargi et al., 2015
Physical Capacity(31)	Estimated VO2max cycle ergometer(31)	RCT(31)	Hospital(31)	Multimodal Intervention(31)	Jarden et al., 2009
Respiratory Muscle Strength(32)	Mouthpiece device(32)	RCT(32)	Inpatient post(32)	Inspiratory muscle training(32)	Bargi et al., 2015
Strength(51) *N* = 1	Isometric Test Digimax(51)	RCT(51)	Hospital(51)	Exercise Training(51)	Baumann et al., 2011
Strength Capacity(30)	Isokinetic Test Knee Extensors(30)	RCT(30)	Hospital(30)	Whole Body Vibration Training(30)	Pahl et al., 2020
Submaximal Exercise Capacity(32)	The 6 Minutes Walk Test(32)	RCT(32)	Inpatient post(32)	Inspiratory muscle training(32)	Bargi et al., 2015
Trunk strength(17)	N/A	Pilot Study(17)	Hospital(17)	Exercise(17)	Schuler et al., 2016
Upper Limb Muscle Strength(16)	Hand-Held Dynamometer(16)	Feasibility(16)	Hospital(16)	Exercise(16)	Santa mina et al., 2020

HSCT					
Outcomes	Instruments	Design	Phase	Intervention	Reference
Endurance(23, 34) *N* = 2	The 2 Minute Walk Test(23)	RCT(23)	Hospital(23)	Exergaming(23)	Schumacher et al., 2018
	The WHO Scheme(34)	RCT(34)	Hospital(34)	Exercise Therapy(34)	Baumann et al., 2010
	Treadmill(23)	RCT(23)	Hospital(23)	Exergaming(23)	Schumacher et al., 2018
Handgrip Strength(23, 41) *N* = 2	Hand Grip Dynamometer(23, 41)	RCT(23, 41)	Hospital(23) Outpatient post(41)	Exergaming(23) Outpatient physical exercise(41)	Schumacher et al., 2018 Knols et al., 2011
Aerobic Fitness(21)	Ventilatory Threshold (21)	Pilot Study(21)	Outpatient post(21)	Home based aerobic exercise(21)	Wilson et al., 2005
Blood count(34)	*N*/A	RCT(34)	Hospital(34)	Exercise Therapy(34)	Baumann et al., 2010
Body Composition(41,25)	Dual x-ray absorptiometry(41)	RCT(41)	Outpatient post(41)	Outpatient physical exercise(41)	Knols et al., 2011
	Bioimpendance Analysis(25)	Pilot Study(25)	Outpatient pre(25)	Exercise Training and Nutritional Support(25)	Rupnik et al., 2020
Cardiorespiratory Fitness(53)	Cardiopulmonary Exercise Testing(53)	Feasibility(53)	Outpatient pre(53)	Home based interval exercise training(53)	Wood et al., 2016
	The 6 Minutes Walk Test(53)	Feasibility(53)	Outpatient pre(53)	Home based interval exercise training(53)	Wood et al., 2016
Exercise Capacity(42)	Shuttle Walk Test (SWT)(42)	RCT(42)	Outpatient post(42)	Exercise_Relaxation_Information(42)	Bird et al., 2010
Functional Ability(40)	15 Foot Walk Time(40)	RCT(40)	Hospital(40)	Strength Training(40)	Hacker et al., 2017
	30 Second Sit to Stand Test(40)	RCT(40)	Hospital(40)	Strength Training(40)	Hacker et al., 2017
	Timed Stair Climb(40)	RCT(40)	Hospital(40)	Strength Training(40)	Hacker et al., 2017
	Timed Up And Go Test(40)	RCT(40)	Hospital(40)	Strength Training(40)	Hacker et al., 2017
Functional Exercise Capacity(41)	The 6 Minutes Walk Test(41)	RCT(41)	Outpatient post(41)	Outpatient physical exercise(41)	Knols et al., 2011
Functional Capacity (27)	6 min step test (27)	Feasibility(27)	Hospital(27)	Individualized Exercise Training(27)	Fioritto et al., 2021

Knee Extension Strength(41)	Hand-Held Dynamometer(41)	RCT(41)	Outpatient post(41)	Outpatient physical exercise(41)	Knols et al., 2011
Muscle Strength(40)(25)	Arm curl test(40)	RCT(40)	Hospital(40)	Strength Training(40)	Hacker et al., 2017
	Hand Grip Dynamometer(40,25)	RCT(40) Pilot Study (25)	Hospital(40) Outpatient pre(25)	Strength Training(40) Exercise Training and Nutritional Support (25)	Hacker et al., 2017 Rupnik et al., 2020
	Rectus femoris cross sectional area(40)	RCT(40)	Hospital(40)	Strength Training(40)	Hacker et al., 2017
Nausea(35)	SF36(50)	RCT(50)	Outpatient pre(50)	Exercise and Stress Management(50)	Jacobsen et al., 2014
Physical Performance(18)(25)	8 Foot Walk (18)	Feasibility(18)	Hospital(18)	Electric Muscle Stimulation(18)	Bewarder et al., 2019
	Balance Test(18)	Feasibility(18)	Hospital(18)	Electric Muscle Stimulation(18)	Bewarder et al., 2019
	Chair Stands(18)	Feasibility(18)	Hospital(18)	Electric Muscle Stimulation(18)	Bewarder et al., 2019
	The 6 Minutes Walk Test(18,25)	Feasibility(18) Pilot Study (25)	Hospital(18) Outpatient pre (25)	Electric Muscle Stimulation(18) Exercise Training and Nutritional Support (25)	Bewarder et al., 2019 Rupnik et al., 2020
	The Short Physical Performance Battery(18)	Feasibility(18)	Hospital(18)	Electric Muscle Stimulation(18)	Bewarder et al., 2019
	30 Second Sit to Stand Test (25)	Pilot Study (25)	Outpatient pre (25)	Exercise Training and Nutritional Support (25)	Rupnik et al., 2020
Pulmonary Function(34)	Spirometry(34)	RCT(34)	Hospital(34)	Exercise Therapy(34)	Baumann et al., 2010
Respiratory Function(54)	Tidal Volume, minute volume, maximal inspiratory and	Pilot Study(54)	Hospital(54)	Respiratory Physiotherapy(54)	Bom et al., 2012

	expiratory pressures.(54)				
Respiratory Muscle Strength (20)	Maximal Expiratory Pressure (20)	Feasibility(20)	Hospital(20)	Inspiratory muscle training(20)	De almeida et al., 2020
	Maximal Inspiratory Pressure(20)	Feasibility(20)	Hospital(20)	Inspiratory muscle training(20)	De almeida et al., 2020
Respiratory Signs(20)	Peripheral Oxygen Saturation(20)	Feasibility(20)	Hospital(20)	Inspiratory muscle training(20)	De almeida et al., 2020
	Respiratory Rate (20)	Feasibility(20)	Hospital(20)	Inspiratory muscle training(20)	De almeida et al., 2020
Respiratory Symptoms(20)	Medical Records(20)	Feasibility(20)	Hospital(20)	Inspiratory muscle training(20)	De almeida et al., 2020
Strength(34)	Isometric Test Digimax(34)	RCT(34)	Hospital(34)	Exercise Therapy(34)	Baumann et al., 2010
Walking Speed(41)	50-foot walk test(41)	RCT(41)	Outpatient post(41)	Outpatient physical exercise(41)	Knols et al., 2011
Upper Limb Muscle Strength(27)	Handgrip Dynamometer(27)	Feasibility(27)	Hospital(27)	Individualized Exercise Training(27)	Fioritto et al., 2021
Lower Limb Muscle Strength	1 min STS (27)	Feasibility(27)	Hospital (27)	Individualized Exercise Training(27)	Fioritto et al., 2021
Physical Function (47)	The 6 Minutes Walk Test(47) Timed Up And Go Test(47) The Physical Performance Test(47)	RCT (47)	Hospital (47)	Multidirectional Walking(47)	Potiaumpai et al., 2020

2.3.1 Core Area Feasibility

In the core area of “Feasibility”, n = 8 different outcomes were measured 30 times using n = 15 different instruments (**Table 2**). The outcome feasibility was the most frequently measured outcome in this core are. It was measured two times in studies that only included allogeneic HSCT patients and seven times in studies including mixed HSCT patients.

2.3.2 Core Area Life Impact

In the core area “life impact”, n = 37 different outcomes were measured 105 times using n = 49 different instruments (**Table 2**). Fatigue was the most frequently measured outcome (n = 15) in all of the studies, regardless of design, setting, or the included population. It was measured using n= 12 different instruments. In studies that only included allogeneic HSCT patients, fatigue was measured 8 times using n = 7 different instruments. Studies including mixed HSCT patients measured fatigue 7 times using n = 8 different instruments.

Quality of Life (n = 5) and Health Related Quality of Life (n = 4) were measured 9 times using n = 2 different instruments in studies that only included allogeneic HSCT patients. The most frequently used instrument used to measure quality of life in this population was the EORTC QLQ-C30 [55]. In studies including a mixed HSCT population, Quality of Life (n = 5) and Health related Quality of Life (n = 7) were measured 12 times using n = 6 different instruments.

Depression was measured 11 times in studies including allogeneic HSCT (n = 5) or mixed HSCT (n = 6) patients. The Hospital Anxiety and Depression Scale [56] was the most frequently used instrument used to measure depression in studies including mixed HSCT patients. Studies including allogeneic HSCT patients only used n = 6 different instruments.

Anxiety was measured eight times. In studies including allogeneic HSCT patients only, anxiety was measured in n = 3 studies using n = 3 different instruments. In studies including mixed HSCT patients, it was measured in n = 5 studies using n = 2 different instruments. The most frequently used instrument used to measure anxiety was the Hospital Anxiety and

Depression Scale [56]. Anxiety was measured in seven out of eight studies during the "Hospital" phase.

2.3.3 Core Area Pathophysiology

In the core area "pathophysiological manifestations", 39 different outcomes were measured 85 times using 61 instruments (**Table 2**). Endurance (n = 4) and handgrip Strength (n = 4) were the most frequently used outcomes. Both outcomes were used two times in studies including both allogeneic HSCT patients only and mixed HSCT patients. All four studies used a handgrip dynamometer to measure handgrip strength. Endurance was measured using five different instruments, always during the "Hospital" phase.

2.3.4 Timing of Measurement

In 23 out of 39 of the studies, measurements were performed at two time points (**Table 3**). The maximum number of measurements was n = 7 time points. Regardless of the setting, the initial measurements (T1) were not always performed on admission. A total of 22 studies were conducted in a hospital setting; in n = 13 studies, measurements were performed on admission, while in n = 9 studies, measurements were not performed on admission. A total of 17 studies were conducted in a non-hospital setting; in n = 13 studies, measurements were performed on admission, and in n = 4 studies, measurements were not performed on admission.

Table 3. *Scoping Review timing of measurement*

HOSPITAL SETTING							
Allogeneic HSCT							
	T1	T2	T3	T4	T5	T6	T7
Before Hospitalization	(37)						
On Admission	(34)(52)(31) (36)(30)(16) (17)(37)						
At Baseline							
At discharge		(34)(31)(36) (30)(17)(37)					
Before the intervention	(33)						
After the intervention		(33)					
First Session	(38)						
Second Session		(38)					
One week before HSCT		(16)					
Day -2 before HSCT							
Day -1 before HSCT							
Day +2 after HSCT							
Before HSCT							
After HSCT							
Second week of Hospitalization							
Day +7 after HSCT							
Day +8 after HSCT							
Day +10 after HSCT							
Day +14 after HSCT							
Day +20 after HSCT							
Day +30 after HSCT							
7 weeks after Hospitalization			(37)				
Day +60 after HSCT							
3 months after HSCT			(17)				
Day +100 after HSCT		(52)	(16)				
6 months after HSCT			(30)				
9 months after HSCT							
One year after HSCT				(16)			
Hospital Setting							
HSCT							
	T1	T2	T3	T4	T5	T6	T7
Before Hospitalization	(40)						
On Admission	(34)(20)(39) (44)(23)						
At Baseline	(45)(27)(47)						
At discharge		(34)(18)(20) (27)		(44)			
Before the intervention	(18)(19)						
After the intervention		(19)					
First Session							
Second Session							
One week before HSCT		(47)					
Day -2 before HSCT	(46)						
Day -1 before HSCT	(54)	(44)					
Day +2 after HSCT		(54)					
Before HSCT							
After HSCT							
Second week of Hospitalization		(45)					
Day +7 after HSCT			(54)(44)				
Day +8 after HSCT		(39)					
Day +10 after HSCT		(46)					
Day +14 after HSCT		(23)	(39)				

Day +20 after HSCT			(46)				
Day +30 after HSCT			(47)(23)				
7 weeks after Hospitalization		(40)					
Day +60 after HSCT					(44)		
3 months after HSCT			(45)				
Day +100 after HSCT				(23)		(44)	
6 months after HSCT				(45)			(44)
9 months after HSCT							
One year after HSCT							
NON Hospital Setting							
Allogeneic HSCT							
	T1	T2	T3	T4	T5	T6	T7
Before Hospitalization							
On Admission	(28)						
At Baseline							
At discharge		(28)					
Before the intervention	(32)(35)(29)						
After the intervention		(32)(35)(29)					
First Session							
Second Session							
One week before HSCT							
Day -2 before HSCT							
Day -1 before HSCT							
Day +2 after HSCT							
Before HSCT							
After HSCT							
Second week of Hospitalization							
Day +7 after HSCT							
Day +8 after HSCT							
Day +10 after HSCT							
Day +14 after HSCT							
Day +20 after HSCT							
Day +30 after HSCT							
7 weeks after Hospitalization							
Day +60 after HSCT							
3 months after HSCT							
Day +100 after HSCT							
6 months after HSCT							
9 months after HSCT							
One year after HSCT							
Non Hospital Setting							
HSCT							
	T1	T2	T3	T4	T5	T6	T7
Before Hospitalization							
On Admission							
At Baseline	(24) (49)(22)(48) (50)(41)(25) (21)						
At discharge		(22)(42)(41)					
Before the intervention	(42)(43)						
After the intervention		(24)(43)(21)(41)					
First Session							
Second Session							
One week before HSCT		(25)					
Day -2 before HSCT							
Day -1 before HSCT							
Day +2 after HSCT							
Before HSCT	(53)						

After HSCT	(53)			
Second week of Hospitalization				
Day +7 after HSCT				
Day +8 after HSCT				
Day +10 after HSCT				
Day +14 after HSCT				
Day +20 after HSCT				
Day +30 after HSCT	(50)			
7 weeks after Hospitalization				
Day +60 after HSCT		(50)		
3 months after HSCT				
Day +100 after HSCT			(50)	
6 months after HSCT	(49)(48)			(50)
9 months after HSCT		(49)(48)		
One year after HSCT			(49)(48)	

2.4 Discussion

In this review, we observed a tendency toward the use of the same specific outcomes and outcome measurement instruments within the two core areas Feasibility and Life Impact; however, we saw a much more diverse use of outcomes and tools in the core area “Pathophysiological Manifestations”. Despite the use of the same outcomes and outcome measurement instruments, the scientific efforts in this field do not fully exploit the potential for evidence synthesis, clinical interpretation, and constructive implications for further research. The main reasons for this are measurement bias due to the heterogeneity and inconsistency of outcomes and outcome measurement instruments used, which is in line with similar statements in the COMET Handbook [57] that describe problems related to outcome reporting bias and inconsistency in outcome measurement. Below, we discuss four main aspects of measurement bias that we encountered based on our results.

2.4.1 Outcome Excess and Inconsistent Use

The 84 different outcomes that were measured in the studies that we included in this scoping review as well as the wide variety of terms used for the same outcomes indicate an excess of outcomes and the inconsistent use of terms in the body of literature that we reviewed. For example, in the “Pathophysiology” core area, thirteen terms were used to describe similar outcomes, of which we only recognize three distinct outcomes, all of which are related to, in different degrees, the body’s capacity to produce energy through aerobic metabolic pathways (peak aerobic capacity, peak oxygen consumption, aerobic fitness, functional aerobic capacity, cardiorespiratory fitness, and aerobic endurance performance capacity) or to move itself in a specific manner within a specific timeframe (exercise capacity, functional exercise capacity, maximal exercise capacity, submaximal exercise capacity, and endurance) as well as a third more complex outcome that includes multiple components of fitness (physical capacity and physical performance).

This heterogeneous use of terminology hampers communication between researchers and impedes synthesis in secondary research. It also generates confusion concerning the content of each outcome, which could lead to aberrant inclusions or exclusions in reviews or even incorrect interpretations by clinicians.

Researchers in the field of rehabilitation for patients treated with allogeneic HSCT should seek to reduce the number of the outcomes they measure by reaching consensus about the relevant outcomes to be collected and reported, thus defining a core outcome set (COS). Ideally, COS development should involve patients, so that their needs and insights are taken in consideration.

Strength is an important outcome in the core area “Pathophysiology” because its reduction due to corticosteroid regimens can determine functional performance in post-allogeneic HSCT long-term survivors [58,59]. Handgrip strength can be used as a surrogate marker of strength among patients undergoing allogeneic HSCT, and it can detect strength loss and be regained post-allogeneic HSCT [60]. It is a widely used outcome in HSCT research, something that is probably due to the practicability of its measurement. Other authors underline the importance of this outcome during hospitalization for allogeneic HSCT since detecting strength loss can improve fall prevention [61]. However, in addition to handgrip strength, eight other aspects of strength were measured in the studies that we included (i.e., isokinetic leg performance, knee extension strength, muscle strength, peripheral muscle strength, strength, strength capacity, trunk strength, and upper limb muscle strength). As a result, again, there is heterogeneity in the outcomes being measured, which hampers synthesis and adds data waste to this research field. Given the importance of the outcome strength for patients treated with HSCT, researchers should reach consensus on which aspect of strength is the most relevant to be measured.

In the “Feasibility” core area, we observed the interchangeable use of terms (for example, “accrual acceptance”, “acceptability”, “rate of participant enrolment”, “recruitment”, and “recruitment rate”) since similar terms were used to describe identical phenomena. The most frequently used outcome in this core area, the outcome feasibility, is in our view, a

multidimensional construct that comprises dimensions such as safety, attrition, acceptability, and adherence. Some researchers in the field of allogeneic HSCT rehabilitation have already begun to approach feasibility in the manner in which we see it [14,62]. In this review, we noticed that various authors classified specific terms as distinct outcomes (i.e., “acceptability”, “adherence”, and “attrition”), while others used these terms as instruments to measure the outcome feasibility. This difference in definitions and outcome operationalization leads to incomparable data and is a waste of resources.

Dimensions such as safety, attrition, acceptability, and adherence should not be considered outcome measurement instruments and should not be used and reported as such because they refer to what is measured, i.e., an outcome, while an instrument refers to how an outcome is measured. Ideally, the research community in this field should reach a consensus on the definition of feasibility and on how to measure it.

2.4.2 Outcome Measurement Instrument Excess and Inconsistent Use

The 84 outcomes that were found were measured by 134 different measurement instruments. In the “Pathophysiology” core area alone, 59 different instruments were used to measure 39 different outcomes. This diverseness in the outcome measurement instruments indicates an excess of outcome measurement instruments.

This excess of outcome measurement instruments makes synthesis across studies more difficult. A meta-analytical systematic review studying the effects of physical activity on fatigue confirms our statement [63]. In that study, the authors had to describe intervention effects using standardized mean differences—which are more difficult to interpret—rather than weighted mean differences, because the studies that they reviewed used different outcome instruments to measure fatigue.

Patients undergoing allogeneic HSCT commonly experience fatigue both during hospitalization and in the long-term [64]. Different items could be relevant to measure fatigue in one situation but not in the other since fatigue during hospitalization (i.e., cancer treatment

related fatigue) may have different characteristics than long-term fatigue (i.e., cancer-related fatigue). However, the variety of instruments used to measure fatigue remains wide, making comparing fatigue measurements difficult. An item response theory (IRT) -based item bank, such as the Patient-Reported Outcomes Measurement Information System (PROMIS) [65] Fatigue Item bank, could address problems related to measuring different levels of fatigue, as tailored shortforms for different patient populations can be developed or computer adaptive testing could be used.

The variety of outcome instruments has a positive impact when it serves the practicability of measurement conduction in different settings and phases. For example, in our review, we found that (n = 5) different instruments were used to measure the outcome “endurance.” Patients treated with allogeneic HSCT are unable to perform the six-minute walk test or the cardiopulmonary exercise testing during hospitalization, as they are generally restricted to their rooms to reduce the risk of infection and because they are connected to medication-administering devices. In this case, an endurance test that can be performed in a small space, such as the six-minute step test, has better practicability than the six-minute walk test. The appropriate use of a wide variety of outcome measurement instruments requires specific context- and phase-including guidelines, which would serve the avoidance of inconsistent scientific output. Ideally, such guidelines should be informed based on clinimetric studies to confirm the reliability and validity of the indicated instruments in defined settings and phases.

We noticed that some instruments such as the EORTC QlQ-C30 and the FACT were often used to measure distinct outcomes such as Health-Related Quality of Life and Quality of Life [66]. We made the same observation for the six-minute walk test, which was used to measure different outcomes. Using a single measurement instrument to measure different outcomes is often not a correct practice because the measurement properties of a measurement instrument may be sufficient to measure one outcome but insufficient to measure another outcome. Therefore, before use, researchers should ensure that the clinimetric properties of each outcome measurement instrument are appropriate for measurement in the population of interest.

2.4.3 Timing and Setting of Measurement Inconsistency

In this review, we found notable heterogeneity in the timing of measurements across studies. Our findings confirm those of van Haren et al. [67] that time-point heterogeneity does not allow for follow-up measurement synthesis in systematic reviews. The general condition of patients treated with allogeneic HSCT fluctuates depending on the phase of their treatment. At the beginning of hospitalization, they may be sturdy, but, later on and depending on chemotherapy intensity, they may suffer from severe fatigue, infection symptoms, and nutritional deficits due to mucositis or other reasons. When patients begin to recover, they gradually show an improved general condition. However, those who suffer from severe symptoms during hospitalization are usually weaker at discharge than at admission. Therefore, heterogeneity in the timing of measurements is an important source of bias since timing is associated with the general condition of the patient. For example, if the “baseline” measurements of one study are performed on admission and the final measurements are performed at discharge, then the results of these measurements or their differences are incomparable to those of another study in which the measurements were performed at day four or ten after admission and at three months after discharge.

Due to the fluctuating condition of patients treated with allogeneic HSCT, not all measurements are always feasible or even meaningful across settings. Measurements might have less value for patients, increase their workload during a period in which filling in questionnaires is not their highest priority, add to data waste, and increase heterogeneity in measurement timing. In order to avoid unnecessary patient effort and the production of data waste and in an effort to improve our understanding of phenomena with established clinical significance, researchers should agree on some basic assumptions: (a) the phases they recognize in the process of allogeneic HSCT (i.e., before allogeneic HSCT, during hospitalization, 100 days after allogeneic HSCT, one year after HSCT—Van der Lans et al. have already made efforts to recognize different phases based on patient insights during recovery) [68]; (b) the outcomes to be measured in each phase; and (c) the timing at which

the measurements for each outcome are taken and the method used to measure them in each phase.

2.4.4 Allogeneic HSCT vs. HSCT Population

In this review, we found that 64% of the reported research projects recruited both allogeneic HSCT and autologous HSCT patients. There are some arguments for combining these populations in a study, though there are no formal restrictions at all since the EBMT Handbook [69] does not even have a dedicated article on rehabilitation from which arguments for the distinction of these two populations could arise. Both populations suffer from hematological malignancies, and both populations undergo transplantation. Therefore, researchers in the field of rehabilitation include samples from both populations to achieve the targeted sample size much more quickly.

However, major differences exist between these two populations, which could lead to problems during the interpretation of study results. First, although both undergo “transplantation”, the two populations do not undergo the same medical treatment. Chemotherapeutic and, more importantly, immunosuppressive treatments differ with regard to duration and side effects. Second, allogeneic HSCT patients normally undergo a longer and more strict isolation period in addition to a longer planned hospital stay. Third, allogeneic HSCT patients often suffer from GvHD and require additional medical treatment, resulting in significant physical and psychological deterioration.

Consequently, these two different populations cannot be combined in research due to differences in measurement timing and the relevance of the outcomes.

There are many published studies indicating that patients from both populations have been recruited. However, the scientific community should consider whether recruiting patients from both populations is appropriate practice and should reach consensus concerning future practice.

2.4.5 Limitations

To our knowledge, this review is the first attempt to describe the outcomes and measurement instruments used in the study of rehabilitative interventions for patients undergoing allogeneic HSCT. Although we managed to elucidate major issues concerning heterogeneity in the outcomes and measurement instruments used, our findings must be interpreted in light of the limitations of this review. First, we only included interventional studies and we only included research published in German and English. This strategy may have prevented the retrieval and inclusion of publications in other languages and from a wider range of disciplines. As a result, this scoping review focuses on the main body of work on psychological and physical rehabilitative interventions. Second, we classified the outcomes we retrieved based on two different frameworks, as the Boers et al. framework was designed for another purpose and thus does not offer a distinct classification for feasibility outcomes. Finally, we extracted and classified outcomes and instruments according to the terms used by the authors, without modification or interpretation, and therefore, the extracted terms were not always appropriate.

2.5 Conclusions

Research in the field of rehabilitation for patients with hematological malignancies treated with allogeneic HSCT covers measurements in all relevant core areas. However, this field of study is hampered by excess outcomes and inconsistent outcome terminology. Furthermore, we detected the inconsistent use of measurement instruments in terms of setting and timing. The combined recruitment of allogeneic and autologous HSCT patients may exacerbate these problems, thus reducing the successful exploitation of the study results by hampering synthesis and clinical interpretation. We recommend that researchers reach a consensus with regard to the use of common terminology for the outcomes of interest and homogeneity in measurement instrument selection and measurement timing.

2.6 References

1. Majhail N.S., Farnia S.H., Carpenter P.A., Champlin R.E., Crawford S., Marks D.I., Omel J.L., Orchard P.J., Palmer J., Saber W., et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol. Blood Marrow Transplant. 2015;21:1863–1869. doi: 10.1016/j.bbmt.2015.07.032.

2. Copelan E.A. Hematopoietic stem-cell transplantation. N. Engl. J. Med. 2006;354:1813–1826. doi: 10.1056/NEJMra052638.

3. Ghimire S., Weber D., Mavin E., Wang X.N., Dickinson A.M., Holler E. Pathophysiology of GvHD and Other HSCT-Related Major Complications. Front. Immunol. 2017;8:79. doi: 10.3389/fimmu.2017.00079.

4. Kurosawa S., Yamaguchi T., Mori T., Kanamori H., Onishi Y., Emi N., Fujisawa S., Kohno A., Nakaseko C., Saito B., et al. Patient-reported quality of life after allogeneic hematopoietic cell transplantation or chemotherapy for acute leukemia. Bone Marrow Transplant. 2015;50:1241–1249. doi: 10.1038/bmt.2015.137.

5. Sorror M., Storer B., Sandmaier B.M., Maloney D.G., Chauncey T.R., Langston A., Maziarz R.T., Pulsipher M., McSweeney P.A., Storb R. Hematopoietic cell transplantation-comorbidity index and Karnofsky performance status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. Cancer. 2008;112:1992–2001. doi: 10.1002/cncr.23375.

6. Wade D.T. What is rehabilitation? An empirical investigation leading to an evidence-based description. Clin. Rehabil. 2020;34:571–583. doi: 10.1177/0269215520905112.

7. Morishita S., Tsubaki A., Hotta K., Fu J., Fujii S. The benefit of exercise in patients who undergo allogeneic hematopoietic stem cell transplantation. J. Int. Soc. Phys. Rehabil. Med. 2019;2:54–61. doi: 10.4103/jisprm.jisprm_2_19.

8. Inoue J., Ono R., Okamura A., Matsui T., Takekoshi H., Miwa M., Kurosaka M., Saura R., Shimada T. The impact of early rehabilitation on the duration of hospitalization in patients after allogeneic hematopoietic stem cell transplantation. Transplant. Proc. 2010;42:2740–2744. doi: 10.1016/j.transproceed.2010.05.153.

9. Cunningham B.A., Morris G., Cheney C.L., Buergel N., Aker S.N., Lenssen P. Effects of resistive exercise on skeletal muscle in marrow transplant recipients receiving total parenteral nutrition. J. Parenter. Enter. Nutr. 1986;10:558–563. doi: 10.1177/0148607186010006558.

10. Mohananey D., Sarau A., Kumar R., Lewandowski D., Abreu-Sosa S.M., Nathan S., Okwuosa T.M. Role of Physical Activity and Cardiac Rehabilitation in Patients Undergoing Hematopoietic Stem Cell Transplantation. JACC Cardio Oncol. 2021;3:17–34. doi: 10.1016/j.jaccao.2021.01.008. Published 2021 Mar 16.

11. Persoon S., Kersten M., Van der Weiden K., Buffart L., Nollet F., Brug J., Chinapaw M. Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: A systematic review and meta-analysis. Cancer Treat. Rev. 2013;39:682–690. doi: 10.1016/j.ctrv.2013.01.001.

12. Hirsch B.R., Califf R.M., Cheng S.K., Tasneem A., Horton J., Chiswell K., Schulman K.A., Dilts D.M., Abernethy A.P. Characteristics of oncology clinical trials: Insights from

a systematic analysis of ClinicalTrials.gov. JAMA Intern. Med. 2013;173:972–979. doi: 10.1001/jamainternmed.2013.627.

13. Boers M., Beaton D.E., Shea B.J., Maxwell L.J., Bartlett S.J., Bingham C.O., III, Conaghan P.G., D'Agostino M.A., de Wit M.P., Gossec L., et al. OMERACT Filter 2.1: Elaboration of the Conceptual Framework for Outcome Measurement in Health Intervention Studies. J. Rheumatol. 2019;46:1021–1027. doi: 10.3899/jrheum.181096.

14. El-Kotob R., Giangregorio L.M. Pilot and feasibility studies in exercise, physical activity, or rehabilitation research. Pilot Feasibility Study. 2018;4:137. doi: 10.1186/s40814-018-0326-0.

15. Thabane L., Ma J., Chu R., Cheng J., Ismaila A., Rios L.P., Robson R., Thabane M., Giangregorio L., Goldsmith C.H. A tutorial on pilot studies: The what, why and how. BMC Med. Res. Methodol. 2010;10:1. doi: 10.1186/1471-2288-10-1.

16. Santa Mina D., Dolan L.B., Lipton J.H., Au D., Camacho Pérez E., Franzese A., Alibhai S.M., Jones J.M., Chang E. Exercise before, during, and after Hospitalization for Allogeneic Hematological Stem Cell Transplant: A Feasibility Randomized Controlled Trial. J. Clin. Med. 2020;9:14. doi: 10.3390/jcm9061854.

17. Schuler M.K., Hornemann B., Pawandenat C., Kramer M., Hentschel L., Beck H., Kasten P., Singer S., Schaich M., Ehninger G., et al. Feasibility of an exercise programme in elderly patients undergoing allogeneic stem cell transplantation—A pilot study. Eur. J. Cancer Care. 2016;25:839–848. doi: 10.1111/ecc.12400.

18. Bewarder M., Klostermann A., Ahlgrimm M., Bittenbring J.T., Pfreundschuh M., Wagenpfeil S., Kaddu-Mulindwa D. Safety and feasibility of electrical muscle

stimulation in patients undergoing autologous and allogeneic stem cell transplantation or intensive chemotherapy. Support. Care Cancer. 2019;27:1013–1020. doi: 10.1007/s00520-018-4390-z.

19. Lu D.F., Hart L.K., Lutgendorf S.K., Oh H., Silverman M. Effects of healing touch and relaxation therapy on adult patients undergoing hematopoietic stem cell transplant: A feasibility pilot study. Cancer Nurs. 2016;39:E1–E11. doi: 10.1097/NCC.0000000000000272.

20. De Almeida L.B., Trevizan P.F., Laterza M.C., Hallack Neto A.E., Perrone A., Martinez D.G. Safety and feasibility of inspiratory muscle training for hospitalized patients undergoing hematopoietic stem cell transplantation: A randomized controlled study. Support. Care Cancer. 2020;28:3627–3635. doi: 10.1007/s00520-019-05209-x.

21. Wilson R.W., Jacobsen P.B., Fields K.K. Pilot study of a home-based aerobic exercise program for sedentary cancer survivors treated with hematopoietic stem cell transplantation. Bone Marrow Transplant. 2005;35:721–727. doi: 10.1038/sj.bmt.1704815.

22. 22.Baydoun M., Barton D.L., Peterson M., Wallner L.P., Visovatti M.A., Arslanian-Engoren C., Choi S.W. Yoga for Cancer-Related Fatigue in Survivors of Hematopoietic Cell Transplantation: A Feasibility Study. J. Pain Symptom Manag. 2020;59:702–708. doi: 10.1016/j.jpainsymman.2019.11.012.

23. Schumacher H., Stüwe S., Kropp P., Diedrich D., Freitag S., Greger N., Junghanss C., Freund M., Hilgendorf I. A prospective, randomized evaluation of the feasibility of exergaming on patients undergoing hematopoietic stem cell transplantation. Bone Marrow Transplant. 2018;53:584–590. doi: 10.1038/s41409-017-0070-8.

24. Amonoo H.L., Kurukulasuriya C., Chilson K., Onstad L., Huffman J.C., Lee S.J. Improving Quality of Life in Hematopoietic Stem Cell Transplantation Survivors Through a Positive Psychology Intervention. Biol. Blood Marrow Transplant. 2020;26:1144–1453. doi: 10.1016/j.bbmt.2020.02.013.

25. Rupnik E., Skerget M., Sever M., Zupan I.P., Ogrinec M., Ursic B., Kos N., Cernelc P., Zver S. Feasibility and safety of exercise training and nutritional support prior to haematopoietic stem cell transplantation in patients with haematologic malignancies. BMC Cancer. 2020;20:1142. doi: 10.1186/s12885-020-07637-z.

26. Peters T., Erdmann R., Hacker E.D. Exercise Intervention: Attrition, Compliance, Adherence, and Progression Following Hematopoietic Stem Cell Transplantation. Clin. J. Oncol. Nurs. 2018;22:97–103. doi: 10.1188/18.CJON.97-103.

27. Fioritto A.P., Oliveira C.C., Albuquerque V.S., Almeida L.B., Granger C.L., Denehy L., Malaguti C. Individualized in-hospital exercise training program for people undergoing hematopoietic stem cell transplantation: A feasibility study. Disabil. Rehabil. 2019;43:386–392. doi: 10.1080/09638288.2019.1626493.

28. Carlson L.E., Smith D., Russell J., Fibich C., Whittaker T. Individualized exercise program for the treatment of severe fatigue in patients after allogeneic hematopoietic stem-cell transplant: A pilot study. Bone Marrow Transplant. 2006;37:945–954. doi: 10.1038/sj.bmt.1705343.

29. Shleton M.L., Lee J.Q., Morris S., Massey P.R., Kendall D.G., Munsell M.F. A randomized control trial of a supervised versus a self-directed exercise program for

allogenic stem cell transplant patients. Psycho-Oncology. 2009;18:353–359. doi: 10.1002/pon.1505.

30. Pahl A., Wehrle A., Kneis S., Gollhofer A., Bertz H. Whole body vibration training during allogeneic hematopoietic cell transplantation-the effects on patients' physical capacity. Ann. Hematol. 2020;99:635–648. doi: 10.1007/s00277-020-03921-x.

31. Jarden M., Nelausen K., Boesen E., Hovgaard D., Adamsen L. The effect of a multimodal intervention on treatment-related symptoms in patients undergoing hematopoietic stem cell transplantation: A randomized controlled trial. J. Pain Symptom Manag. 2009;38:174–190. doi: 10.1016/j.jpainsymman.2008.09.005.

32. Bargi G., Guclu M.B., Aribas Z., Aki S.Z., Sucak G.T. Inspiratory muscle training in allogeneic hematopoietic stem cell transplantation recipients: A randomized controlled trial. Support. Care Cancer. 2016;24:647–659. doi: 10.1007/s00520-015-2825-3.
33. Kim S.D., Kim H.S. Effects of a relaxation breathing exercise on fatigue in haemopoietic stem cell transplantation patients. J. Clin. Nurs. 2005;14:51–55. doi: 10.1111/j.1365-2702.2004.00938.x.

34. Baumann F.T., Kraut L., Schule K., Bloch W., Fauser A.A. A controlled randomized study examining the effects of exercise therapy on patients undergoing haematopoietic stem cell transplantation. Bone Marrow Transplant. 2010;45:355–362. doi: 10.1038/bmt.2009.163.

35. Lounsberry J.J., Macrae H., Angen M., Hoeber M., Carlson L.E. Feasibility study of a telehealth delivered, psychoeducational support group for allogeneic hematopoietic stem cell transplant patients. Psycho-Oncology. 2010;19:777–781. doi: 10.1002/pon.1617.

36. Kaeding T.S., Frimmel M., Treondlin F., Jung K., Jung W., Wulf G., Trümper L., Hasenkamp J. Whole-body vibration training as a supportive therapy during allogeneic haematopoietic stem cell transplantation—A randomised controlled trial. Eur. Oncol. Haematol. 2018;14:33–39. doi: 10.17925/EOH.2018.14.1.33.

37. Wiskemann J., Dreger P., Schwerdtfeger R., Bondong A., Huber G., Kleindienst N., Ulrich C.M., Bohus M. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. Blood. 2011;117:2604–2613. doi: 10.1182/blood-2010-09-306308.

38. 38.Doro C.A., Neto J.Z., Cunha R., Doro M.P. Music therapy improves the mood of patients undergoing hematopoietic stem cells transplantation (controlled randomized study) Support. Care Cancer. 2017;25:1013–1018. doi: 10.1007/s00520-016-3529-z.

39. Jafari H., Janati Y., Yazdani J., Bali N., Hassanpour S. The Effect of Relaxation Technique on Fatigue Levels after Stem Cell Transplant. Iran. J. Nurs. Midwifery Res. 2018;23:388–394. doi: 10.4103/ijnmr.IJNMR_26_17.

40. Hacker E.D., Collins E., Park C., Peters T., Patel P., Rondelli D. Strength Training to Enhance Early Recovery after Hematopoietic Stem Cell Transplantation. Biol. Blood Marrow Transplant. 2017;23:659–669. doi: 10.1016/j.bbmt.2016.12.637.

41. Knols R.H., de Bruin E.D., Uebelhart D., Aufdemkampe G., Schanz U., Stenner-Liewen F., Hitz F., Taverna C., Aaronson N.K. Effects of an outpatient physical exercise program on hematopoietic stem-cell transplantation recipients: A randomized clinical trial. Bone Marrow Transplant. 2011;46:1245–1255. doi: 10.1038/bmt.2010.288.

42. Bird L., Arthur A., Niblock T., Stone R., Watson L., Cox K. Rehabilitation programme after stem cell transplantation: Randomized controlled trial. J. Adv. Nurs. 2010;66:607–615. doi: 10.1111/j.1365-2648.2009.05232.x.

43. Grossman P., Zwahlen D., Halter J.P., Passweg J.R., Steiner C., Kiss A. A mindfulness-based program for improving quality of life among hematopoietic stem cell transplantation survivors: Feasibility and preliminary findings. Support. Care Cancer. 2015;23:1105–1112. doi: 10.1007/s00520-014-2452-4.

44. McCabe C., Roche D., Hegarty F., McCann S. 'Open Window': A randomized trial of the effect of new media art using a virtual window on quality of life in patients' experiencing stem cell transplantation. Psycho-Oncology. 2013;22:330–337. doi: 10.1002/pon.2093.

45. El-Jawahri A., Traeger L., Greer J.A., VanDusen H., Fishman S.R., LeBlanc T.W., Pirl W.F., Jackson V.A., Telles J., Rhodes A., et al. Effect of inpatient palliative care during hematopoietic stem-cell transplant on psychological distress 6 months after transplant: Results of a randomized clinical trial. J. Clin. Oncol. 2017;35:3714–3721. doi: 10.1200/JCO.2017.73.2800.

46. Balck F., Zschieschang A., Zimmermann A., Ordemann R. A randomized controlled trial of problem-solving training (PST) for hematopoietic stem cell transplant (HSCT) patients: Effects on anxiety, depression, distress, coping and pain. J. Psychosoc. Oncol. 2019;37:541–556. doi: 10.1080/07347332.2019.1624673.

47. Potiaumpai M., Cutrono S., Medina T., Koeppel M., Pereira D.L., Pirl W.F., Jacobs K.A., Eltoukhy M., Signorile J.F. Multidirectional Walking in Hematopoietic Stem Cell

Transplant Patients. Med. Sci. Sports Exerc. 2021;53:258–266. doi: 10.1249/MSS.0000000000002474.

48. DuHamel K.N., Mosher C.E., Winkel G., Labay L.E., Rini C., Meschian Y.M., Austin J., Greene P.B., Lawsin C.R., Rusiewicz A., et al. Randomized clinical trial of telephone-administered cognitive-behavioral therapy to reduce post-traumatic stress disorder and distress symptoms after hematopoietic stem-cell transplantation. J. Clin. Oncol. 2010;28:3754–3761. doi: 10.1200/JCO.2009.26.8722.

49. Applebaum A.J., DuHamel K.N., Winkel G., Rini C., Greene P.B., Mosher C.E., Redd W.H. Therapeutic alliance in telephone-administered cognitive-behavioral therapy for hematopoietic stem cell transplant survivors. J. Consult. Clin. Psychol. 2012;80:811–816. doi: 10.1037/a0027956.

50. Jacobsen P.B., Le-Rademacher J., Jim H., Syrjala K., Wingard J.R., Logan B., Wu J., Majhail N.S., Wood W., Rizzo J.D., et al. Exercise and stress management training prior to hematopoietic cell transplantation: Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0902. Biol. Blood Marrow Transplant. 2014;20:1530–1536. doi: 10.1016/j.bbmt.2014.05.027.

51. Baumann F.T., Zopf E.M., Nykamp E., Kraut L., Schüle K., Elter T., Fauser A.A., Bloch W. Physical activity for patients undergoing an allogeneic hematopoietic stem cell transplantation: Benefits of a moderate exercise intervention. Eur. J. Haematol. 2011;87:148–156. doi: 10.1111/j.1600-0609.2011.01640.x.

52. DeFor T.E., Burns L.J., Gold E.M., Weisdorf D.J. A randomized trial of the effect of a walking regimen on the functional status of 100 adult allogeneic donor hematopoietic

cell transplant patients. Biol. Blood Marrow Transplant. 2007;13:948–955. doi: 10.1016/j.bbmt.2007.04.008.

53. Wood W.A., Phillips B., Smith-Ryan A.E., Wilson D., Deal A.M., Bailey C., Meeneghan M., Reeve B.B., Basch E.M., Bennett A.V., et al. Personalized home-based interval exercise training may improve cardiorespiratory fitness in cancer patients preparing to undergo hematopoietic cell transplantation. Bone Marrow Transplant. 2016;51:967–972. doi: 10.1038/bmt.2016.73.

54. Bom E.A., de Souza C.V., Thiesen R.A., Miranda E.C., de Souza C.A. Evaluation of respiratory conditions in early phase of hematopoietic stem cell transplantation. Rev. Bras. Hematol. Hemoter. 2012;34:188–192. doi: 10.5581/1516-8484.20120047.

55. Fayers P., Bottomley A., on behalf of the EORTC Quality of Life Group and of the Quality of Life Unit Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. Eur. J. Cancer. 2002;38((Suppl. 4)):S125–S133. doi: 10.1016/S0959-8049(01)00448-8.

56. Zigmond A.S., Snaith R.P. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 1983;67:361–370. doi: 10.1111/j.1600-0447.1983.tb09716.x.

57. Williamson P.R., Altman D.G., Bagley H., Barnes K.L., Blazeby J.M., Brookes S.T., Clarke M., Gargon E., Gorst S., Harman N., et al. The COMET Handbook: Version 1.0. Trials. 2017;18((Suppl. 3)):280. doi: 10.1186/s13063-017-1978-4.

58. Mitchell S.A., Leidy N.K., Mooney K.H., Dudley W.N., Beck S.L., LaStayo P.C., Cowen E.W., Palit P., Comis L.E., Krumlauf M.C., et al. Determinants of functional performance in long-term survivors of allogeneic hematopoietic stem cell

transplantation with chronic graft-versus-host disease (cGVHD) Bone Marrow Transplant. 2010;45:762–769. doi: 10.1038/bmt.2009.238.

59. Morishita S., Kaida K., Yamauchi S., Sota K., Ishii S., Ikegame K., Kodama N., Ogawa H., Domen K. Relationship between corticosteroid dose and declines in physical function among allogeneic hematopoietic stem cell transplantation patients. Support Care Cancer. 2013;21:2161–2169. doi: 10.1007/s00520-013-1778-7.

60. Kramer M., Heussner P., Herzberg P.Y., Andree H., Hilgendorf I., Leithaeuser M., Junghanss C., Freund M., Wolff D. Validation of the grip test and human activity profile for evaluation of physical performance during the intermediate phase after allogeneic hematopoietic stem cell transplantation. Support. Care Cancer. 2013;21:1121–1129. doi: 10.1007/s00520-012-1634-1.

61. Sayre C.A., Belza B., Shannon Dorcy K., Phelan E., Whitney J.D. Patterns of Hand Grip Strength and Detection of Strength Loss in Patients Undergoing Bone Marrow Transplantation: A Feasibility Study. Oncol. Nurs. Forum. 2017;44:606–614. doi: 10.1188/17.ONF.606-614.

62. Hacker E.D., Mjukian M. Review of attrition and adherence in exercise studies following hematopoietic stem cell transplantation. Eur. J. Oncol. Nurs. 2014;18:175–182. doi: 10.1016/j.ejon.2013.10.013. Epub 2013 Nov 22. Erratum in Eur. J. Oncol. Nurs. 2014, 18, 443.

63. Oberoi S., Robinson P.D., Cataudella D., Culos-Reed S.N., Davis H., Duong N., Gibson F., Götte M., Hinds P., Nijhof S.L., et al. Physical activity reduces fatigue in patients with cancer and hematopoietic stem cell transplant recipients: A systematic

review and meta-analysis of randomized trials. Crit. Rev. Oncol. Hematol. 2018;122:52–59. doi: 10.1016/j.critrevonc.2017.12.011.

64. Dirou S., Chambellan A., Chevallier P., Germaud P., Lamirault G., Gourraud P.A., Perrot B., Delasalle B., Forestier B., Guillaume T., et al. Deconditioning, fatigue and impaired quality of life in long-term survivors after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2018;53:281–290. doi: 10.1038/s41409-017-0057-5.

65. Cella D., Yount S., Rothrock N., Gershon R., Cook K., Reeve B., Ader D., Fries J.F., Bruce B., Rose M. The Patient-Reported Outcomes Measurement Information System (PROMIS): Progress of an NIH Roadmap cooperative group during its first two years. Med. Care. 2007;45((Suppl. 1)):S3–S11. doi: 10.1097/01.mlr.0000258615.42478.55.

66. Karimi M., Brazier J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? Pharmacoeconomics. 2016;34:645–649. doi: 10.1007/s40273-016-0389-9.

67. Van Haren I.E., Timmerman H., Potting C.M., Blijlevens N.M., Staal J.B., Nijhuis-van der Sanden M.W. Physical exercise for patients undergoing hematopoietic stem cell transplantation: Systematic review and meta-analyses of randomized controlled trials. Phys. Ther. 2013;93:514–528. doi: 10.2522/ptj.20120181.

68. Van der Lans M.C.M., Witkamp F.E., Oldenmenger W.H., Broers A.E.C. Five Phases of Recovery and Rehabilitation After Allogeneic Stem Cell Transplantation: A Qualitative Study. Cancer Nurs. 2019;42:50–57. doi: 10.1097/NCC.0000000000000494.

69. Carreras E., Dufour C., Mohty M., Kröger N., editors. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies [Internet] 7th ed. Springer; Cham, Switzerland: 2019.

CHAPTER 3 Delphi Study

This chapter corresponds to the following peer-reviewed publication:

Development of Measurement Guidelines Incorporating a Core Outcome Set (COS) for Studies on Rehabilitative Interventions in Patients with Hematological Malignancies Treated with Allogeneic Stem Cell Transplantation: A Delphi Study

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Conceptualization, A.M., L.M., and P.T.; methodology, A.M. and L.M; software, A.M.; validation, L.M., E.A., A.B., R.E., N.G. and P.T.; formal analysis, A.M.; investigation, A.M.; data curation, A.M.; writing—original draft preparation, A.M. and L.M.; writing—review and editing, A.M., L.M., E.A., A.B., R.E., N.G. and P.T. ; visualization, A.M.; supervision, L.M., E.A., A.B., R.E., N.G. and P.T.; project administration, P.T.; All authors have read and agreed to the published version of the manuscript."

Abstract

Background: Rehabilitation for patients with hematological malignancies undergoing allogeneic hematopoietic stem cell transplantation (AlloHSCT) addresses physical and psychosocial deficits before, during, and after hospitalization. However, marked heterogeneity in study designs, interventions, outcomes, and measurement methods complicates evidence synthesis, resulting in uncertainty regarding optimal treatment prescriptions and clinical implications. In this study, we aimed to develop a standardized measurement guideline for rehabilitative intervention studies in AlloHSCT patients to reduce clinical diversity and improve evidence synthesis. Methods: A scoping review preceded a two-round online Delphi consensus process, and a multidisciplinary Steering Committee oversaw the study. Panelists included corresponding authors from included studies in the scoping review, recent gray literature authors, and health professionals from transplant units worldwide. Invitations were sent to 214 experts, with 24 (11%) participating. Consensus was defined as ≥67% agreement on a five-point Likert scale. Proposals for measurement guideline components (scope (i.e., target population and setting), outcomes, instruments and number and timing of measurements) were evaluated, with panelists providing comments to refine their recommendations. Results: Panelists agreed on defining measurement guidelines for two settings: hospital (during transplant hospitalization) and non-hospital (before or after hospitalization). Consensus was reached on specifying both outcomes and measurement instruments (acceptance rate 79%), as well as on including a minimum number of measurements with specified time points (acceptance rate 88%). For hospital studies, measurements were recommended at “baseline” and “once discharge criteria are met”; in non-hospital studies, measurements were recommended at “baseline,” “last day of pre-rehabilitation,” and “one year after transplantation” (for rehabilitation studies only). “Strength” should be measured via Handgrip Dynamometer and a 30 s Sit-to-Stand test, and “exercise capacity” via the 6 min Walk Test. Conclusions: This Del-phi study generated the first consensus-based measurement guideline for rehabilitative interventions in patients with

hematological malignancies treated with AlloHSCT, specifying outcomes, instruments, and timing for both hospital and non-hospital settings. While the measurement guideline is expected to reduce clinical diversity and facilitate robust meta-analyses, future research should expand its scope to include patient-reported outcomes, ensuring greater relevance to patient priorities and needs.

3.1 Introduction

Rehabilitation for patients with hematological malignancies who undergo allogeneic stem cell transplantation (AlloHSCT) aims to address physical and psychosocial deficits before, during, and after hospitalization. There is evidence supporting the inclusion of AlloHSCT patients in rehabilitation programs, however, further high-quality research is needed to determine optimal exercise prescriptions and to clarify additional implications [1]. As in other areas of oncology, studies investigating rehabilitative interventions for AlloHSCT patients exhibit significant variability with regards to participants, interventions, outcomes, study designs, and sources of bias [2].This variability is the primary source of heterogeneity, which complicates the synthesis of findings in secondary research and limits our ability to draw definitive conclusions about the effects of these interventions.

According to the Cochrane Handbook [3], there are two main sources of heterogeneity among studies included in a systematic review with meta-analysis: clinical diversity and methodological diversity. Clinical diversity refers to variability in participant characteristics, interventions, and outcomes studied, while methodological diversity refers to differences in study designs and risk of bias.

Core Outcome Sets (COSs) can help reduce clinical diversity arising from outcome variability, especially when widely adopted by the scientific community [4]. While COSs clearly identify which outcomes are essential to measure, there remains an opportunity to further support researchers by providing more explicit guidance on how these outcomes should be

assessed in terms of which measurement instruments are most suitable to measure these outcomes, i.e., a measurement set [5]. Supplementing a determined COS and the corresponding measurement set with additional measurement recommendations and consolidating them into measurement guidelines could help address heterogeneous decisions across studies, thereby reducing additional sources of clinical diversity [6].

As an example, if a COS specifies that exercise capacity and fatigue are the minimum outcomes to be measured in studies investigating the effects of exercise in lung cancer patients, clinical diversity could still originate from several sources.

Treatment Phase: Measurements may be taken during different treatment phases (e.g., during chemotherapy, before lobectomy, after lobectomy), which can significantly affect exercise capacity, fatigue, and other patient characteristics.

Study Setting: Measurements may occur in different settings (e.g., hospital vs. rehabilitation center), and the condition of hospitalized patients often differs markedly from that of non-hospitalized patients, influencing study outcomes.

Measurement Instruments: Different tools may be used to assess the same outcome. For instance, leg strength can be measured via isokinetic dynamometry (the gold standard) or via the 30-Second Sit-to-Stand test, which is more feasible but less specific. Even with statistical methods to address this heterogeneity, the underlying constructs measured may not be equivalent, leading to the synthesis of data from different patient attributes.

Timing of Measurement: Even if studies use the same intervention, treatment phase, outcome, and measurement instruments, clinical diversity can still result from differences in measurement time points. Unlike healthy subjects, patients may experience rapid and unpredictable changes due to factors such as surgery, medical interventions, spontaneous recovery or deterioration, and rehabilitation. Standardizing measurement time points relative to key events in the patient journey could help reduce this source of clinical diversity.

Studies examining the impacts of rehabilitative interventions among patients with hematological malignancies treated with allogeneic stem cell transplantation (AlloHSCT) vary considerably, largely due to the factors outlined above.

The aim of this study is to define measurement guidelines, including a COS and a measurement set, for use in studies of rehabilitative interventions in patients with hematological malignancies treated with AlloHSCT by reaching consensus, not only on what to measure (e.g., fatigue or exercise capacity) but also on how (i.e., which outcome measurement instruments) and when (i.e., which time points) to measure these outcomes, thus ad-dressing clinical diversity more efficiently.

In this first study, we have chosen to focus exclusively on clinician-reported and performance-based outcomes. While patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs) are important in the evaluation of rehabilitative interventions, their inclusion would have introduced additional complexity, as well as practical and time-related challenges. By narrowing our scope to clinician-reported and performance-based outcomes at this stage, we aim to establish robust and feasible measurement guidelines, which can serve as a foundation for future research that should expand to include PROs and PROMs.

Although researchers are free to add any further measurements, they deem necessary, the adoption of this measurement guideline as a minimum standard will help minimize research **waste** and facilitate the inclusion of all relevant studies in future reviews and meta-analyses.

3.2 Methods

3.2.1 Preparation of the Delphi Study

Prior to the Delphi study, we conducted a scoping review [7] to map outcomes, out-come measurement instruments, and measurement time points being used in studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with AlloHSCT. The overview obtained in this review was used to make proposals in this Delphi study.

3.2.2 Design of the Delphi Study

A Delphi study is an appropriate design when subject agreement shows methodological or conceptual divergence, or subjects are difficult to study empirically [8].

3.2.3 Steering Committee

The Steering Committee comprised advisory members representing the following disciplines: Nursing Science (A.E., R.E.), Exercise Physiology (P.T.), Hematology (A.B.), Physiotherapy (N.G.), and Methodology (L.M.). The Steering Committee reviewed and approved the study concept, the content of each survey round, the analysis and conclusions of each round, the feedback reports, and the final study reporting. In cases where consensus was not achieved or proposals remained inconclusive after the second round, final decisions were made by the Steering Committee. If panelists provided promising proposals during the second round, these were carefully considered by the Steering Committee in their deliberations. Steering Committee members did not participate as panelists. Their activities were coordinated by the principal investigator (A.M.).

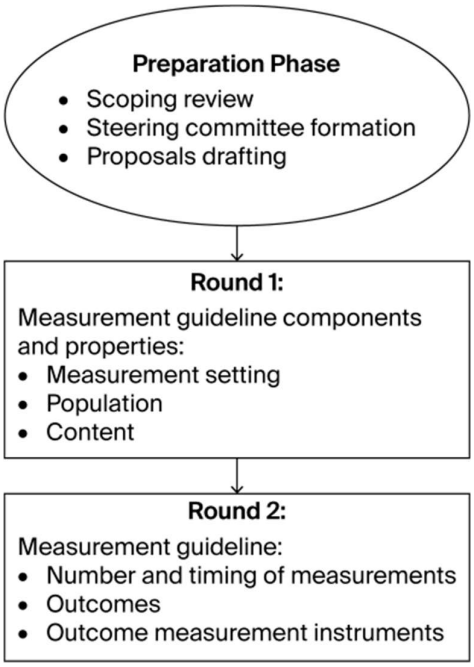
3.2.4 Panelists

We aimed to include persons who were corresponding authors of any of the studies included in the scoping review [7], as well as authors from gray literature concerning rehabilitation for patients with hematological malignancies treated with AlloHSCT. In addition, we invited health professionals working in stem cell transplantation units worldwide. We invited all participants via email, and they received no financial compensation for their participation.

3.2.5 Procedure and Content of the Rounds

This Delphi study consisted of two online survey rounds in which we presented proposals based on the results of the scoping review [7] (**Figure 2).**

Figure 2. *Delphi Study procedure and content of each round*



In each round, we asked panelists to rate their agreement with each proposal. Agreement was rated on a five-point Likert scale (i.e., strongly disagree to strongly agree, with 'no opinion' in the middle). In addition, a response option 'no expertise' was added to each question.

Panelists were asked to provide reasons for their ratings, which allowed for a more nuanced interpretation of their views and facilitated the iterative improvement of proposals. Promising participant suggestions from the first round were used to improve proposals in the next round even if consensus had been reached.

3.2.6 Content of Round 1

In round 1, we aimed to reach consensus on both the scope and the components of the measurement guideline. Regarding the scope, we elaborated on the target population and the measurement setting. For the components, we discussed the outcomes, outcome measurement instruments, and the number and timing of measurements.

3.2.7 Content of Round 2

In round 2, we aimed to reach consensus on the content of each included component of the measurement guideline for studies on rehabilitative interventions in patients with hematological malignancies treated with AlloHSCT.

3.2.8 Analysis

Consensus was reached when at least 67% of the panelists agreed or strongly agreed with a proposal. If less than 67% agreement was reached on a proposal, the proposal was rejected after final agreement of the Steering Committee. If a panelist rated ‘no expertise’, the panelist was not considered in the calculation of agreement for that proposal.

A.M. read all arguments and compiled the summary of them; all arguments were provided in the feedback reports and sent to all panelists and Steering Committee members.We used SurveyMonkey (SurveyMonkey Inc., San Mateo, CA, USA) to create and disseminate the

survey. All responses were analyzed anonymously and included in a separate feedback report per round.

3.3 Results

3.3.1 Panelists

We invited 214 panelists to participate in rounds 1 and 2. While we controlled the list of invited experts (n = 214), we could not identify who among them chose to participate. The survey link was distributed through a bulk invitation, and all responses were recorded anonymously. Consequently, it was not possible to collect or report participants' demographic information in the results section. In both rounds, 24 panelists (11%) responded.

3.3.2 Scope of the Measurement Guidelines

3.3.2.1 Target Population

In round 1, a majority of panelists did not support our proposal to restrict the measurement guidelines to patients treated with allogeneic HSCT (AlloHSCT) only; specifically, only 52% agreed or strongly agreed with this restriction; this lack of consensus likely reflects the common practice in rehabilitation research after HSCT to include both allogeneic and autologous HSCT patients. In their comments, panelists argued with the following comments that both populations should be considered (see also **Table 4**, proposal 3):

1. *"I would prefer a measurement set which whenever possible encompass both patients treated with allogeneic and autologous stem cell transplantation. Irrelevant questions for one of the groups could just be left out depending on the study population."*
2. *"I guess there can be parts that are also useful for autologous transplant."*

3. *"Maybe first allo to develop. But in practice, I notice that autologous HSCT patients and their family sometimes have a harder time than allogeneic HSCT patients to get their lives back to a new normal."*
4. *"Depends on your goal. How diverse do you want the measurement set to be? How generic/specific should it be possible to apply it?"*

Therefore, the scope of these measurement guidelines includes studies involving patients treated with autologous HSCT.

Table 4. *Delphi Study Round 1 participant responses.*

Proposals and Agreement Rate	Participant Comments
Proposal 1 (Agreement 91%) The Measurement Set we intend to develop should define the number of measurements during a study and the time points of measurements as well.	1. I find it realy hard to answer this question because the wording rehabilitation is very broad and so do rehabilitative interventions. The set of measurments strongly depends on the intervention in studies and there for I guess only a core set with intervention specific submodules can be developed 2. I do prefer to recommend a number of measurements instead of "define the number of measurements. The number of measurements may depend on the single project, the purpose, and circumstances. 3. Beside the measurement instruments the rehabilitation intervention should be described in detail: only describing the intervention as exercises is not transparant enough to determine the efecctiveness. Moreover also the adherence to the intervention should be part of the publication. In my opinion in this frail patient group it seems to be most adequate if the intervention is not standardised but fitts the physical and mental condition of the patient (so the decison protocol is standardised to fitt the load of the intervention to the physical and mental level of the patient) and is goal-oriented.
Proposal 2 (Agreement 79%) The Measurement Set we intend to develop should not include only the minimum number of common "outcomes" that should be measured in future studies. The "outcome measurement instruments" should be included as well whenever this is possible.	1. given the restrictions above 2. I would prefer to do so, however especially valid patient reported outcome measurements (PROM's) are not always available in the mother tongue of the research environment. Moreover, simple translations are not adequate in case of cultural differences between different countries. 3. Minimum dataset it crucial but an additional toolbox depending on the question would be helpful as well
Proposal 3 (Agreement 52%) The Measurement Set we intend to develop should apply only for patients with haematological malignancies treated with "allogeneic" stem cell	1. I would prefer a measurement set which whenever possible encompass both patients treated with allogeneic and autologous stem cell transplantation. Irrelevant questions for one of the groups could just be left out depending on the study population.

transplantation (both reduced intensity conditioning and myeloablative). This measurement set is not appropriate for patients treated with autologous stem cell transplantation due to different medical treatment, iatrogenic clinical manifestations and timing of procedures.	2. A participatory research approach would be very helpful to reflect the patient voice 3. Ultimately I do believe that rehabilitative interventions would benefit patients undergoing autologous transplantation and cellular therapies also. Candidates for these therapies are often older with frailty. It appears that the scope of your project is to study only allogeneic patients initially. I agree that this group is more homogenous and factors such as cardiovascular and other effects of immunosuppression/steroids can be considered. 4. I guess there can be parts that are also useful for autologous transplant 5. Maybe first allo to develop. But in practice, I notice that autologous HSCT patients and their family sometimes have a harder time than allogeneic HSCT patients to get their lives back to a new normal 6. Depends on your goal. How diverse do you you want the measurement set to be? How generic/specific should it be possible to apply it? 7. This statement is not valid I think: of course there is influence of the medical treatment and clinical manifestations and yes there is influence on the timing of the measurements, but when the same set is chosen and at least most of the measurements can be timed at the same time points the difference in recovery trajectories becomes transparant.
Proposal 4 (Agreement 67%) This Delphi Study should deliver two different Measurement Sets. One for studies during hospitalisation for stem cell transplantation and one adjusted for non-hospital settings.	1. this distinction is absolutely necessary and correct 2. I favour a single measurement set with parameters that can be serially assessed over time so that changes in individual patient functionality can be assessed across the pre-tranpslant/in-patient/post-transplant outpatient journey and comparisons/contrasts between patients can also be performed. 3. What would “non-hospital settings” be? Would “hospital settings” consider both inpatient stay and outpatient follow up? 4. One for all 5. rehabilitation starts already before en during the hospitalization 6. The measurement set should work regardless of patients being treated either hospitalized or in a out-patient setting. 7. Depends on your goal. How diverse do you you want the measurement set to be? How generic/specific should it be possible to apply it? 8. I prefer that the Measurement sets are adapted to each other to facilitate longitudinal research designs. Each patient will go from the hospital to the non-hospital setting (or back again). We need more longitudinal studies and data sampling in clinical practice to be able to include as much as patients and to avoid drop-outs in the randomisation process. 9. That depends on the set of measurements.

3.3.2.2 Clinical Setting

In round 1, we reached consensus on considering two different settings to define measurement sets (agreement 67%) in studies that investigate the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic stem cell transplantation. “Hospital setting” refers to studies being conducted during hospitalization for stem cell transplantation, and “non-hospital setting” refers to studies being conducted before or after hospitalization for stem cell transplantation, regardless of whether they are inpatient or outpatient settings.

3.3.3 Components of a Measurement Guideline

In round 1, consensus was reached that the key components of a measurement guideline are as follows: outcomes to be measured and their measurement instruments (agreement: 79%), as well as the number and timing of measurements (agreement: 91%).

In round 2, the panel specified that “Strength” (agreement: 87%) should be measured using both the Handgrip Dynamometer (agreement: 74%) and the 30-Second Sit-to-Stand Test (agreement: 83%). The latter replaced the initially proposed 5-Times Sit-to-Stand Test due to the following relevant participant comments (see also **Table 5**, proposal 11):

- *“We have found it easier to measure a 30 second sit to stand.”*
- *“Or 30 time sit to stand.”*
- *“Either 5 times sit to stand or 30 second sit to stand test, they both appear to be used in this population, so perhaps the measure that can be more validly measured using telehealth would be best.”*
- *“30 second sit to stand.”*
- *“Exercise Capacity” (agreement: 96%) should be measured using the 6-Minute Walk Test (agreement: 75%).*

For timing, consensus was reached on “baseline” and “once discharge criteria are met” as relevant time points, replacing “on admission” (agreement: 79%) and “at discharge” (agreement: 75%) due to the following relevant participant comments (see also **Table 5**, proposals 1 and 3):

3.3.3.1 Comments for Proposal 1

“Very important timepoint if this is the baseline assessment. Less but still important if the patient has been pre-assessed in the outpatient setting for prehabilitation or assessed at the final pretransplant review.”

“This is the best baseline timing for measurement.”

“I prefer the expression “Baseline” (defined as the starting point before HSCT and or the intervention) and fixed time points during follow-up, e.g., 3-month and 6-month follow-up. During the course of treatment, the number of “admissions” may vary quite a lot between patients.”

3.3.3.2 Comments for Proposal 3

“I can’t entirely agree with the deadline set “at discharge” because discharge is extremely variable from one patient to another, perhaps reassessing every one or two weeks could establish a pattern.”

“Timepoint shortly before discharge-day of discharge is often very busy for patients.”

The proposed time point “day +10” was rejected (agreement: 45%).

Additionally, “baseline” (agreement: 79%), “last day of pre-rehabilitation”, and “one year after transplantation” (agreement: 75%) were agreed upon as relevant time points based on

participant comments and Steering Committee approval, with the latter applicable only to rehabilitation studies.

Table 5. *Delphi Study Round 2 participant responses*

Proposals and Agreement Rate	Participant Comments
Proposal 1 (Agreement 79%) In the first round of our study, 87.5% of the participants agreed that we should recommend a minimum of fixed time-points for measurements in studies including patients treated with allogeneic stem cell transplantation. We are now referring to studies during hospitalization. To what extend do you agree with the fixed time-point "on admission"? Please rate your agreement on a scale from 1 to 5.	1. Very important timepoint if this is the baseline assessment. Less but still important if the patient has been pre-assessed in the out-patient setting for pre-habilitation or assessed at the final pre-transplant review. 2. This is the best baseline timing for measurement 3. I prefer the expression "Baseline" (defined as the starting point before HSCT and or the intervention) and fixed time points during follow-up, e.g., 3-month and 6-month follow-up. During the course of treatment, the number of "admissions" may vary quite a lot between patients. 4. Lot of appointments at day of admission. Rather day +2
Proposal 2 (Agreement 45%) During hospitalization measurements should be performed at day +10 after the transplantation. In this time—point severe cytopenia is often present, at least for patients treated with myeloablative conditioning. Symptom severity might have reached its peak in this time—point. To what extend do you agree with the fixed time-point "day +10"? Please rate your agreement on a scale from 1 to 5.	1. Not much which can be done at that time and physiotherapy should be performed anyway 2. I think patients will be limited in their capacity to do anything at this time. Usually cytopenic/infected/hooked up to drip stand for immunosuppression/TPN/opiate analgesia. 3. It depends what you are measuring and whether they are sensitive to confounding factors. For example, physical measures taken when the patient is experiencing severe cytopenia may score very poorly or reach a floor effect however this may be due to symptoms such as fatigue and nausea whilst not necessarily representing physical performance. 4. It's a good timepoint. In my practical experience, the time when patients with an allogeneic HSCT are at their worst is day 7, when many start to have a fever. 5. At day +10 the symptom severity peak is expected. Only patients participating in a study where the severity of symptoms at that time point are relevant for the specific research project should be bothered to answer questionnaires. 6. it would yield sub optimal results on majority of patients suffering from acute toxicities from conditioning. 7. Fixed time-point as day +10 with a possible variance of ±3 days?
Proposal 3 (Agreement 75%) During hospitalization measurements should be performed at discharge. In this time-point oral administration of immunosuppression has been achieved and intravenous lines can be removed for the purpose of the measurements. To what extend do you agree with the fixed time-point "at discharge"? Please	1. At that time it makes sense to assess the patient to make plans for outpatient care 2. I think this is the most important timepoint to maximize early rehab potential. 3. I can't entirely agree with the deadline set "at discharge" because discharge is extremely variable from one patient to another, perhaps reassessing every one or two weeks could establish a pattern. 4. I prefer the expression "Baseline" (defined as the starting point before HSCT and or the intervention) and fixed time points during follow-up, e.g., 3-month and 6-

rate your agreement on a scale from 1 to 5.	month follow-up. During the course of treatment, the number of and length of “admissions” may vary quite a lot between patients. 5. Timepoint shortly before discharge—day of discharge is often very busy for patients 6. Discharge is variable based on the patient. Consider a standard time point like D+21 instead. 7. i think you need to explain what/when you can respons with N/A. it is not the same as ‘no expertise’, like so expertise to answer this specific question. in that case, the respondent is not taken into account for calculating the % concensus for this question. But, if some answers ‘NA’, not applicable, why would it not be applicable, and how is it different from strongly disagree with a proposal? is this clear enough for panelists? will this response still be taken into account when calculating the % consensus
Proposal 4 (Agreement 58%) During hospitalization, in the time-point 2 (day +10 post HSCT) performance-based tests might be too strenuous or even impossible for some of these patients. Therefore, only clinician-observed outcomes or patient reported outcomes should be measured. Please rate your agreement with this statement on a scale from 1 to 5.	1. I would still consider watching the performance. Patients’ subjective and objective assessments are often not congruent. 2. think there should be some attempt at performance based measurement 3. As indicated above, rather add flexible timepoint 4. Some performance tests can be performed safely—but might need something like gait speed that is simpler t perform.
Proposal 5 (Agreement 79%) In the previous round of our study, 66.67% of the participant agreed that we should recommend two measurement sets. One for studies in hospital setting and one for studies in outpatient setting. We are now referring to studies in outpatient setting. In outpatient setting studies (rehabilitation and prehabilitation studies) measurements should be performed “on admission”. Please rate your agreement with this proposal on a scale from 1 to 5.	1. Was bedeutet “admission” im outpatient setting? Die Patienten sind ja nur ambulant an diesem Tag da. 2. Wording here is unclear—I am assuming this means ‘on admission’ here means first presentation to the outpatient service 3. 4 4. It is possible to do measurements at the counselling or pre-admission appointment in outpatient setting 5. I prefer the expression “Baseline” (defined as the starting point before HSCT and or the intervention) and fixed time points during follow-up, e.g., 3-month and 6-month follow-up. During the course of treatment, the number of “admissions” may vary quite a lot between patients in an outpaint setting. 6. I think this measurement should be done @ pre admission consultation, and on/during admission 7. can you add more lay-out? for example, indicate the proposal in bold.
Proposal 6 (Agreement 71%) In outpatient setting studies (rehabilitation and prehabilitation studies) measurements should be performed at discharge.	1. Siehe Anmerkung oben 2. depending on the therapy setting 3. As above—does this mean on discharge from the outpatient service… i.e., end of follow-up (perhaps transition to a survivorship clinic). 4. As I have argued above I prefer fixed and defined time points related to days, months, or years since HSCT. 5. see previous comment
Proposal 7 (Agreement 75%) In outpatient setting studies measurements should be performed one year after discharge (only for rehabilitative	1. Also possibility at 100 days post transplant 2. One year would be ideal, however may not be realistic and may have many lost to follow up. 3. One year follow-up may be relevant in prehabilitative studies too. A time point defined as one year after patients

interventions studies—not for prehabilitative).	received the stem cells is more in line with the general recommendation for control visits and follow-up after HSCT. It is definitely a better choice if the results in new studies should be compared with former results from other studies. 4. consider 6 months. 1 year is long follow-up 5. this may be a bit confusing: first it is for both rehabilitation and prehabilitation studies, and next in in not for prehabilitative studies… i would formulate this differently. perhaps avoid the term 'outpatient setting': e.g., only for rehabilitative interverion studies, measurements should …
Proposal 8 (Agreement 87%) The outcome "strength" should be measured in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.	1. 5 2. I'm very uncertain about what you mean or how you define "strength"? If you mean physical strength, when it is still very uncertain what kind of physical strength. Cardiorespiratory? Muscle strength? Or, is it related to health related quality of life? or do you include all? I would say yes to measuring all mentioned above.
Proposal 9 (Agreement 96%) The outcome "exercise capacity" should be measured in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.	1. 5 2. I agree, if you define "Exercise capacity" as the maximum amount of physical exertion that a patient can sustain.
Proposal 10 (Agreement 74%) In the previous round of our study, 79.16% of the participants agreed that we should recommend not only outcomes that should be measured but also the measurement instruments with which they should be measured. We intend to suggest the measurement of the outcome "strength" by two measurement instruments: The "Hand held dynamometer" and the "5 times sit to stand test". Please rate your agreement with the following proposal on a scale from 1 to 5: The outcome strength should be measured with the measurement instrument "hand held dynamometer" in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.	1. There are no comparative values to classify the hand strength Alternatively, a bioimpedant analysis could be used 2. It can be masured by other ways but hand grip dynamometer is one of them, gait speed, or others 3. not currently measured in my service 4. evidence base weaker
Proposal 11 (Agreement 83%) The outcome strength should be measured with the measurement	1. We have found it easier to measure a 30 s sit to stand. 2. Is another way to measure this but I agree is a valid one. 5 3. Or 30 time sit to stand

instrument “5 times sit to stand test” in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.	4. Either 5 times sit to stand or 30 s sit to stand test, they both appear to be used in this population, so perhaps the measure that can be more validly measured using telehealth would be best. 5. 30 s sit to stand
Proposal 12 (Agreement 75%) The outcome “exercise capacity” should be measured with the measurement instrument “6 min walk test” in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.	1. Yes but only for impaired patients 2. This is an easy maesurement and can be done in any setting and is also recommended and valid. 5 3. The gold standard is the cardiorespiratory capacity test, but this test is difficult to choose as a mandatory part of the test battery as it is ressource comsuming (time and equipment). I am uncertain about the 6-min walk test’s sensibility to detect differences and its applicability related to the target audience (patients treated with HSCT).

3.3.4 Measurement Guidelines

Table 6 and **Table 7** illustrate the measurement recommendations for studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with AlloHSCT.

Table 6. *Delphi Study Measurement guidelines for studies in hospital settings*.

Recommended Outcome	Recommended Outcome Measurement Instrument	Recommended Time Points
Strength	• Handgrip Dynamometer • 30-Second Sit-to-Stand	1. Baseline 2. Once discharge criteria are met
Exercise Capacity	• 6-Minute Walk Test	1. Baseline 2. Once discharge criteria are met

Table 7. *Delphi Study Measurement guidelines for studies in non-hospital settings.*

Recommended Outcome	Recommended Outcome Measurement Instrument	Recommended Time Points
Strength	• Handgrip Dynamometer • 30 s Sit-to-Stand	1. Baseline 2. Last day of pre-rehabilitation 3. One year after transplantation
Exercise Capacity	• 6 min Walk Test	1. Baseline 2. Last day of pre-rehabilitation 3. One year after transplantation

3.4 Discussion

Through this study, we provide measurement guidelines for clinical trials investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with AlloHSCT and/or autologous HSCT in hospital and non-hospital settings. To our knowledge, this is the first study to develop either a COS or measurement guidelines using the Delphi process in this field.

Core Outcome Sets (COSs) and measurement sets in cancer research are predominantly disease-specific [9]; notably, a major effort in the field of hematological malignancies did not consider patients who have undergone allogeneic hematopoietic stem cell transplantation (AlloHSCT) [10], although AlloHSCT recipients represent a unique and clinically distinct population within hematological malignancies, since the post-transplant course, complications such as graft-versus-host disease, and long-term outcomes in AlloHSCT patients differ substantially from those in other patient groups.

In the field of oncology rehabilitation, the development of a COS for lung cancer patients is currently in progress [11]; in this ongoing work [10], similar to in the present study, researchers aim to define the outcome measurement instruments (OMIs) that should be used by clinical trialists in addition to the outcomes. Despite explicit recommendations for the selection of OMIs in/after COS development [6], this step is frequently neglected in new studies [12].

One of the strengths of this study is its comprehensive approach to addressing sources of clinical diversity. The measurement guidelines recommend not only what and how to measure but also specify when and in which clinical setting (i.e., hospital or non-hospital) to do so, thereby directly addressing major sources of heterogeneity in clinical research; therefore, we introduce a new term: “measurement guideline.” By considering heterogeneity in this manner, the study not only enhances the reliability of meta-analytic results but also facilitates the use of weighted mean difference (WMD) rather than standardized mean difference (SMD). Pooling results using WMD allows outcomes to be ex-pressed in clinical units, making findings directly interpretable and clinically meaningful for health professionals [13].

Another strength of this study is that the recommendations were informed by an ex-tensive scoping review [7], conducted during the preparatory phase to provide a comprehensive overview of outcomes, relevant measurement instruments, and their timing.

Furthermore, we considered the panelists’ arguments by giving them the opportunity to comment and express the reasoning for their responses, rather than simply rating their degree of agreement with each proposal; this approach enabled us to gain a deeper under-standing of their perspectives, which we then used to refine our proposals and inform our conclusions.

Despite its strengths, this study is not without limitations. A notable limitation of this Delphi study is the low response rate among invited panelists. Low participation can threaten the validity and representativeness of the results, as it may introduce selection bias and reduce

the diversity of expert perspectives [14,15]. De-spite efforts to recruit a broad and knowledgeable panel, the limited number of respond-ents may have affected the generalizability of the consensus reached. Furthermore, due to the anonymity of the process, we cannot determine the demographic composition of the participants in terms of academic or professional background. Nevertheless, by inviting only individuals with proven academic activity (i.e., corresponding authors of published RCTs) or established clinical expertise (clinical experts from transplantation units), we ensured that the responses were provided by a highly qualified group of professionals.

Although published and widely accepted recommendations advocate for the inclusion of people with lived experience as key stakeholders in the development of measurement sets [16], we chose not to involve them in this study, a decision which was primarily made due to practical constraints, including limited time and resources, as well as the challenges of providing adequate support and debriefing for this vulnerable population. As this was the first study of its type in this patient group, careful expectancy management and sufficient participant support were essential considerations that our team was not fully equipped to address. Consequently, the necessary level of engagement and support for people with lived experience could not be ensured, and we acknowledge this as a significant limitation of the measurement guidelines; this exclusion also meant that we were unable to meaningfully define and incorporate patient-reported outcomes (PROs) in the measurement guidelines. Since patients are essential to identifying outcomes that matter most to them, particularly life impact outcomes within core outcome sets (COSs) [17], which are typically captured using patient-reported outcome measures (PROMs) [18], the absence of their input may have resulted in a measurement guideline that does not fully reflect patient priorities.

Future research in this area should prioritize the meaningful involvement of people with lived experience, where feasible and appropriate. Although we believe that using this measurement guideline in its current form can help reduce heterogeneity in clinical re-search, expanding it to include patient-reported outcomes (PROs) and patient-reported outcome

measures (PROMs) would further enhance its value. Such an expansion should be grounded not only in patient inclusivity, but also in meaningful patient engagement, ensuring that the selected outcomes are both relevant and important to patients [19]. Finally, the fact that the two guidelines we developed refer to different settings (hospital vs. non-hospital) offers the opportunity to define more relevant PROs and PROMs for each context, as lived experience can vary significantly between these settings.

3.5 Conclusions

The results of this study advance the field of rehabilitation research for patients with hematological malignancies undergoing allogeneic hematopoietic stem cell transplantation (AlloHSCT) by offering the first Delphi-based consensus recommendations for standardized measurement guidelines in this specific population. While the development of Core Outcome Sets (COSs) is well-established in cancer research, in our work, we uniquely address the neglected area of AlloHSCT and provides detailed guidance not only on what outcomes to measure, but also on how, when, and in which settings to measure them, thereby directly tackling major sources of clinical diversity and heterogeneity that have previously complicated the synthesis of research findings. The proposals we conducted in the Delphi study were informed by an extensive scoping review and enriched by insights from expert panelists, whose comments were integral to refining our proposals. However, our deliberate exclusion of patients from the consensus process introduces important limitations, most notably the inability to meaningfully incorporate patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs), which are crucial for capturing life impact outcomes and ensuring that research priorities align with patient needs. Looking ahead, future research should prioritize meaningful patient engagement to expand the measurement guidelines with relevant PROs and PROMs, using qualitative methods to identify and organize patient needs before further consensus-building efforts. Ultimately, while the current measurement guidelines promise to reduce heterogeneity and facilitate robust meta-analyses, their ongoing

refinement through inclusive, patient-centered re-search will be essential to maximize their clinical relevance and value.

3.6 References

1. Persoon, S.; Kersten, M.J.; van der Weiden, K.; Buffart, L.M.; Nollet, F.; Brug, J.; Chinapaw, M.J. Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: A systematic review and meta-analysis. Cancer Treat. Rev. 2013, 39, 682–690. https://doi.org/10.1016/j.ctrv.2013.01.001. PMID: 23485478.

2. Hirsch, B.R.; Califf, R.M.; Cheng, S.K.; Tasneem, A.; Horton, J.; Chiswell, K.; Schulman, K.A.; Dilts, D.M.; Abernethy, A.P. Characteristics of oncology clinical trials: Insights from a systematic analysis of ClinicalTrials.gov. JAMA Intern. Med. 2013, 173, 972–979. https://doi.org/10.1001/jamainternmed.2013.627; Erratum in JAMA Intern. Med. 2013, 173, 1560. PMID: 23699837.

3. Higgins, J.P.T.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.J.; Welch, V.A. (Eds.) Cochrane Handbook for Systematic Reviews of Interventions (Version 6.3, Updated February 2022). Cochrane. Available online: https://training.cochrane.org/handbook/current (accessed on 20 May 2025).

4. Bellucci, C.; Hughes, K.; Toomey, E.; Williamson, P.R.; Matvienko-Sikar, K. A survey of knowledge, perceptions and use of core outcome sets among clinical trialists. Trials 2021, 22, 937. https://doi.org/10.1186/s13063-021-05891-5. PMID: 34924001; PMCID: PMC8684586.

5. Williamson, P.R.; de Ávila Oliveira, R.; Clarke, M.; Gorst, S.L.; Hughes, K.; Kirkham, J.J.; Li, T.; Saldanha, I.J.; Schmitt, J. Assessing the relevance and uptake of core

outcome sets (an agreed minimum collection of outcomes to measure in re-search studies) in Cochrane systematic reviews: A review. BMJ Open 2020, 10, e036562. https://doi.org/10.1136/bmjopen-2019-036562.

6. Prinsen, C.A.; Vohra, S.; Rose, M.R.; Boers, M.; Tugwell, P.; Clarke, M.; Williamson, P.R.; Terwee, C.B. Guideline for Selecting Outcome Measurement Instruments for Outcomes Included in a Core Outcome Set; COSMIN Initiative: Amsterdam, The Nether-lands, 2018. Available online: https://www.cosmin.nl/wp-content/uploads/COSMIN-guideline-selecting-outcome-measurement-COS.pdf (accessed on 20 May 2025).

7. Manettas, A.I.; Tsaklis, P.; Kohlbrenner, D.; Mokkink, L.B. A Scoping Review on Outcomes and Outcome Measurement In-struments in Rehabilitative Interventions for Patients with Haematological Malignancies Treated with Allogeneic Stem Cell Transplantation. Curr. Oncol. 2022, 29, 4998–5025. https://doi.org/10.3390/curroncol29070397. PMID: 35877257; PMCID: PMC9322392.

8. Niederberger, M.; Schifano, J.; Deckert, S.; Hirt, J.; Homberg, A.; Köberich, S.; Kuhn, R.; Rommel, A.; Sonnberger, M.; DEWISS Network. Delphi studies in social and health sciences-Recommendations for an interdisciplinary standardized re-porting (DELPHISTAR). Results of a Delphi study. PLoS ONE 2024, 19, e0304651. https://doi.org/10.1371/journal.pone.0304651. PMID: 39186713; PMCID: PMC11346927.

9. Ramsey, I.; Eckert, M.; Hutchinson, A.D.; Marker, J.; Corsini, N. Core outcome sets in cancer and their approaches to identi-fying and selecting patient-reported outcome measures: A systematic review. J. Patient Rep. Outcomes 2020, 4, 77.

https://doi.org/10.1186/s41687-020-00244-3. PMID: 32930891; PMCID: PMC7492323.

10. Lang, K.; Bereczky, T.; Geissler, J.; Bolanos, N.; Morgan, K.; Plate, A.; Vallejo, A.; Wintrich, S.; York, N.; Loffelhardt, P.; et al. Updated Pan-Stakeholder Core Outcome Set (COS) Definition for Hematological Malignancies in the framework of the EU project HARMONY Healthcare Alliance for Resourceful Medicine Offensive against Neoplasms in Hematology. HARMO-NY Alliance. Available online: https://www.harmony-alliance.eu/delphi-projects (20 May 2025).

11. Edbrooke, L.; Granger, C.L.; Francis, J.J.; John, T.; Kaadan, N.; Halloran, E.; Connolly, B.; Denehy, L. Rehabilitation out-comes for people with lung cancer (UNITE): Protocol for the development of a core outcome set. BMJ Open Respir. Res. 2023, 10, e001571. https://doi.org/10.1136/bmjresp-2022-001571. PMID: 37336620; PMCID: PMC10347493.

12. Connolly, B.A.; Barclay, M.; Davies, C.; Hart, N.; Pattison, N.; Sturmey, G.; Williamson, P.R.; Needham, D.M.; Denehy, L.; Blackwood, B. Development of a Core Outcome Set for Physical Rehabilitation in Critically Ill Adults: An International Consensus Study (PRACTICE). Ann. Am. Thorac. Soc. 2024, advance online publication. https://doi.org/10.1513/AnnalsATS.202406-581OC.

13. Andrade, C. Mean difference, standardized mean difference (SMD) and their use in meta-analysis: As simple as it gets. J. Clin. Psychiatry 2020, 81, 20f13681. https://doi.org/10.4088/JCP.20f13681.

14. Veugelers, R.; Gaakeer, M.I.; Patka, P.; Huijsman, R. Improving design choices in Delphi studies in medicine: The case of an exemplary physician multi-round panel

study with 100% response. BMC Med. Res. Methodol. 2020, 20, 156. https://doi.org/10.1186/s12874-020-01029-4. PMID: 32539717; PMCID: PMC7294633.

15. Nasa, P.; Jain, R.; Juneja, D. Delphi methodology in healthcare research: How to decide its appropriateness. World J. Methodol. 2021, 11, 116–129. https://doi.org/10.5662/wjm.v11.i4.116. PMID: 34322364; PMCID: PMC8299905.

16. Kirkham, J.J.; Davis, K.; Altman, D.G.; Blazeby, J.M.; Clarke, M.; Tunis, S.; Williamson, P.R. Core outcome Set-STAndards for development: The COS-STAD recommendations. PLoS Med. 2017, 14, e1002447. https://doi.org/10.1371/journal.pmed.1002447.
17. Dodd, S.; Clarke, M.; Becker, L.; Mavergames, C.; Fish, R.; Williamson, P.R. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. J. Clin. Epidemiol. 2018, 96, 84–92.

18. Barrington, H.; Young, B.; Williamson, P.R. Patient participation in Delphi surveys to develop core outcome sets: Systematic review. BMJ Open 2021, 11, e051066. https://doi.org/10.1136/bmjopen-2021-051066. PMID: 34475183; PMCID: PMC8413947.

19. Campbell, R.; Ju, A.; King, M.T.; Rutherford, C. Perceived benefits and limitations of using patient-reported outcome measures in clinical practice with individual patients: A systematic review of qualitative studies. Qual. Life Res. 2022, 31, 1597–1620. https://doi.org/10.1007/s11136-021-03003-z. PMID: 34580822.

Chapter 4 : Discussion and Conclusions

4.1 Core Outcome Set & Measurement Guideline

This dissertation advances the field of research in oncology rehabilitation by delivering a clinical core outcome set (COS) and accompanying measurement guidelines tailored to patients with hematological malignancies undergoing AlloHSCT. This population represents a distinct clinical group, burdened by unique complications such as GvHD, prolonged immunosuppression, corticosteroid-induced muscle weakness, fluctuations in nutritional status, and decreased physical vitality. These manifestations transcend underlying malignancy type, thereby justifying the focus of this research on defining standardized outcomes and measurement instruments for this subgroup.

What distinguishes this work from other COS is its comprehensive approach to the challenge of heterogeneity in clinical research. Instead of merely developing a COS, which is already recognized as a means to reduce outcome-reporting bias and facilitate comparability, this dissertation examined and addressed the entire spectrum of heterogeneity encountered in studies involving this population, including clinical, methodological, and consequently statistical heterogeneity.

A systematic scoping review was conducted to accurately map and identify the sources of heterogeneity, revealing that clinical heterogeneity, particularly variations in patient condition, interventions, study settings and outcome definitions, is the predominant issue in this field, accompanied by methodological heterogeneity due to variations in outcome measurements instruments and study methods. Building upon these findings, a Delphi study

was performed, which further elaborated and dissected these sources by engaging expert stakeholders and synthesizing their perspectives.

As a result, this dissertation delivers not only a core outcome set but also incorporates it within a detailed measurement guideline. The guideline we developed provides explicit recommendations regarding which outcomes should be measured, how those outcomes should be measured and when the measurements should be performed. Moreover, the guideline provides recommendation regarding the clinical settings in which the measurements should be conducted, such as inpatient or outpatient, thus supporting improved evidence synthesis, trial design, and clinical interpretation in rehabilitative research for AlloHSCT patients.

4.2 Measurement Guideline Implementation

A key contribution of this dissertation is the introduction and detailed development of a measurement guideline that supplements the clinical COS by specifying not only that the clinical outcomes strength and exercise capacity should be measured, but also how and when these measurements should be performed. Specifically, the guideline recommends assessing strength using a hand-grip dynamometer and a 30-Second Sit-to-Stand test, and exercise capacity using the 6-Minute Walk Test. These assessments should be conducted at baseline and once discharge criteria are met in hospital settings, as well as at baseline, at the last day of pre- or rehabilitation, and one year after transplantation in non-hospital settings. The scoping review conducted as part of this work revealed considerable inconsistency in both the instruments used and the timing of outcome measurements across studies. For example, muscle strength, a prevalent and clinically meaningful outcome, was measured by 6 different measurement instruments using 8 different outcome names, which complicates meta-analysis and evidence synthesis. The measurement guideline therefore recommends the use of high-quality instruments validated for the population of interest, recognizing that measurement

properties can vary by setting and clinical phase. Furthermore, it emphasizes that the timing of outcome measurement should correspond to recognized phases in the AlloHSCT trajectory, thereby reducing bias attributable to patient fluctuations in health status. The measurement guidelines also differentiate between hospital and non-hospital setting to account for practicability and patient needs in outcome monitoring.

The adoption of such a measurement guideline has the potential to enhance evidence synthesis in two main directions. First, by standardizing key aspects of outcome measurement, particularly the choice of outcome used and the setting across trials (hospital vs non-hospital), the guideline promotes greater clinical and methodological homogeneity among included studies. This increased homogeneity improves the appropriateness of conducting meta-analyses using fixed effect models, rather than defaulting to random effects models that are typically required when study populations and methodologies vary substantially. Fixed effect models, when justified, tend to yield more precise and interpretable estimates, further increasing the reliability of synthesized evidence.

Second, standardizing measurement tools across studies ensures consistent scales and units, increasing the number of studies reporting all outcomes. This reduces reporting bias by encouraging the publication of all results, even those that are less significant or unexpected. This, in turn, increases the feasibility of synthesizing results using weighted mean differences (WMD) instead of standardized mean differences (SMD). Meta-analyses that use WMDs enhance clinical interpretability, as findings are expressed in familiar, clinically meaningful units rather than as abstract statistical metrics. This facilitates the translation of research findings into clinical practice, bridging the gap between research and patient care.

In summary, measurement guidelines constructed in this manner facilitate robust, clinically relevant evidence synthesis, ultimately supporting more informed decision-making in clinical settings.

An important step towards implementing this measurement guideline is its inclusion in the COMET Database. This internationally recognized resource provides researchers planning clinical trials with guidance on selecting and reporting core outcome sets (COS) through a user-friendly search function. To support broad implementation, the clinical COS should be registered in the COMET Database to enhance its discoverability. In addition, dissemination should be strengthened through presentations at national and international conferences, publication in peer-reviewed journals, and targeted communication with researchers registering new clinical trials in relevant databases. Such proactive dissemination strategies are expected to facilitate adoption and integration of the measurement guideline in future clinical research.

4.3 Limitations

Despite its strengths, this study is constrained by two principal limitations. First, patient participation was not incorporated into the Delphi consensus process. Although current standards increasingly recommend engaging individuals with lived experience in core outcome set development, this research focused on creating a "clinical" COS, with consensus reached solely among professional stakeholders due to practical barriers such as limited resources and the need for specialized support for patient involvement. Consequently, patient-reported outcomes and measures were not prioritized, which may restrict the COS's representation of issues most valued by patients.

Second, the Delphi process experienced a relatively low response rate among invited panelists. This diminished participation could compromise the diversity and breadth of expert perspectives included in the consensus, potentially affecting the generalizability and representativeness of the resulting measurement guideline.

Third, the steering committee did not include a nutrition scientist, which may have limited the integration of specialized nutritional perspectives into the core COS. Muscle loss, sarcopenia,

and cachexia represent distinct yet prevalent entities among patients with hematological malignancies undergoing allogeneic stem cell transplantation, often exacerbated by factors such as mucositis during hospitalization, reduced physical activity due to isolation protocols, gastrointestinal involvement from graft-versus-host disease leading to cachexia, and corticosteroid-induced myopathies. Addressing these through combined nutritional and exercise interventions is crucial, and incorporating muscle mass measurements into the COS could have enhanced its relevance. However, the committee instead comprised two oncological nurses, under the assumption that they adequately represented nutritional and psycho-oncological dimensions. Finally, methodological constraints in the COS development precluded the consideration of muscle mass measurements, as recommendations were restricted to outcomes commonly assessed in our preparatory scoping review, from which such measurements were absent.

4.4 Future Research

Looking ahead, future research should prioritize meaningful engagement of patients and other key stakeholders to expand this clinical COS and its accompanying measurement guideline into a comprehensive COS and measurement guideline, by integrating patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs), tailored to both hospital and non-hospital contexts. Qualitative studies to elucidate patient needs, expectations, and preferred outcomes will ensure greater clinical relevance and inclusivity. The use of comprehensive COS incorporated in measurement guidelines can result to more patient-centered research, while decreasing heterogeneity in research findings.

Additionally, systematic reviews in this field should systematically quantify clinical heterogeneity in meta-analyses by leveraging validated tools such as the Clinical Diversity in Meta-analysis (CDIM) instrument and further investigate its underlying sources and impact on evidence synthesis. Understanding how clinical, methodological, and statistical heterogeneity

interact is crucial for interpreting pooled effects and improving the reliability of systematic reviews using COS.

Finally, there is a strong need for observational research to evaluate how the implementation of COS has affected heterogeneity in other medical fields, learning from these examples and applying best practices to studies of rehabilitative interventions for HSCT patients. Such comparative research could clarify the degree to which the adoption of COS leads to more consistent outcome reporting and more informative meta-analyses in practice.

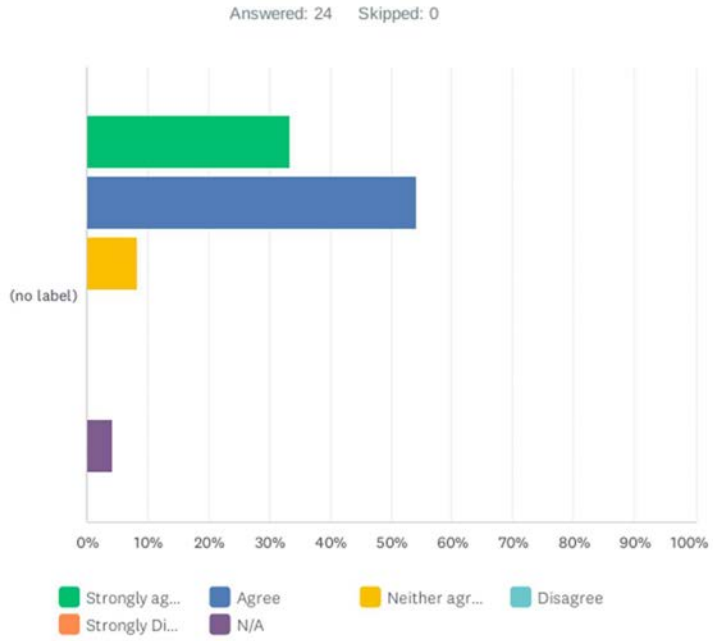
4.5 Conclusions

This dissertation provides the first structured attempt to standardize outcome measurement in trials of rehabilitative interventions for patients with hematological malignancies undergoing HSCT. By combining a clinical COS with an innovative measurement guideline, it lays essential groundwork to reduce outcome-reporting heterogeneity, address measurement bias, and improve the clinical interpretability of research findings. Although limitations, most notably low response rates and the absence of patient involvement, curtail some aspects of validity and inclusivity, this guideline nonetheless represents a starting point to methodologically and conceptually advance research in oncology rehabilitation.

APPENDIX

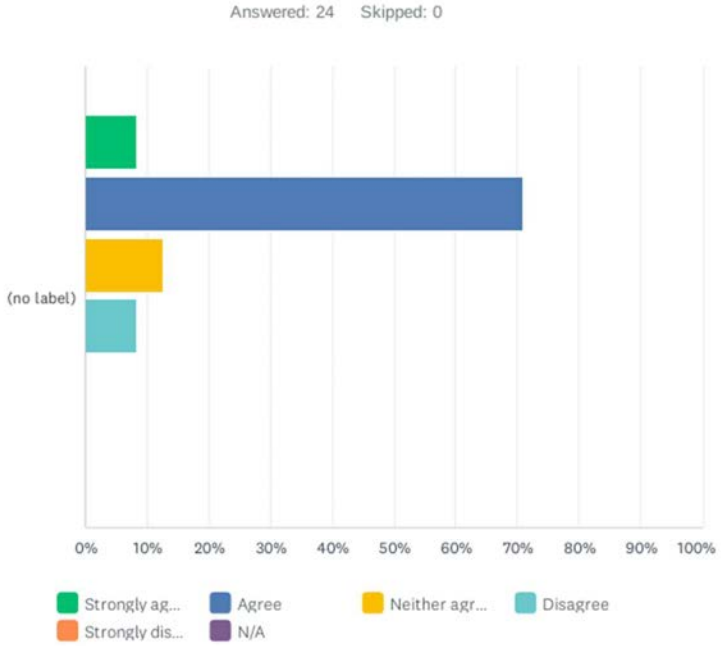
Appendix A. Delphi Study Round 1 Results

Q1. Please rate the degree to which you agree or disagree with the following statement: The Measurement Set we intend to develop should define the number of measurements during a study and the time points of measurements as well.



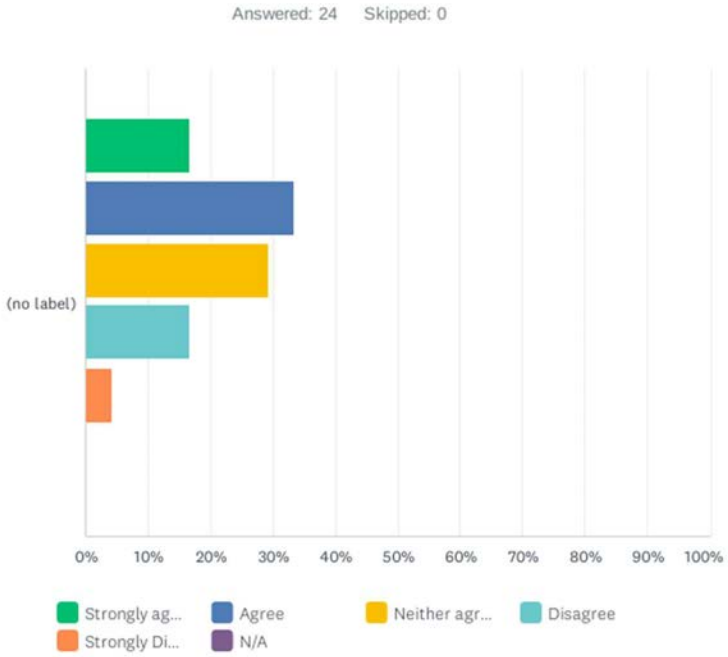
	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	N/A	TOTAL	WEIGHTED AVERAGE
(no label)	33.33% 8	54.17% 13	8.33% 2	0.00% 0	0.00% 0	4.17% 1	24	1.74

Q2. Please rate the degree to which you agree or disagree with the following statement: The Measurement Set we intend to develop should not include only the minimum number of common ‘’outcomes’’ that should be measured in future studies. The ‘’outcome measurement instruments’’ should be included as well whenever this is possible.



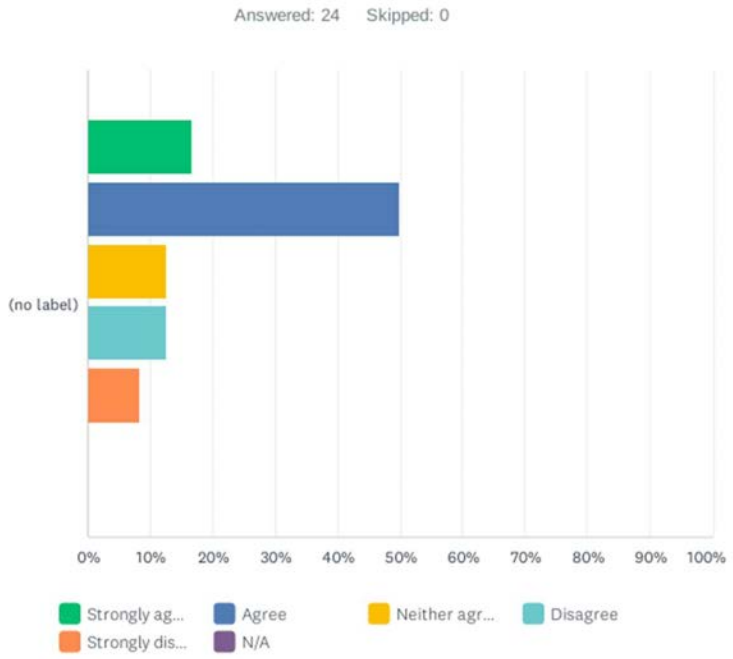
	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	N/A	TOTAL	WEIGHTED AVERAGE
(no label)	8.33% 2	70.83% 17	12.50% 3	8.33% 2	0.00% 0	0.00% 0	24	2.21

Q3. Please rate the degree to which you agree or disagree with the following statement: The Measurement Set we intend to develop should apply only for patients with hematological malignancies treated with ‘’allogeneic’’ stem cell transplantation (both reduced intensity conditioning and myeloablative). This measurement set is not appropriate for patients treated with autologous stem cell transplantation due to different medical treatment, iatrogenic clinical manifestations and timing of procedures.



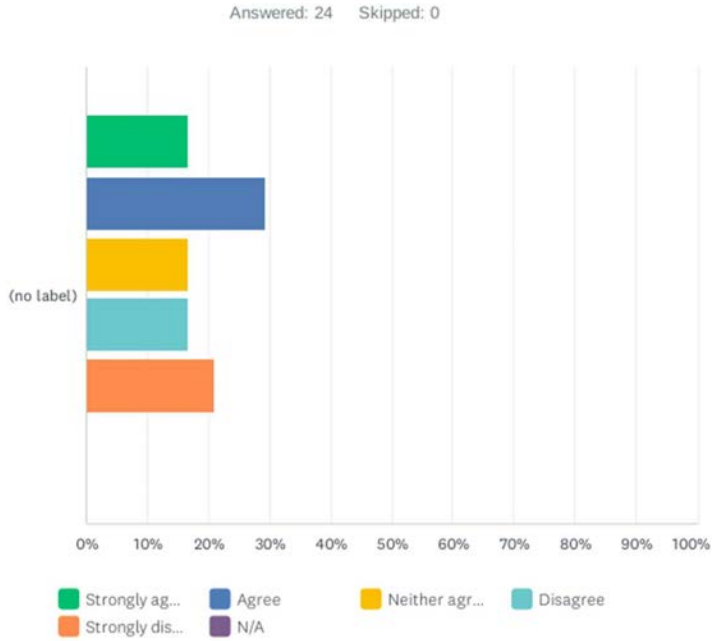
	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	N/A	TOTAL	WEIGHTED AVERAGE
(no label)	16.67% 4	33.33% 8	29.17% 7	16.67% 4	4.17% 1	0.00% 0	24	2.58

Q4. Please rate the degree to which you agree or disagree with the following statement: This Delphi Study should deliver two different Measurement Sets. One for the studies during hospitalization for stem cell transplantation and one adjusted for non-hospital settings.



	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	N/A	TOTAL	WEIGHTED AVERAGE
(no label)	16.67% 4	50.00% 12	12.50% 3	12.50% 3	8.33% 2	0.00% 0	24	2.46

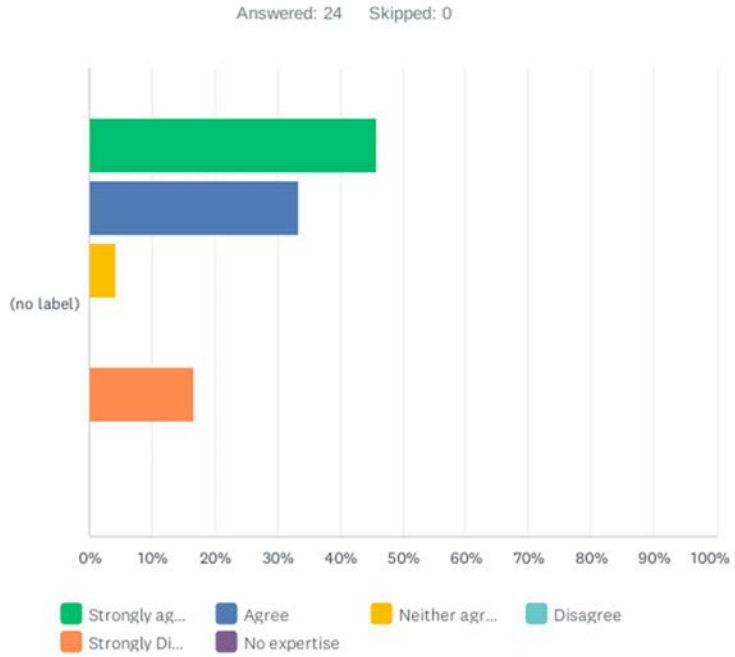
Q5. Please rate the degree to which you agree or disagree with the following statement : The Measurement Set we intend to develop will not include Patient Reported Outcomes (PROs) and their Measurement instruments (PROMs). PROs and PROMs should be added in this measurement set in a next step through a dedicated patient-focused study.



	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	N/A	TOTAL	WEIGHTED AVERAGE
(no label)	16.67% 4	29.17% 7	16.67% 4	16.67% 4	20.83% 5	0.00% 0	24	2.96

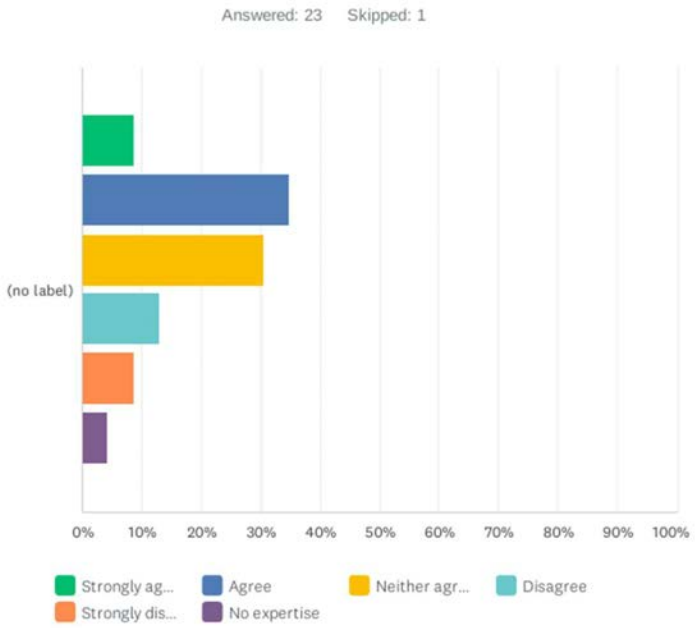
Appendix B. Delphi Study Round 2 Results

Q1. In the first round of study, 87.5% of the participants agreed that we should recommend a minimum of fixed time-points for measurements in studies including patients treated with allogenetic stem cell transplantation. We are now referring to studies during hospitalization. To what extent do you agree with the fixed time-point ‘’on admission’’ ? Please rate your agreement on scale from 1 to 5.



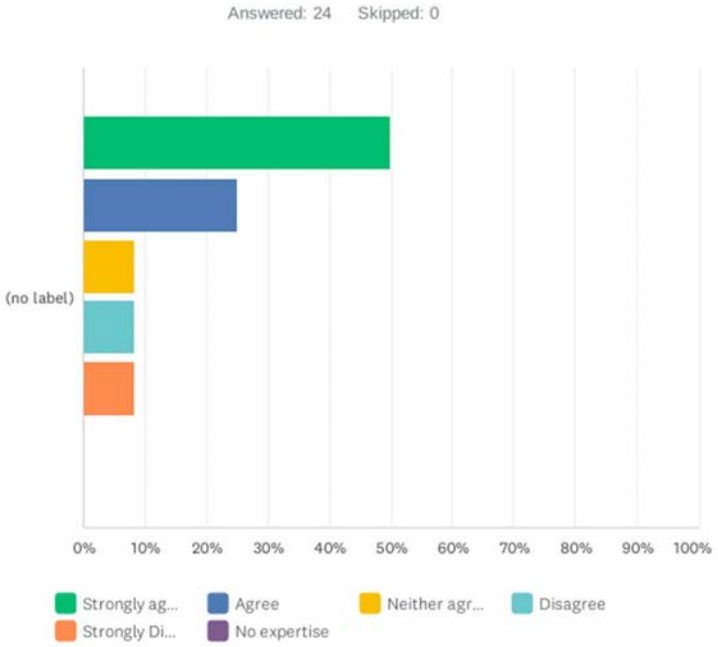
	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	NO EXPERTISE	TOTAL	WEIGHTED AVERAGE
(no label)	45.83% 11	33.33% 8	4.17% 1	0.00% 0	16.67% 4	0.00% 0	24	2.08

Q2. During hospitalization, measurements should be performed at day 10+ after the transplantation. In this time-point severe cytopenia is often present, at least for patients treated with myeloablative conditioning. Symptoms severity might have reached its peak in this time-point. To what extent do you agree with the fixed time-point ‘’day 10+’’ ? Please rate your agreement on a scale from 1 to 5.



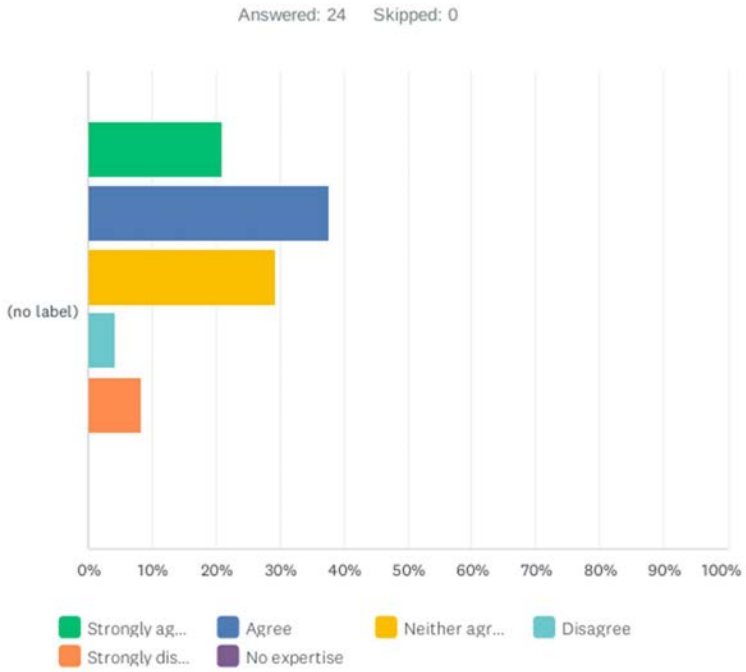
	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	NO EXPERTISE	TOTAL	WEIGHTED AVERAGE
(no label)	8.70% 2	34.78% 8	30.43% 7	13.04% 3	8.70% 2	4.35% 1	23	2.77

Q3. During Hospitalization, measurements should be performed at discharge. In this time-point oral administration of immunosuppression has been achieved and intravenous lines can be removed for the purpose of the measurements. To what extend do you agree with the fixed time-point ‘’at discharge’’ ? please rate your agreement on a scale from 1 to 5.



	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	NO EXPERTISE	TOTAL	WEIGHTED AVERAGE
(no label)	50.00% 12	25.00% 6	8.33% 2	8.33% 2	8.33% 2	0.00% 0	24	2.00

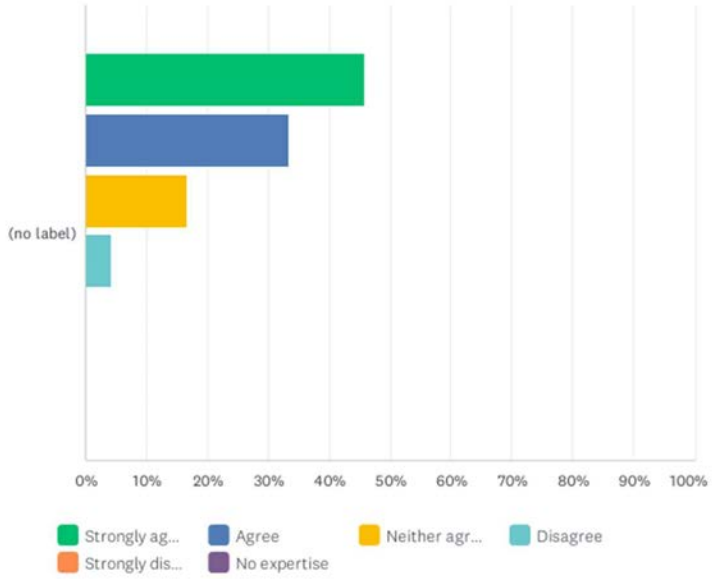
Q4. During hospitalization, in the time-point 2 (day + 10 post HSCT) performance-based tests might be too strenuous or even impossible for some patients. Therefore, only clinician-observed outcomes or patient reported outcomes should be measured. Please rate your agreement with this statement on a scale of 1 to 5.



	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	NO EXPERTISE	TOTAL	WEIGHTED AVERAGE
(no label)	20.83% 5	37.50% 9	29.17% 7	4.17% 1	8.33% 2	0.00% 0	24	2.42

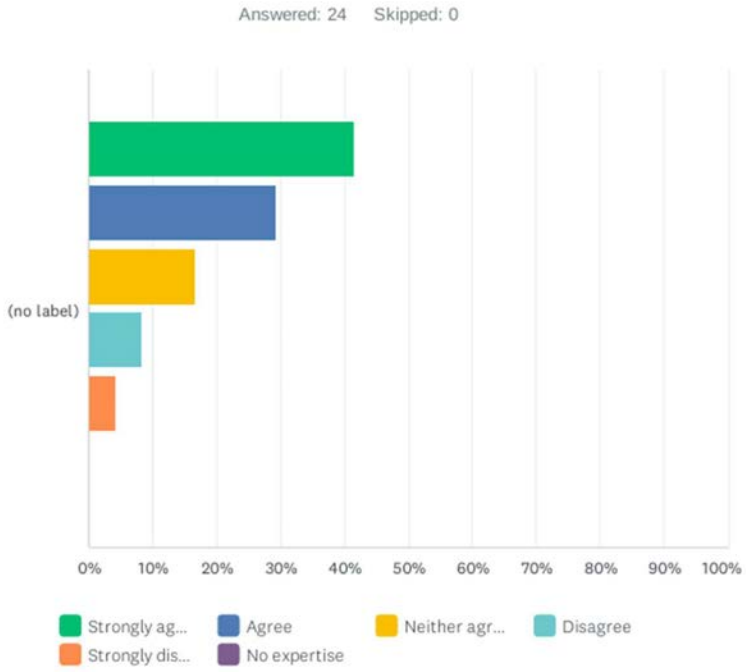
Q5. In the previous round of our study, 66.67% of the participant agreed that we should recommend two measurement sets. One for studies in hospital setting and one for studies in outpatient setting. We are now referring to studies in outpatient setting. In outpatient setting studies (rehabilitation and prehabilitation studies) measurements should be performed “on admission”. Please rate your agreement with this proposal on a scale from 1 to 5.

Answered: 24 Skipped: 0



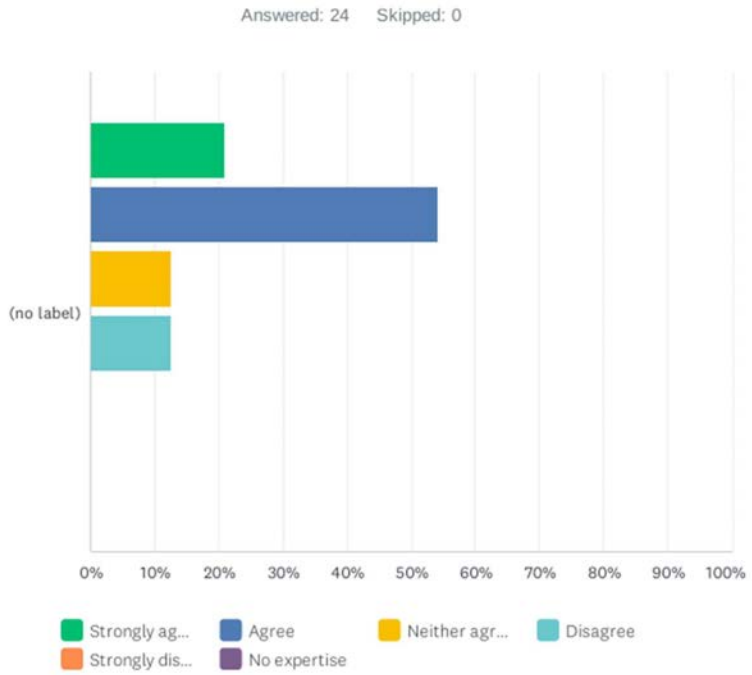
	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	NO EXPERTISE	TOTAL	WEIGHTED AVERAGE
(no label)	45.83% 11	33.33% 8	16.67% 4	4.17% 1	0.00% 0	0.00% 0	24	1.79

Q6. Please rate your agreement with the following proposal on a scale from 1 to 5: In outpatient setting studies (rehabilitation and prehabilitation studies) measurements should be performed at discharge.



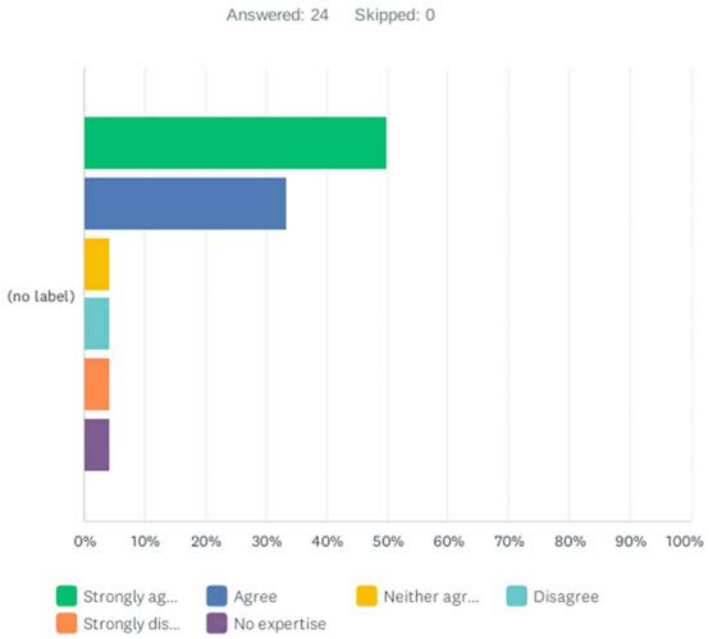
	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	NO EXPERTISE	TOTAL	WEIGHTED AVERAGE
(no label)	41.67% 10	29.17% 7	16.67% 4	8.33% 2	4.17% 1	0.00% 0	24	2.04

Q7. Please rate your agreement with the following proposal on a scale from 1 to 5: In outpatient setting studies measurements should be performed one year after discharge (only for rehabilitative interventions studies - not for prehabilitative).



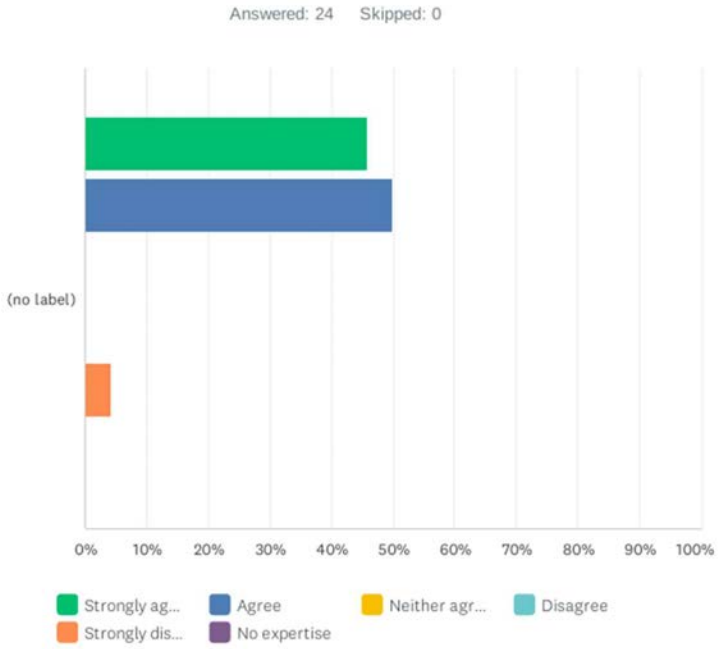
	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	NO EXPERTISE	TOTAL	WEIGHTED AVERAGE
(no label)	20.83% 5	54.17% 13	12.50% 3	12.50% 3	0.00% 0	0.00% 0	24	2.17

Q8. Please rate your agreement with the following proposal on a scale from 1 to 5: The outcome “strength” should be measured in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.



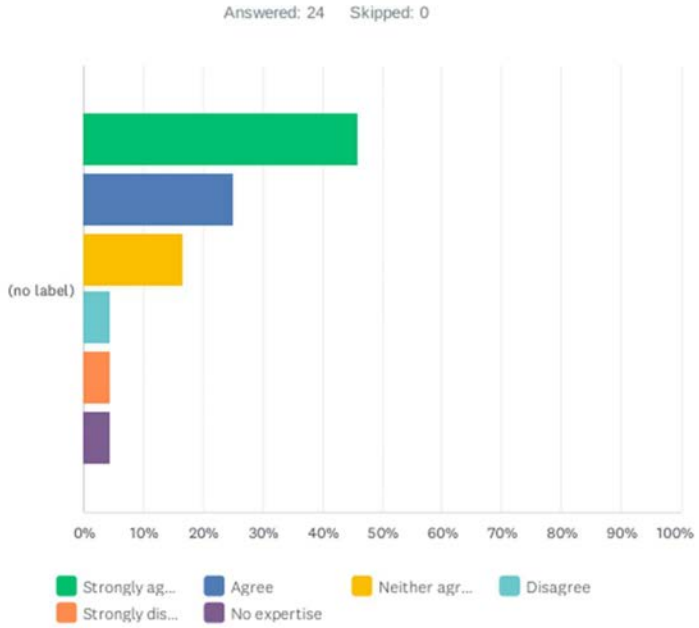
	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	NO EXPERTISE	TOTAL	WEIGHTED AVERAGE
(no label)	50.00% 12	33.33% 8	4.17% 1	4.17% 1	4.17% 1	4.17% 1	24	1.74

Q9. Please rate your agreement with the following proposal on a scale from 1 to 5: The outcome “exercise capacity” should be measured in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.



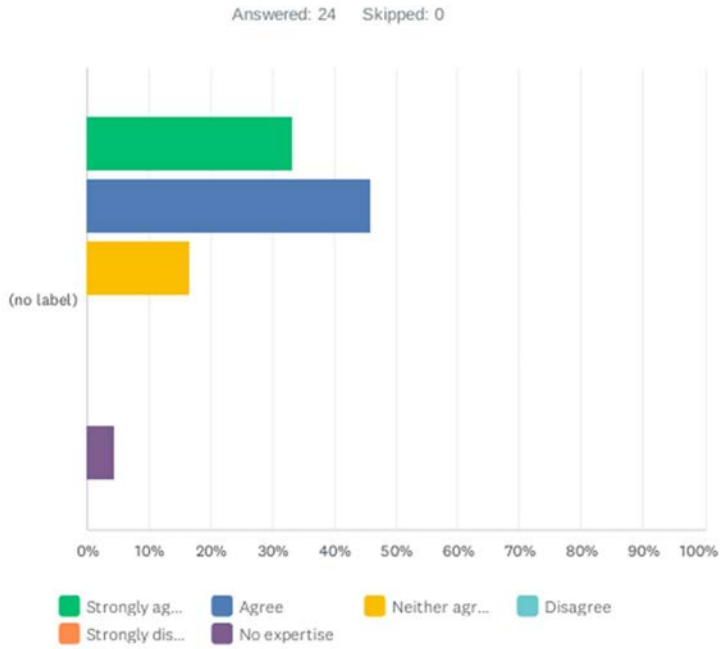
	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	NO EXPERTISE	TOTAL	WEIGHTED AVERAGE
(no label)	45.83% 11	50.00% 12	0.00% 0	0.00% 0	4.17% 1	0.00% 0	24	1.67

Q10. In the previous round of our study, 79.16% of the participants agreed that we should recommend not only outcomes that should be measured but also the measurement instruments with which they should be measured. We intend to suggest the measurement of the outcome “strength” by two measurements instruments: The “Handgrip dynamometer” and the “5 times sit to stand test”. Please rate your agreement with the following proposal on a scale from 1 to 5: The outcome strength should be measured with the measurement instrument “handgrip dynamometer” in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.



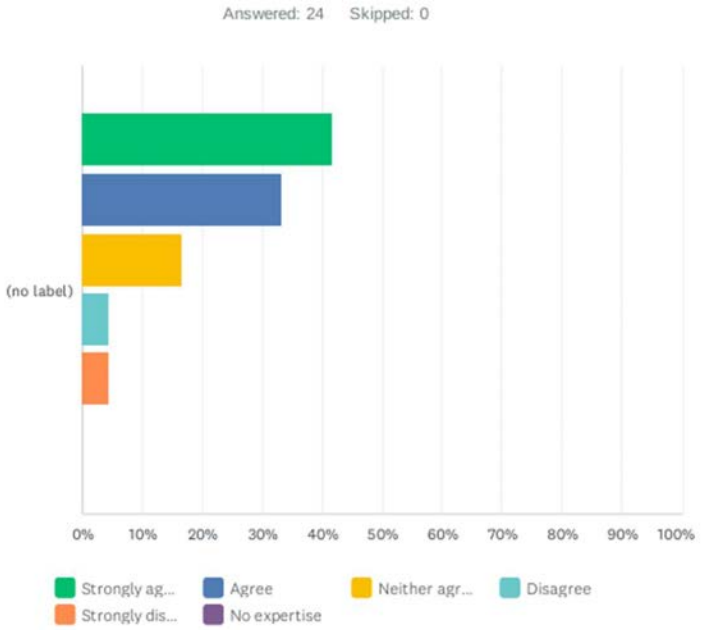
	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	NO EXPERTISE	TOTAL	WEIGHTED AVERAGE
(no label)	45.83% 11	25.00% 6	16.67% 4	4.17% 1	4.17% 1	4.17% 1	24	1.91

Q11. Please rate your agreement with the following proposal on a scale from 1 to 5: The outcome strength should be measured with the measurement instrument “5 times sit and stand test” in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.



	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	NO EXPERTISE	TOTAL	WEIGHTED AVERAGE
(no label)	33.33% 8	45.83% 11	16.67% 4	0.00% 0	0.00% 0	4.17% 1	24	1.83

Q12. Please rate your agreement with the following proposal on a scale from 1 to 5: The outcome “exercise capacity” should be measured with the measurement instrument “6 minute walk test” in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.



	STRONGLY AGREE	AGREE	NEITHER AGREE NOR DISAGREE	DISAGREE	STRONGLY DISAGREE	NO EXPERTISE	TOTAL	WEIGHTED AVERAGE
(no label)	41.67% 10	33.33% 8	16.67% 4	4.17% 1	4.17% 1	0.00% 0	24	1.96

Appendix C. Delphi Study Round 1 Summarized Results

Proposal	Proposal Approval	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A	Total Responses
1. The Measurement Set we intend to develop should define the number of measurements during a study and the time points of measurements as well.	YES	33.33%	54.17%	8.33%	0.00%	0.00%	4.17%	24
2. The Measurement Set we intend to develop should not include only the minimum number of common ‘’outcomes’’ that should be measured in future studies. The ‘’outcome measurement instruments’’ should be included as well whenever this is possible.	YES	8.33%	70.83%	12.50%	8.33%	0.00%	0.00%	24
3. The Measurement Set we intend to develop should apply only for patients with hematological malignancies treated with ‘’allogeneic’’	NO	16.67%	33.33%	29.17%	16.67%	4.17%	0.00%	24

stem cell transplantation (both reduced intensity conditioning and myeloablative). This measurement set is not appropriate for patients treated with autologous stem cell transplantation due to different medical treatment, iatrogenic clinical manifestations and timing of procedures.								
4. This Delphi Study should deliver two different Measurement Sets. One for the studies during hospitalization for stem cell transplantation and one adjusted for non-hospital settings.	YES	16.67%	50.00%	12.50%	12.50%	8.33%	0.00%	24
5. The Measurement Set we intend to develop will not include Patient Reported Outcomes (PROs) and their Measurement instruments (PROMs). PROs and PROMs should be added in this measurement set in a next step through a dedicated patient-focused study.	NO	16.67%	29.17%	16.67%	16.67%	20.83%	0.00%	24

Appendix D. Delphi Study Round 2 Summarized Results

Proposal	Proposal Approval	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A	Total Responses
1. In the first round of study, 87.5% of the participants agreed that we should recommend a minimum of fixed time-points for measurements in studies including patients treated with allogenetic stem cell transplantation. We are now referring to studies during hospitalization. To what extent do you agree with the fixed time-point ‘’on admission’’ ?	YES	45.83%	33.33%	4.17%	0.00%	16.67%	0.00%	24
2. During hospitalization, measurements should be performed at day 10+ after the transplantation. In this time-point severe cytopenia is often present, at least for patients treated with myeloablative conditioning. Symptoms severity might	NO	8.70%	34.78%	30.43%	13.04%	8.70%	4.35%	23

have reached its peak in this time-point. To what extent do you agree with the fixed time-point ‘’day 10+’’ ?								
3. During Hospitalization, measurements should be performed at discharge. In this time-point oral administration of immunosuppression has been achieved and intravenous lines can be removed for the purpose of the measurements. To what extend do you agree with the fixed time-point ‘’at discharge’’ ?	YES	50.00%	25.00%	8.33%	8.33%	8.33%	0.00%	24
4. During hospitalization, in the time-point 2 (day + 10 post HSCT) performance-based tests might be too strenuous or even impossible for some patients. Therefore, only clinician-observed outcomes or patient reported outcomes should be measured.	NO	20.83%	37.50%	29.17%	4.17%	8.33%	0.00%	24
5. In the previous round of our study, 66.67% of the participant agreed that we should recommend two	YES	45.83%	33.33%	16.67%	4.17%	0.00%	0.00%	24

measurement sets. One for studies in hospital setting and one for studies in outpatient setting. We are now referring to studies in outpatient setting. In outpatient setting studies (rehabilitation and prehabilitation studies) measurements should be performed “on admission”.									
6. In outpatient setting studies (rehabilitation and prehabilitation studies) measurements should be performed at discharge.	YES	41.67%	29.17%	16.67%	8.33%	4.17%	0.00%	24	
7. In outpatient setting studies measurements should be performed one year after discharge (only for rehabilitative interventions studies - not for prehabilitative).	YES	20.83%	54.17%	12.50%	12.50%	0.00%	0.00%	24	
8. The outcome “strength” should be measured in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.	YES	50.00%	33.33%	4.17%	4.17%	4.17%	4.17%	24	

9. The outcome “exercise capacity” should be measured in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.	YES	45.83%	50.00%	0.00%	0.00%	4.17%	0.00%	24
10. The outcome strength should be measured with the measurement instrument “handgrip dynamometer” in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.	YES	45.83%	25.00%	16.67%	4.17%	4.17%	4.17%	24
11. The outcome strength should be measured with the measurement instrument “5 times sit and stand test” in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.	YES	33.33%	45.83%	16.67%	0.00%	0.00%	4.17%	24
12. The outcome “exercise capacity” should be measured with the measurement instrument “6	YES	41.67%	33.33%	16.67%	4.17%	4.17%	0.00%	24

	minute walk test” in all studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic HSCT.

Appendix E. Delphi Study invitation e-mail round 1

Dear Sir or Madam,

I would like to invite you to fill in a questionnaire with five questions for a Delphi study because of your

expertise in the management of patients with hematological malignancies treated with allogeneic stem cell transplantation. In this study we want to develop a measurement set for studies which investigate the efficacy of rehabilitative interventions in patients with hematological malignancies treated with allogeneic stem cell transplantation.

Purpose of the study

Randomized Controlled Trials (RCTs) are conducted to investigate the efficacy of an intervention in improving an outcome in comparison to another intervention. Meta-Analysis of more than one RCTs provides us with better conclusions in regards with the efficacy of an intervention. However, the validity of Meta-Analysis results and conclusions is often hampered due to heterogeneity and inconsistency of the included studies. This is the case also for studies investigating the efficacy of rehabilitative interventions in patients with hematological malignancies treated with allogeneic stem cell transplantation. Therefore, we intend to develop a measurement set for studies investigating the effects of rehabilitative interventions for patients with hematological malignancies treated with allogeneic stem cell transplantation. The availability of a measurement set should ameliorate the problem of heterogeneity and inconsistency in future secondary research efforts. The reason for that is that researchers who conduct RCTs in a common field will be facilitated to deliver a minimum core of outcome measurements in a manner that enables synthesis.

The Delphi study

We will conduct a Delphi study to reach consensus on a measurement set. This Delphi study will consist of three to four short online survey rounds. In each round, we will ask your opinion on proposals regarding the identification of the specific research question addressed in the study. The proposals are based on a Scoping Review we published in 2022. Based on your ratings (on a five-point Likert scale) and your arguments, we will either reach consensus or make better or more specific proposals to be rated in the next Delphi round. This Delphi study is part of the Thesis of Anastasios Manettas.

Who I am:

I am Anastasios Manettas, PhD candidate in the University of Thessaly, Greece (Department of Physical Education and Sport Science) and clinical expert for oncological and hematological physiotherapy in the University Hospital of Zurich, Switzerland.

Potential panelists

For this Delphi study we have invited clinical experts for patients with hematological malignancies treated with allogeneic stem cell transplantation. We also included authors cited in the following Scoping Review published in 2022, whenever their email address could be retrieved: Manettas AI, Tsaklis P, Kohlbrenner D, Mokkink LB. A Scoping Review on Outcomes and Outcome Measurement Instruments in Rehabilitative Interventions for Patients with Haematological Malignancies Treated with Allogeneic Stem Cell Transplantation. Curr Oncol. 2022 Jul 15;29(7):4998-5025. doi: 10.3390/curroncol29070397. PMID: 35877257; PMCID: PMC9322392.

In addition, we included authors who recently published their related work in the field of nutrition, psychological care, nursing, complementary medicine, exercise, physiotherapy and spiritual care for cancer patients. If you agree to participate, we do ask you to hang in there for all three to four rounds. Premature dropout will decrease the value of the study, and the final results may overestimate how much the sample of participants agreed in the proposals. Each round will require approximately 10 minutes of your time. We ask you to complete each round within two weeks. After approximately one month we will send you a link for the next round. Participants who complete at least one Delphi questionnaire will be acknowledged in the final article (after their approval). If you know any other eligible colleagues who would be interested, please share their name, function, affiliation and email address with us. If you have any questions, please do not hesitate to contact me at (Anastasios.Manettas@usz.ch).

Thank you very much for your consideration.

Yours sincerely,

Anastasios Manettas

Appendix F. Delphi Study invitation e-mail round 2

Dear sir or madam,

Thank you for participating in the first round of this Delphi study, which aims to develop a measurement set for studies investigating the effects of rehabilitative interventions in patients with hematological malignancies treated with allogeneic stem cell transplantation.

The purpose of this measurement set is to reduce heterogeneity and inconsistency of measurement in clinical trials in this field of research, thus improving the conditions under which meta-analysis can be performed.

To achieve this goal, we seek to recommend a minimum set of outcomes that should be measured in all studies. However, we noticed that the timing of measurement and the choice of measurement instrument used to measure the outcome are significant sources of heterogeneity in trials.

Therefore, we invite you to participate in this second round of our Delphi study, to help us deliver valuable recommendations referring not only to the outcomes that should be measured, but also to the timing of measurements and the choice of measurement instruments that should be used.

We took your responses and your comments from the first round into consideration, and we cross-checked them with our previous study (1), in order to develop the second round of proposals: We now refer to recommendations rather than definitions. We seek to recommend a whole toolkit (when and how to measure) rather than just a list of outcomes that should be measured. Last but not least, although we recommend different measurement time-points for different settings, we adhere to your suggestion that the same outcomes should be measured in a longitudinal manner throughout the whole patient journey.

Thank you in advance for participating in the second round!

Anastasios Manettas

1. Manettas AI, Tsaklis P, Kohlbrenner D, Mokkink LB. A Scoping Review on Outcomes and Outcome Measurement Instruments in Rehabilitative Interventions for Patients with Haematological Malignancies Treated with Allogeneic Stem Cell Transplantation. Curr Oncol. 2022 Jul 15;29(7):4998-5025. doi: 10.3390/curroncol29070397. PMID: 35877257; PMCID: PMC9322392.