

Review

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

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**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 haematological 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; haematological malignancies



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## 1. Introduction

### 1.1. Rationale

Allogeneic hematopoietic stem cell transplantation (HSCT) improves the survival rate of patients with haematological 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 haematological 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 of 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.

### 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. 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](http://www.prisma-statement.org), (accessed on 28 February 2022)).

### 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 haematological 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. 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.

## 3. Results

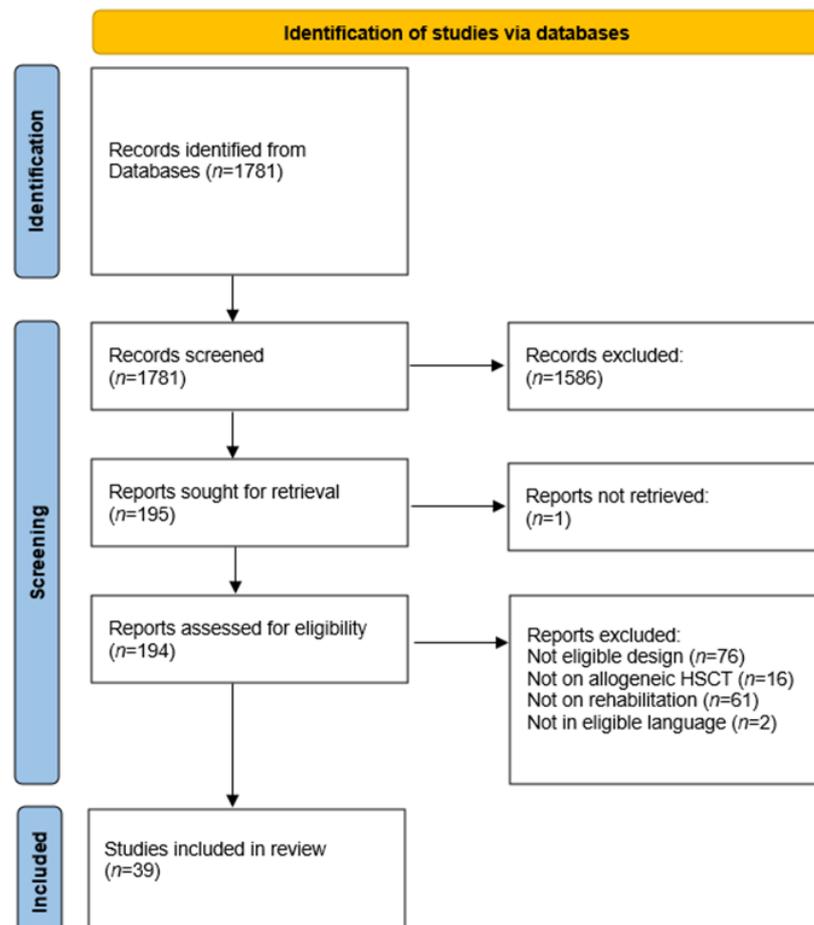
Our search yielded a total of  $n = 1781$  publications after duplicates were removed (Figure 1). Of these, we assessed  $n = 195$  for eligibility based on the full text. A total of  $n = 39$  studies of the following types met the inclusion criteria [16–54]:  $n = 24$  randomized clinical trials,  $n = 9$  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.** 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%)

**Table 1.** Cont.

Study Characteristics	
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%)



**Figure 1.** Study selection flowchart.

**Table 2.** 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

Table 2. Cont.

	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] 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

Table 2. Cont.

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-Åsberg 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

Table 2. Cont.

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

Table 2. Cont.

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			
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			
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	
Health related Quality of Life [21, 23,25,27,41,43,47] N = 7	The Spielberger Trait Anxiety Scale (STAI) [43]	Feasibility [43]	Outpatient post [43]	Mindfulness based Intervention [43]	Grossman et al., 2015			
				Exercise Relaxation Information [42]	Bird et al., 2010			
				FACT [43]	Feasibility [43]	Outpatient post [43]	Mindfulness based Intervention [43]	Grossman et al., 2015
				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	

Table 2. Cont.

	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]	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 et 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

Table 2. Cont.

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

Table 2. Cont.

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 behavioural therapy [49]	Applebaum et al., 2012
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-Minute 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

Table 2. Cont.

	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-Minute 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-Minute 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]	Bioimpedance 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-Minute 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

Table 2. Cont.

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 differential 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-Minute 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

Table 2. Cont.

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 [25,41]	Dual x-ray absorptiometry [41]	RCT [41]	Outpatient post [41]	Outpatient physical exercise [41]	Knols et al., 2011
	Bioimpedance 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-Minute 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-Minute 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 [25,40]	Arm curl test [40]	RCT [40]	Hospital [40]	Strength Training [40]	Hacker et al., 2017
	Hand Grip Dynamometer [25,40]	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

Table 2. Cont.

	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-Minute 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 expiratory pressures [54]	Pilot Study [54]	Hospital [54]	Respiratory Physiotherapy [54]	Bom et al., 2012
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

Table 2. Cont.

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-Minute 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

### 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 area. It was measured two times in studies that only included allogeneic HSCT patients and seven times in studies including mixed HSCT patients.

### 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.

### 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.

### 3.4. Timing of Measurement

In 23 out of 39 of the studies, measurements were performed at two time points (see 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.** Timing of measurement.

HOSPITAL SETTING							
Allogeneic HSCT	T1	T2	T3	T4	T5	T6	T7
Before Hospitalization	[37]						
On Admission	[16,17,30,31,34,36,37,52]						
At Baseline							
At discharge		[17,30,31,34,36,37]					
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



Table 3. Cont.

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	[21,22,24,25,41,48–50]							
At discharge		[22,41,42]						
Before the intervention	[42,43]							
After the intervention		[21,24,43]	[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]						

**Table 3.** *Cont.*

7 weeks after Hospitalization		
Day + 60 after HSCT		[50]
3 months after HSCT		
Day + 100 after HSCT		[50]
6 months after HSCT	[48,49]	[50]
9 months after HSCT		[48,49]
One year after HSCT		[48,49]

#### 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.

#### 5. 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.

## 6. 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 QIQ-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.

### **7. 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.

### **8. 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 haematological 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.

## 9. 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.

## 10. Conclusions

Research in the field of rehabilitation for patients with haematological 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.

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## Abbreviations

HSCT	Hematopoietic Stem Cell Transplantation
GvHD	Graft Versus Host Disease
IST	Immunosuppressive Therapy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
EORTC	European Organization for Research and Treatment of Cancer
COS	Core Outcome Set
IRT	Item Response Theory
PROMIS	Patient-Reported Outcomes Measurement Information System
FACT	Functional Assessment of Cancer Therapy
EBMT	European Society for Blood and Marrow Transplantation

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