PATIENT REPORTED OUTCOMES IN VIEW OF SYMPTOM EXPERIENCE OF LATE EFFECTS AND SELF-MANAGEMENT OF ADULT LONG-TERM SURVIVORS AFTER ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION – A MIXED METHODS STUDY

Inauguraldissertation

Zur Erlangung der Würde eines Dr. sc. med.

vorgelegt der

Medizinischen Fakultät der Universität Basel

von

Monika Kirsch

aus Neuss, Deutschland

Basel, 2014

Genehmigt von der Medizinischen Fakultät

auf Antrag von:

Referat:	Prof. Dr. Sabina De Geest
Co-Referat:	Prof. Dr. Fabienne Dobbels
Externer Experte:	Prof. Dr. med. William A. Wood
Experte:	PD Dr. med. Jörg Halter
Experte:	PD Dr. med. Georg Stüssi

Basel, den 26.08.2014

Dekan: Prof. Dr. med Christoph Beglinger

Für alle Patienten und Patientinnen und die Menschen, die sie unterstützen.

Man muss seinen Traum finden, dann wird der Weg leicht.
Aber es gibt keinen immerwährenden Traum, jeden löst ein neuer ab, und keinen darf man festhalten wollen.

Hermann Hesse

Wir können noch lang beteuern
Was uns am Herzen liegt
Doch ein Funke macht kein Feuer
So wie der Tropfen schnell versiegt
Oder wir gehen den Weg zusammen
Und nehmen's in die Hand
Was wir nicht tun, macht niemand

Joy Denalane

Printed by Reproplan

Cover Drawing: Alicia Teopel

Layout and cover design: Arlette T. Bernasconi

Chapters 3, 4, 6 and 8 have been published and are reproduced with the permission of the publisher.

Chapters 5 and 7will be submitted to a scientific journal.

CONTENTS

LIST OF ABBREVIATIONS

AERA	American Educational Research Association
BAASIS	Basel Assessment of Adherence with Immunosuppressive Medication Scale
BCT	Behaviour Change Technique
BMI	Body Mass Index
CI	Contingence Interval
CVI	Content Validity Index
cGVHD	chronic Graft versus Host Disease
EBMT	European Group for Blood and Marrow Transplantation
EFA	Exploratory Factor Analysis
FDA	Food and Drug Administration
HADS	Hospital Anxiety and Depression Scale
HLA	Human Leukocyte Antigen
I-CVI	Item Content Validity Index
INS	Institute of Nursing Science
IOM	Institute of Medicine
IS	Immunosuppressive
ITP	Immune Thrombocytopenia
IQR	Interquartile Range
MNA	Medication nonadherence
NCI	National Cancer Institute of the United States
NIH	National Institute of Health
OECD	Organisation for Economic Co-operation and Development
PRO	Patient-Reported Outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PROVIVO	Patient reported outcomes in view of symptom experience and self-management of long-term survivors after stem cell transplantation
QoL	Quality of Life
S-CVI/Ave	Scale Content Validity Index/Average Method
SD	Standard Deviation
SCT	Hematopoietic Stem Cell Transplantation

SHS	Swiss Health Survey
STCS	Swiss Transplant Cohort Study
SPF	Sun Protective Factor
TBI	Total Body Irradiation
VAS	Visual Analogue Scale
WHO	World Health Organization

ACKNOWLEDGEMENTS

This doctoral thesis was undertaken at the University of Basel Medical Faculty's Institute of Nursing Science (INS). It is my privilege to express my gratitude to all the people who have contributed, both directly and indirectly, to the realization of this thesis.

My deepest gratitude goes to my advisor, Professor Dr. Sabina De Geest, whose trust, support and scientific guidance supported me throughout the dissertation process, and whose passion for nursing and research inspired me and stimulated my thinking in uncounted ways. Her extraordinary mentorship provided me with opportunities, challenges, and support and has broadened my mind, skills and expertise.

I also wish to express special thanks to the other members of my PhD committee, all of whom have given close support and guidance, enabling my learning and progress on numerous levels throughout the dissertation process. I am particularly thankful to Professor Dr. Fabienne Dobbels, who served both as a constant source of help and encouragement, and as a magnificent role model of a scientist and mother. I also owe many thanks to PD Dr. med. Jörg Halter for his motivating mentorship. He gave me the opportunity to gain in-depth knowledge of clinical follow-up care after stem cell transplantation. I admire his passion and advocacy for the patients treated in Basel. Also, I greatly appreciate PD Dr. med. Georg Stüssi's cheerful and motivating mentorship throughout the process. Furthermore, I gratefully acknowledge Prof. Dr. med. William A. Wood, of the Lineberger Comprehensive Cancer Center at the University of North Carolina for his willingness to evaluate this thesis as an external expert. I have the highest respect both for Professor Wood's broad scientific expertise in outcomes and health services research in stem cell transplantation and hematologic malignancies, and for his openness and willingness to share his expertise.

I am deeply thankful to Professor Dr. med. Alois Gratwohl, former head of the Haematology Department of the University Hospital Basel, and to Professor Dr. med. Jakob Passweg for supporting me and giving me the opportunity to work in a setting that fosters tremendous scientific and clinical exchange. I also wish to express my gratitude to Professor Dr. med. André Tichelli for inspiring discussions.

I especially wish to thank Dr. Sandra Mitchell from the Division of Cancer Control and Population Sciences at the US National Cancer Institute, Bethesda, and Professor Dr. med. Ethan Basch of the Lineberger Comprehensive Cancer Center at the University of North Carolina, for their excellent collaboration, particularly concerning the PRO-CTCAE item library.

In the University Hospital Basel's Department of Haematology, nurse manager Christel Pino Molina, who supported me throughout my professional development in her department, deserves special thanks, as do many more of my clinical colleagues. My fellow Zellersatzambulatorium team colleagues and team leader Sigrun Reitwiessner warrant particular recognition for their stellar collaboration in clinical practice and on the PROVIVO project. Their help, their critical questions and their interest in implementing my findings into clinical care were invaluable.

I also gratefully acknowledge Dr. med. Gayathri Nair, Dr. med. Urs Schanz, Erik Aerts, and all the members of the University Hospital Zurich Haematology outpatient clinic team, who welcomed me and assisted substantially with the organization of data collection at their centre.

Again at the University Hospital of Basel, I am especially thankful to Germaine Eze, former Divisional Director of the Medical Nursing Department, and acknowledge the tremendous engagement of Anja Ullrich, Divisional Director of the Medical Nursing Department, Dr. Jacqueline Martin, Head of Department of Nursing & Allied Health Professions, and Dr. Irena Anna Frei, Head of Nursing Development Unit, for their support and visionary leadership in developing and implementing advanced nursing practice.

My deep gratitude goes to my colleagues from the Institute of Nursing Science for their support and the many opportunities they offered to discuss my work during doctoral seminars and research meetings, where I always enjoyed the open and inspiring atmosphere. I am also thankful to Hanna Burkhalter, who accompanied me through my undergraduate and graduate studies, offering not only generous scientific and emotional support but also a close and enduring friendship.

I gratefully recognize the members of the "Leuven Basel Adherence Research Group" for our international collaboration and stimulating exchanges throughout the biannual meetings over the last years.

Additional gratitude goes to my colleagues from the "European Group for Blood and Marrow Transplantation (EBMT) Nurses Group", particularly Eva Johansson, Simona Calza, Corien Eeltink, Jacqui Stringer, Sarah Liptrott and Patrick Crombez for their inspiring input and supportive research collaboration.

Many thanks go to Marina Fontana, Monika Grossert, Silvana Nicca and Gani Gashi, who supported me as assistants throughout the PROVIVO study. Further gratitude goes to Sabine Degen Kellerhals for her encouragement and excellent clinical input.

I further wish to recognize Anna Götz, Barbara Gresch, Matthias Naegele, Sabina Valenta and Nadine Gerwig, all of whom conducted their master theses within our shared research program. It was always inspiring to discuss scientific and clinical topics. In addition I thank Lynn Leppla and Katharina Bosshart who assisted in the PROVIVO project by doing research practicums.

Many thanks go to Dr. Kris Denhaerynck and Dr. Pamela Rackow for their statistical advice. I thank Chris Shultis for his highly appreciated editorial support on the dissertation and Arlette Bernasconi, who helped me edit the final manuscript. Furthermore, I thank Jessica Thompson and Mary Louise Daly, who contributed to the translation of the PRO-CTCAE item library.

Our deepest gratitude goes to the funding sources of this research project, the Foundation for Cancer Research Switzerland (KFS 2705-08-2010) and the 'Stiftung zur Krebsbekämpfung' (2010/ 280). We also thank the Swiss Federal Statistical Office for sharing data from the 2007 Swiss Health Survey.

To my friends and my family, for encouraging my work, providing much-needed moral support, and offering so many pleasant diversions to replenish my energy, I offer my loving thanks. Most profoundly, I thank my parents, Hedwig and Bruno Kirsch, who have always supported me, whatever my choices, wherever they took me. Whatever I did, they taught me that the most important ingredient for success is passion. I dedicate this thesis to my son Yannick, who was born in the middle of my PhD studies and always brings love and joy to my life.

Finally, with all my heart, I thank all the patients who participated in the PROVIVO study. Conducting the study has been a moving experience for me and has affected not only my clinical practice but also my view of life in general.

Monika Kirsch, 2014

SUMMARY

Haematopoietic stem cell transplantation (SCT) is an intensive treatment for life-threatening diseases of the blood building system. Worldwide, the number of transplantations has risen to more than 60.000 per year, with the number of treated patients now above one million [1]. Although, for most of these patients, SCT is the only curative treatment, long-term survivors face a life-long increased risk of various adverse side effects, also termed 'late effects' [2-4]. These can appear months or years after treatment has ended, can persist chronically, and are often experienced as distressing and burdensome [5]. Also these complications can cause substantial morbidity and mortality and can impair quality of life [6]. Recurrent disease is still the most common cause of late deaths among SCT patients. Other frequent causes of death include infections, organ failure, secondary cancers and chronic graft versus host disease (cGVHD), which involves attacks by donor T lymphocytes on the patient's organs. Chronic GVHD can affect any organ and can be particular burdensome for patients [7]. As many late effects manifest with symptoms, patient perspectives on symptom experience are extremely important.

According to Leventhal's self-regulatory theory [8], symptom experience involves two distinct dimensions, i.e., cognitive, measured using symptom occurrence (frequency, severity and duration) and emotional, i.e., symptom distress, reflecting a patient's emotional response to a symptom [9]. Symptom experience can be measured efficiently via patient reported outcome (PRO) instruments, i.e., health status reports supplied directly by the patient [10]. PRO instruments are essential for early detection, management and alleviation of symptoms [11, 12].

Late effects and associated symptoms pose an immense long-term challenge for SCT patients [7, 13], commonly requiring life-long follow-up care. However, besides assessment, treatment and management of late effects and their symptoms, follow-up care also focuses on prevention and support of patients' self-management capabilities [14], i.e., any actions performed by patients for themselves to manage their illness and treatment, thereby avoiding or delaying health deterioration [15]. According to self-management theory, SCT patients have to work simultaneously on three fronts: (1) coping with the emotions they experience concerning their chronic illness, including the uncertainties and anxieties surrounding possible relapse; (2) managing their new life roles to maximize meaning and fulfilment, and (3) dealing with their medical regimens, in view of both general and disease-specific health behaviour tasks [15]. While disease-specific tasks include responsibilities such as medication taking, organizing clinic visits or recommended vaccinations, general health behaviours embrace "any activities undertaken by an individual, regardless of actual or perceived health status, for the purpose of promoting, protecting or maintaining health, whether or not such behaviour is objectively effective towards that end."[16].

Although evidence is scarce on the prevalence of SCT recipients' problems regarding self-management and overall health behaviours, studies from the US have indicated widespread shortfalls. For example, only 29 to 36% of survivors exercise regularly [17, 18]. Overweight was observed in 52%, with only 5% reporting a healthy diet, i.e., one low in fat and high in fruits and vegetables [18]. And, disturbingly, 7 to 14% of survivors continued to smoke [17-19].

So far, no study has specifically examined long-term sun-protective behaviours and medication intake following SCT. In other areas, findings increasingly demonstrate that supporting self-management particularly health behaviours-improves outcomes [20-22]. Likewise, studies in mixed samples of cancer survivors encourage increased physical activity, smoking cessation and long-term dietary changes [23-25].

Designing interventions aiming at supporting patient self-management and health behaviours demands a clear knowledge of current practice patterns. However, despite the weight of empirical evidence for various behavioural interventions, whether educational/cognitive, counselling/ behavioural, or psychological/affective [26], little is known about which are actually applied in clinical practice. Specifically regarding SCT patients, no studies have indicated how many healthcare providers offer health-behavioural interventions adequate to their needs. One promising strategy to assist healthcare professionals both to facilitate symptom self-management strategies and to implement health behaviour enhancing interventions is to provide a comprehensive evaluation of symptom experience and health behaviours. To date, no validated, comprehensive PRO instrument measuring symptom experience of SCT late effects exists, and little knowledge is available on health behaviours which might influence their occurrence or intensity. Therefore, to build a knowledge base for further intervention research, this multicentre research project had three overall aims: 1) to develop and validate a PRO instrument for assessing late effect symptom experiences in SCT long-term survivors; 2) to describe health behaviour patterns of this patient population; and 3) to evaluate healthcare providers' patterns of practice supporting health behaviours, using the example of medication adherence, in SCT settings. This doctoral thesis involves a study sample of adult allogeneic SCT recipients from two Swiss centres ≥1 year post-transplant. The research program involved several studies, summarized as follows.

Following the US Food and Drug Administration's state-of-the-art guidelines to develop a PRO instrument measuring patients' SCT late effect symptom experiences [10], we began by conducting a sequential transformative mixed methods study [27]. Therefore, the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events 3.0 (PRO-CTCAE) an item library consisting of 78 symptom terms was translated into German and linguistically validated using recommended translation protocols [28, 29]. Next, patient cognitive debriefing (n=15) was used to select an item bundle significant for SCT associated late effects according to two predefined criteria: (1) *PRO-CTCAE symptoms prevalent in ≥50% of SCT survivors* and (2) *recognized as important by SCT experts* (n=9). Additional concepts concerning symptom experience were elicited from both patients and experts. A first draft of the PROVIVO (**P**atient-**R**eported **O**utcomes of long-term sur**vivo**rs after allogeneic SCT) instrument was then drafted. Additional cognitive debriefings of 15 further patients

were used to assess the instrument's content validity. Finally, nine clinical experts were surveyed to provide item and scale content validity indices (CVIs). The final instrument comprises 49 items and captures both dimensions – occurrence and distress – of physical, emotional and cognitive symptoms. To improve the instrument's utility for clinical decision-making, questions assessing limitations in activities of daily living, frequent infections, and overall wellbeing were also included. Cognitive debriefing was used to ensure that items were well- understood and relevant to the SCT survivor experience. As preliminary evidence of PROVIVO's content validity, scale and item CVIs (respectively 0.94 and median = 1 (range 0.75-1)) were very high.

Second, we refined the newly developed PROVIVO instrument and examined its validity and reliability. Therefore we used the data of a cross-sectional study in a sample of 376 patients ≥1 year after allogeneic SCT. Following the American Educational Research Association guidelines, we tested the questionnaire on three evidence levels: construct validity based on internal structure was tested by an exploratory factor analysis; and Cronbach's alphas and inter-item correlations were calculated to examine internal consistency reliability. Relations to other variables were tested based on a set of evidence-based hypotheses. Based on performance testing, four original PROVIVO items were dropped. The exploratory factor analysis revealed an eight-factor model explaining 57.05% of variance. Internal consistency reliability was good for the entire scale (Cronbach's alphas .90), but only acceptable for the eight factor scores. Additional evidence supported relations between variables, e.g., between the number of symptoms and cGVHD occurrence, number of late and performance status. The initial evidence for the validity of the PROVIVO symptom experience scale was provided. The PROVIVO questionnaire may be useful to identify late effect symptoms warranting further testing.

Next, we conducted a comparative cross-sectional multicentre study exploring the prevalence of SCT recipients' health behaviours versus those of the general Swiss population. A convenience sample of 376 survivors from 2 Swiss SCT centres (54.8% males; mean age 50.4 years (SD=12.8); median 7 years post allogeneic SCT (IQR=8.75), 40.6% cGVHD) was compared to case matched controls derived by propensity score matching from the data set of the 2007 Swiss Health Survey (SHS), a large-scale nationwide representative study (n=18760 participants) repeated at 5-year intervals. Propensity score matching was performed based on gender, age, educational status, living region and community type Health behaviours relevant to physical activity, dietary habits, alcohol consumption, smoking, influenza vaccination, and sun protection were compared. Statistical analysis was performed using McNemar or Wilcoxon signed-rank paired tests as appropriate. The results showed both favourable and unfavourable differences from national norms. Survivors were much more likely to be physically inactive (26.8% vs. 12.5%; p=<.001), and typically consumed fewer portions of vegetables (≥3 pieces: 10% vs. 21.6%; p<.001), fruits (≥3 pieces: 6.5% vs. 10.6%; p<.001), and fish (31.2% vs. 60.9% weekly fish dish; p<.001). More desirably, survivors were more likely to consume dairy products daily (92.5% vs. 62.9%; p<.001), to use sun protection regularly (94.5% vs. 85.3%, p<.001) and to have received influenza vaccinations in the last year (58.4% vs. 21.5%; p<.001). Also, fewer smoked (13.4% vs. 35.4%; p<.001),

and their weekly alcohol consumption was lower than their controls' (medians: 1.5 servings (IQR 4) vs. 4.5 (IQR 10.3); p<.001).

Among allogeneic SCT recipients, correct immunosuppressant (IS) intake is essential to prevent and treat cGVHD. So far, no previous study had investigated the prevalence and consequences of post-SCT medication nonadherence (MNA), although research in solid organ transplantation indicates a clear connection with increased mortality [30, 31]. Therefore, our fourth study aimed to examine MNA prevalence and its relationship first with a defined set of clinical and demographic characteristics, then with cGVHD. We performed a secondary data analysis of a subsample of patients taking IS medications (n=99) in the above mentioned cross-sectional study phase. Patient-reported MNA over the previous 30 days was measured using the 6-item BAASIS® questionnaire, which assesses following dimensions of medication taking behaviour: implementation (taking & timing), drug holidays; dose reductions; discontinuation and overall nonadherence). Also, physicians estimated patients MNA (adherent/non-adherent) for the last 30 days. Patients were classified as non-adherent based either on their self-reports (i.e., if they reported nonadherence to at least one of the BAASIS® criteria or on their physicians' collateral reports. Results from the BAASIS® indicated that 33.3% of patients had not taken their IS medication at least once, while 61.2% had not adhered to the recommended intake time; and 3.1% terminated their medication regimens too early. Together, 65.7% of patients were non-adherent to at least one criterion of the BAASIS®. Physicians estimated MNA in 18.9% of patients, which resulted together with the patient-reported MNA in a composite MNA rate of 68.7%. MNA correlated with higher numbers of IS [odds ratio (OR):1.42; p=0.011] and fewer co-medications (OR:0.85; p=0.02). MNA was significantly associated with higher grades of cGVHD (OR: 3.01; p = 0.012). Patients with higher cGVHD were more likely to have problems in the implementation of the medication regimen (OR:2.60; CI:1.14-5.91; p=0.023); in particular regarding taking (OR:2.46; p=0.028) and self-initiated dose reduction (OR:15.57; p=0.022). This study indicates high levels of MNA in SCT patients, calling for adherence-enhancing interventions.

Such a high MNA prevalence indicates a need to understand healthcare professionals' practice patterns regarding medication self-management support. We therefore aimed to identify nurses' practice patterns in view of assessing medication adherence, screening for risk factors, and offering adherence-enhancing interventions. We also assessed nurses' perceptions of the applied methods' effectiveness. A convenience sample of 143 European nurses attending the Meeting of the European Group for Blood and Marrow Transplantation completed a self-developed 29-item questionnaire measuring the frequency and perceived effectiveness of adherence assessment/screening methods and each of three adherence enhancing intervention types (educational/cognitive, counselling/behavioural, and psychological/affective).

The results showed that the most regularly used assessment method was questioning patients about adherence (51.5%). Nurses used a median of 7 interventions (IQR: 6) 'frequently', the most frequent being educational, i.e., providing reading materials (79%), followed by training during inpatient recovery (66.4%). Those perceived as most effective were individual patient/family teaching and providing reading materials. The high preference for educational interventions contrasts with data suggesting limited efficacy of educational interventions alone[32] – a more optimal solution being a combination of educational, behavioural and psychological interventions.

The research reported in this doctoral thesis contribute in four main ways to the evidence base regarding SCT patients' symptom experience, self-management, and, more specifically, adoption of healthy behaviours, including medication adherence. First, following FDA guidelines, we both developed and presented preliminary data on the validity and reliability of a PRO instrument to assess late effect symptom experiences. Second, we used propensity score matching to compare, for the first time, a comprehensive set of health behaviours between SCT survivors and a representative sample of the general Swiss population. Third, we provided detailed information on the prevalence of medication nonadherence in SCT patients taking IS, including a relationship between MNA and higher grades of cGVHD. Fourth, we increased the very limited pool of available knowledge regarding current patterns of medication adherence support practices among nurses working in SCT settings. Our findings indicate a clear need for deeper exploration of the efficacy of interventions to increase survivors' positive health behaviours, including medication adherence.

References

1. Gratwohl A, Baldomero H, Passweg J. Hematopoietic stem cell transplantation activity in Europe. *Curr Opin Hematol* 2013; **20:** 485-93.
2. Socie G, Salooja N, Cohen A, Rovelli A, Carreras E, Locasciulli A *et al.* Nonmalignant late effects after allogeneic stem cell transplantation. *Blood* 2003; **101:** 3373-85.
3. Tichelli A, Rovo A, Gratwohl A. Late pulmonary, cardiovascular, and renal complications after hematopoietic stem cell transplantation and recommended screening practices. *Hematology Am Soc Hematol Educ Program* 2008**:** 125-133.
4. Majhail NS, Rizzo JD. Surviving the cure: long term follow-up of hematopoietic cell transplant recipients. *Bone Marrow Transplant* 2013; **48:** 1145-51.
5. Tichelli A, Socie G. Considerations for adult cancer survivors. *Hematology Am Soc Hematol Educ Program* 2005**:** 516-522.
6. Wingard JR, Majhail NS, Brazauskas R, Wang Z, Sobocinski KA, Jacobsohn D *et al.* Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *J Clin Oncol* 2011; **29:** 2230-9.
7. Wood WA, Chai X, Weisdorf D, Martin PJ, Cutler C, Inamoto Y *et al.* Comorbidity burden in patients with chronic GVHD. *Bone Marrow Transplant* 2013; **48:** 1429-36.
8. Leventhal H, Brissette I, Leventhal EA. The common-sense model of self-regulation of health and illness. In: Florence K, Cameron LD, Leventhal H (eds). *The Self-regulation of Health and Illness Behaviour*. Routledge, 2003, pp 43-65.
9. Andrykowski MA, Lykins E, Floyd A. Psychological health in cancer survivors. *Semin Oncol Nurs* 2008; **24:** 193-201.
10. Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims Federal Register, 2009.
11. Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M *et al.* Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. *J Natl Cancer Inst* 2009; **101:** 1624-32.
12. Vickers AJ, Salz T, Basch E, Cooperberg MR, Carroll PR, Tighe F *et al.* Electronic patient self-assessment and management (SAM): a novel framework for cancer survivorship. *BMC Med Inform Decis Mak* 2010; **10:** 34.
13. Bhatia S. Long-term health impacts of hematopoietic stem cell transplantation inform recommendations for follow-up. *Expert Rev Hematol* 2011; **4:** 437-52.
14. Syrjala KL, Martin PJ, Lee SJ. Delivering care to long-term adult survivors of hematopoietic cell transplantation. *J Clin Oncol* 2012; **30:** 3746-51.
15. Lorig KR, Holman H. Self-management education: history, definition, outcomes, and mechanisms. *Annals of behavioral medicine* 2003; **26:** 1-7.

16. Nutbeam D. Health promotion glossary. *Health Promotion International* 1998; **13:** 349-364.
17. Syrjala KL, Langer SL, Abrams JR, Storer BE, Martin PJ. Late effects of hematopoietic cell transplantation among 10 years adult survivors compared with case-matched controls. *J Clin Oncol* 2005; **23:** 6596-6606.
18. Bishop MM, Lee SJ, Beaumont JL, Andrykowski MA, Rizzo JD, Sobocinski KA *et al.* The preventive health behaviors of long-term survivors of cancer and hematopoietic stem cell transplantation compared with matched controls. *Biol Blood Marrow Transplant* 2009; **16:** 207-214.
19. Armenian SH, Sun CL, Francisco L, Baker KS, Weisdorf DJ, Forman SJ *et al.* Health behaviors and cancer screening practices in long-term survivors of hematopoietic cell transplantation (HCT): a report from the BMT Survivor Study. *Bone Marrow Transplant* 2012; **47:** 283-290.
20. Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. *Eff Clin Pract* 2001; **4:** 256-62.
21. Bissonnette J, Woodend K, Davies B, Stacey D, Knoll GA. Evaluation of a collaborative chronic care approach to improve outcomes in kidney transplant recipients. *Clin Transplant* 2013; **27:** 232-8.
22. Newman S, Steed L, Mulligan K. Self-management interventions for chronic illness. *Lancet* 2004; **364:** 1523-37.
23. Spark LC, Reeves MM, Fjeldsoe BS, Eakin EG. Physical activity and/or dietary interventions in breast cancer survivors: a systematic review of the maintenance of outcomes. *J Cancer Surviv* 2013; **7:** 74-82.
24. Mishra SI, Scherer RW, Geigle PM, Berlanstein DR, Topaloglu O, Gotay CC *et al.* Exercise interventions on health-related quality of life for cancer survivors. *The Cochrane database of systematic reviews* 2012; **15**(8): doi: 10.1002/14651858.CD007566.pub2.
25. Nayan S, Gupta MK, Strychowsky JE, Sommer DD. Smoking cessation interventions and cessation rates in the oncology population: an updated systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 2013; **149:** 200-11.
26. De Bleser L, Matteson M, Dobbels F, Russell C, De Geest S. Interventions to improve medicationadherence after transplantation: a systematic review. *Transpl Int* 2009; **22:** 780-97.
27. Creswell JW. Mixed methods procedures. In: London (ed) *Research Design: qualitative, quantitative and mixed methods approaches*, 2 edn. Thousand Oaks: Sage Publishing, 2003, pp 208-227.
28. Wild D, Eremenco S, Mear I, Martin M, Houchin C, Gawlicki M *et al.* Multinational trials-recommendations on the translations required, approaches to using the same language in different countries, and the approaches to support pooling the data: the ISPOR Patient-Reported Outcomes Translation and Linguistic Validation Good Research Practices Task Force report. *Value Health* 2009; **12:** 43040.

29. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A *et al.* Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health* 2005; **8:** 94-104.
30. Dew MA, DiMartini AF, De Vito Dabbs A, Myaskovsky L, Steel J, Unruh M *et al.* Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation* 2007; **83:** 858-73.
31. Denhaerynck K, Dobbels F, Cleemput I, Desmyttere A, Schafer-Keller P, Schaub S *et al.* Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. *Transpl Int* 2005; **18:** 1121-33.
32. Conn VS, Hafdahl AR, Cooper PS, Ruppar TM, Mehr DR, Russell CL. Interventions to improve medication adherence among older adults: meta-analysis of adherence outcomes among randomized controlled trials. *Gerontologist* 2009; **49:** 447-62.

CHAPTER 1:

INTRODUCTION

1.1 Haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation (SCT) is a curative treatment for life-threatening diseases of the blood building system. Since the first SCT in 1968, the number of transplantations performed worldwide has risen to more than 60.000 per year; the number of treated patients now exceeds 1.000.000 [1]. It is mainly indicated against leukemia, lymphoma, myelodysplasia, myeloma, bone marrow failure conditions, severe red blood cell disorders (e.g., sickle cell disease or thalassemia), and certain solid tumors [2].

In Switzerland, an annual average of 35 men and 26 women per 100.000 inhabitants are newly diagnosed with haematological malignancies [3]. To treat these, haematopoietic stem cells can be obtained from the bone marrow, peripheral blood, or umbilical cord blood either of related or unrelated donors (i.e., allogeneic SCT), or from the patients themselves (i.e., autologous SCT). Roughly 200 allogeneic and 350 autologous SCTs are performed each year in Switzerland [4]. The choices of whether to use allogeneic or autologous SCT and of graft source (bone marrow, peripheral blood, or cord blood) depend mainly on the patient's underlying disease and disease status prior to transplantation. Treatment is stringent. Before SCT, to eradicate cancerous cells and to suppress the patient's immune system, preventing it from attacking the donor hematopoietic cells, the patient is treated with highdose chemotherapy, which may include total body irradiation (TBI). Significant post-transplant problems can result from toxic effects related to the preparatory treatments, infections, relapse of the underlying disease and chronic graft versus Host disease (GVHD) which involves attacks by donor T lymphocytes on the patient's organs. Chronic GVHD can affect any organ and can be particular burdensome for patients [5, 6].

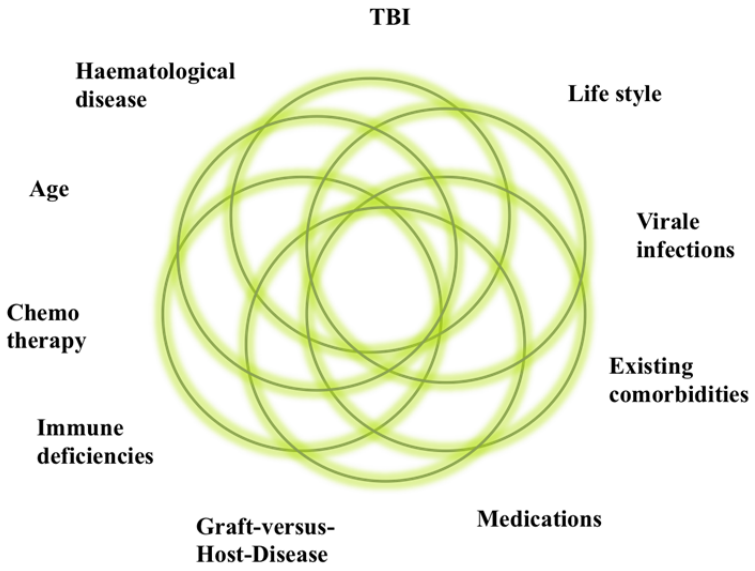


Figure 1: Causes of late effects Adapted from: Deeg H.J., 1999. Delayed complications after haematopoietic cell transplantation, in: Boston Forman S, Blume KG, Thomas ED, Hematopoietic Cell Transplantation, 3 ed. Blackwell Scientific Publications, Inc., pp. 776-806

1.2 Late effects

Side effects occurring more than 3 months post-SCT are classed as late effects. These can be further classified according both to the time of their onset, i.e., as delayed (3 months to 2 years), late (2 to 10 years), and very late events (≥10 years) [7], and to whether they are malignant [8, 9].

Malignant late effects are known complications of high-dose chemotherapy and TBI, and include solid cancers and three types of late haematological malignancy: late relapse of the primary malignant disease, therapy-related secondary haematological malignancies, and donor type leukemia (following allogeneic SCT). Among allogeneic SCT recipients, the estimated risk of malignant late effects is 2% to 6% at 10 years, increasing to 15% at 15 years [10, 11]. Particularly during the first 5 years post-treatment, the most common cause of late deaths (41% of all deaths) remains relapse [12].

Nonmalignant late effects, which can affect any organ, are widely heterogeneous in nature and intensity[11]. Their type and severity depend on the type, duration and intensity of the treatment applied; multiple causes are frequently involved. Common late effects include ocular, endocrine, skeletal, cardiac, gastrointestinal and hepatic dysfunction, the cumulative effects of which have a critical impact on patient morbidity and mortality. Worse still, the number of late effects increases with time. In the first 5 years after SCT, two-thirds of recipients develop at least one chronic health condition; a fifth develops severe or life-threatening conditions [13]. This is particularly problematic for children. Within a median of seven years following childhood SCT, 90% of survivors experience at least one late effect; for 25%, these are severe and even disabling [14, 15].

The effect on health-related quality of life (QoL) can be harsh. Although, for the majority of SCT recipients, longitudinal studies indicate a good to excellent QoL [16], patients with late effects, and especially those suffering from cGVHD, find this quality compromised[5]. Furthermore, for at least 30 years following SCT, across all age groups, recipients' mortality risk is fourfold to nine-fold that of the normal population, reducing estimated life expectancy by 30% [13, 17]. Several excellent reviews systematically describe all known late effects. [7, 9, 13]

1.3 Symptom experience related to late effects after stem cell transplantation

Many late effects manifest as symptoms, a variety of which continue to affect approximately 25% of patients two years after SCT [18]. Not surprisingly, symptoms accompanying cGVHD entail greater distress [5, 19, 20]. However, clinicians might underestimate both the incidence and severity of cancer patients' symptoms, as well as the distress they cause [21]. To correct these false estimates, using patient self-reporting is increasingly recognized as an important source of subjective information[22]. Using a non-validated clinical follow-up questionnaire, a cross-sectional study at the Basel SCT follow-up clinic showed that, on average, at the time of their annual examinations, long-term survivors reported five physical symptoms (IQR 4-10). Most commonly reported were dry skin (47.8%), tiredness (42%), and

dry eyes (42%). Nearly a quarter (23.9%) reported difficulty managing stressful emotional situations, anxiety regarding relapse (22.1%), and memory disturbances (21.2%)[23]. Further research showed that, compared to the general population, SCT survivors suffer significantly more problems with cognitive impairment (20% vs. 7%); muscle weakness (16% vs. 7%), joint stiffness (9% vs. 1%) and leg cramps (16% vs. 4%) [24]. Compared to their matched donor siblings, they also have elevated prevalences of oral symptoms, e.g., dry mouth (10.7% vs 0.9%) and problems chewing or swallowing (7.7% vs. 1.3%). Similarly, more survivors experience neurological concerns, e.g., abnormal sense of taste and smell (10% vs 0.6%), or touch (15.5% vs 9.7%) as well as problems concerning balance, tremor or weakness (13.5% vs 5.3%) [25].

According to the self-regulatory theory [26], symptom experience involves two main dimensions: cognitive (measured according to occurrence, including frequency, severity and duration) and emotional (represented by distress, which may put survivors at risk of uncertainty and fear (e.g., of relapse)) [27 28]. For instance, a patient may experience a mild *numbness in his feet* (≈symptom occurrence) but may report that this is very distressing (≈symptom distress). Measuring symptom experience on these two dimensions is crucial, as research in other patient populations has linked symptom distress to lower perceived QoL, which may trigger medication nonadherence [29].

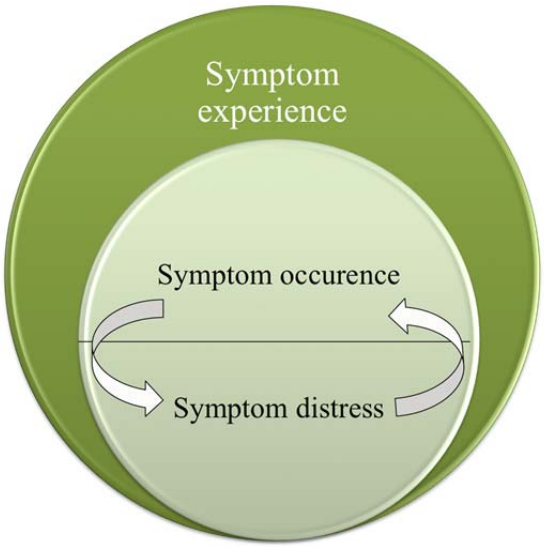


Figure 2: Symptom experience according to the self-regulatory theory

Research suggests that SCT recipients experience a broad range of symptoms, several of which impede daily functions [30]; however, knowledge is limited regarding SCT symptom experience. While several studies have chronicled symptom distress during the first 6 months post-treatment [31-36], few have measured symptom occurrence alongside symptom distress in the first years following SCT [37-39]. One of the few to do so is Larssen et al.'s (2007) examination of the association between perceived health status and symptom experience from discharge to one year post-transplant. The results indicated a strong correlation between perceived health status and the number of symptoms both at discharge

(OR 1.33, p =.009) and at one year post-SCT (OR 2.0, p =.010), i.e., patients reporting "poor health status" had a stable median of 7 to 10 symptoms. However, symptom distress levels did not change significantly over time[37]. Edman et al. (2001) reported that, two to four years after SCT, 88% of 25 survivors had persistent symptoms. Affecting 50% of patients, the most distressing of these were eye problems, sexual dysfunction, tiredness, anxiety, and changes of taste[38]. Another study followed 31 SCT recipients prospectively for two years following treatment, finding that lower symptom distress was a positive predictor of survival [39].

One prospective US study used the generic 23-item Rotterdam Symptom Checklist to examine the evolution of symptom distress from 3 to 6 years post-SCT. The results showed substantial health status and QoL variability based on time since SCT, for which physical symptom distress was a significant predictor. In that case, patients with higher symptom distress reported physical and mental health status significantly lower than healthy population norms. Moreover, in survivors with high symptom distress, the trajectory of physical health reflected impairment throughout and beyond the first decade post-transplantation. Bevans et al. (2013) concluded that post-transplantation comorbid conditions, late treatment effects, cGVHD, and side effects of immunosuppression are particularly related to symptom distress in allogeneic SCT recipients[30].

However, the above-cited studies used various self-report instruments, including the MDASI-BMT [40], FACT-BMT [36], and EORTC-HDC29 [41], all of which were specifically designed for acute treatment and might only address subsets of the long-term post-SCT symptom array. For instance, none capture muscle cramping, blurred vision or skin rash, all of which are common late effects. Furthermore, these instruments have received limited testing in long-term SCT survivors. To our knowledge, only Velikova and colleagues, while developing the EORTC-HDC-29, enlisted survivors more than 1 year post-SCT[41], as is recommended [42, 43]. Also, while the Lee Chronic GVHD Symptom Scale has demonstrated validity for the assessment of cGVHD symptoms in long-term survivors [44], it ignores symptoms caused by late effects other than cGVHD (e.g., palpitations and sensory neuropathy).

1.4 Patient-reported outcome (PRO) instrument in cancer follow-up

Since many symptoms only manifest subjectively and are rarely captured during clinician-based evaluations, self-reporting is crucial for early symptom detection. However, reliably capturing the patient's illness experience requires well-developed and validated instruments. Optimally, SCT patient follow-up should be based on a combination of objective diagnostics and patient reported outcomes (PROs), i.e., reports of the patient's health condition status supplied directly by the patient, without interpretation by a clinician or anyone else [45].

By channelling clear communication between healthcare professionals and patients, PRO instruments facilitate informed decisions regarding symptom management and treatment, and may

even allow prevention of some late effects. Therefore, it is recommended that self-reporting be treated as a guiding element in follow-up care [46]. However, no PRO instrument is yet available to assess late effect symptom experience.

In response to this and similar needs, the US Food and Drug Administration has provided a guidance report, including a five-step breakdown of the PRO development process: (1) Hypothesize a conceptual framework; (2) adjust the conceptual framework and draft the instrument; (3) confirm the conceptual framework and assess other measurement properties; (4) collect, analyse, and interpret the data; and 5) modify the instrument [45].

In **Chapter 3**, the article "Understanding the Importance of Using Patient Reported Outcome (PRO) Measures in patients with Immune Thrombocytopenia" illustrates the value of PROs to gather information on a rare haematological disease. The same article also summarizes the methodological steps necessary to develop PRO instruments, and discusses challenges to their integration into research and clinical practice.

Traditionally, cancer follow-up assessed symptoms indirectly, using adverse event forms or checklists based on the Common Toxicity Criteria for Adverse Events (CTCAE), a long-standing, empirically developed dictionary designed to help clinicians detect and document adverse events in clinical trials [47]. However, in clinical practice and other research settings, the CTCAE might not accurately reflect either patients' illness experiences or the burden of late effects [48, 49].

To improve the CTCAE's precision and reliability regarding cancer treatments' symptomatic toxicities [50, 51], the US National Cancer Institute (NCI) has augmented the CTCAE with a patient - reported outcome item library: the PRO-CTCAE [52]. This is comprised of 124 PRO items, reflecting 78 symptom terms, each of which is assessed according to attributes including presence/absence, frequency, severity, and/or interference with usual or daily activities.

While the PRO-CTCAE is designed to capture the full range of symptomatic treatment effects across a variety of disease sites and treatment modalities, it has received only limited testing in SCT settings. Wood et al. (2013) recently used PRO-CTCAE items to evaluate symptomatic toxicities in the first 100 days post-SCT, but it is currently unknown which items are most suitable to measure late SCT effects. Moreover, while collaborators are developing translations in Chinese and Japanese, the full item bank currently exists only in English and Spanish; no German version is yet available.

Cancer researchers are encouraged to use the PRO-CTCAE item bank to select relevant items for their study populations and to create self-report questionnaires. Yet, as the item bank is designed for cancer populations in general, additional studies are necessary to determine which items fit specific disease populations and to verify each PRO's validity and reliability [53]. Representing a clear gap for

research and clinical care, so far no instrument has been derived and validated specifically for use in patients with SCT. For this reason, we collaborated with the NCI to translate the PRO-CTCAE in German and to select symptom items specific for long-term SCT survivors. Based on the PRO-CTCAE item bank, as patients' and experts' input, we created and preliminary validated a PRO instrument measuring late effect symptom experiences.

C**hapters 4 and 5** describe the development and preliminary psychometric testing of the PROVIVO instrument – a PRO measure of post-allogeneic SCT late effect symptom experience.

1.5 Patient self-management and health behaviours in stem cell transplantation

In addition to assessment, treatment and management of late effects and the associated symptom experiences, follow-up care focuses also on support of patients' self-management capabilities and, where possible prevention of adverse developments. [54]. Self-management involves three main tasks: 'managing emotions', 'managing (new) roles' and 'managing the medical regimen'. Emotional management requires a survivor to deal with the emotional sequels of cancer experience. Its success relies on the balance between the distress a survivor feels and the individual response resources available [27]. Within the scope of `managing life roles', survivors face challenges not only to their social roles, e.g., as partners, parents or friends, but also to their professional roles, which can be particularly troubling. While 60 to 70% of survivors have returned to the workforce two years after SCT [18, 55, 56], only 29% to 31% have returned to full-time employment [18, 56].

While disease specific tasks include responsibilities such as taking medications, organizing clinical visits or receiving recommended vaccinations, health behaviours embrace "any activities undertaken by an individual, regardless of actual or perceived health status, for the purpose of promoting, protecting or maintaining health, whether or not such behaviour is objectively effective towards that end."[57] However, data on the prevalence of problems related to self-management and in particular health behaviours in SCT are scarce.

One notable example is adherence to recommended vaccinations. Thus far, only Bishop et al. (2009) have studied this topic, reporting that SCT survivors (59.7%) were more likely to have had influenza vaccine in the past year than healthy controls (32.7%) but less likely than those over the age of 65 (73%) - for whom the vaccine is also recommended [58]. Also, to our knowledge no studies have measured adherence to sun protection and medication. Since SCT patients are at a high risk for developing skin cancer [59, 60], they should be encouraged to perform frequent skin examinations and to avoid unprotected skin UV exposure. Although most centres recommend wearing protecting clothes and applying sunscreen (SPF 30 or higher) when exposed to sun, it is not known how fully patients adhere to this recommendation.

More data is available on diet. Monitoring for abnormal body mass index (BMI) is crucial, as both under- and overweight are common among SCT survivors [61], and both represent health risks. Overweight is associated with cancer recurrence and increased mortality [62], underweight with fatigue and lack of stamina [63]. As a questionnaire survey indicated that only 5% of 137 allogeneic stem cell recipients regularly ate a healthy diet, i.e., one low in fat and high in fruit and vegetable ingredients, cancer survivors clearly need improved dietary education and support [24].

Another important post-treatment recovery factor is physical activity.[64-66] In the general cancer population, regular exercise has been linked to a range of positive outcomes, including improved physical function [67], less side-effects [68], increased survival [64], enhanced immune function [69], improved quality of life and enhanced psychological well-being [70]. However, symptoms such as fatigue and muscle impairment might deter survivors from exercising [71, 72]. In a questionnaire survey of 2,684 adult acute leukaemia survivors, 53% of respondents fell short of the Centres for Disease Control and Prevention's physical activity recommendations, i.e., 30 minutes of moderate-intensity physical activity ≥5 days per week or 20 min of vigorous-intensity activity ≥3 days per week. Further US studies indicate that 29-36% of SCT survivors exercise for at least 20 - 30 minutes three times per week, compared to 30-45% of matched controls [24, 58].

On the other hand, one well-documented health-endangering behaviour is smoking. Still, data indicate that 7% to 14% of survivors continue to smoke post-transplantation [24, 58, 73]. Among CML patients who received SCT, the 5-year survival rate was highest among non-smokers (68%), compared to low-dose smokers (1-9 pack-years: 62%) and high-dose smokers (>10 pack years, 50% survival) [74]. Monitoring 148 patients undergoing SCT against acute leukaemia for a median of 3.5 years, another study showed that, compared to life-long non-smokers, current smokers required significantly more days of hospitalization (46.2 days versus 25.7 days, p=0.025), and had poorer overall survival rates (hazard ratio =1.88; 95% CI 1.09–3.25) [75].

Another health risk is alcohol consumption. The American Cancer Society recommends limiting alcohol intake to not more than two drinks per day for men and one drink/day for women [76]. It is known that adult SCT patients radically reduce alcohol consumption within the treatment period, and commence drinking after an average of 6 months post-SCT; however they rarely reach pre-transplant consumption levels [77]. Of 2,849 childhood leukaemia survivors with a mean age of 30.1 years (range 16-74.2), 75.5% were alcohol drinkers, 22.3% consumed above weekly recommendations, and 3.5% consumed potentially harmful amounts [78]. Bishopt et al. reported that 20.1% of males and 12.1% of women occasionally drank more than 2 glasses of alcoholic beverages in a day - notably less than in healthy matched controls [58]; and another cross-sectional study reported that highrisk drinking was less prevalent in SCT survivors (9.5%) than in controls (13.3%):[73]

To date, no study has examined a comprehensive set of health behaviours. Further, knowledge is lacking as to whether health behaviours among European SCT survivors differ from those of the general population.

Chapter 6 discusses the results of a comparative cross-sectional multi-centre study. Using propensity score matching to pair survivors with controls from the general Swiss population, "Differences in health behaviours between survivors after allogeneic haematopoietic stem cell transplantation and the general population" explored prevalences of SCT recipients' health behaviours. The findings reveal that survivors are most likely to adopt beneficial health behaviours, namely not smoking and reduced alcohol consumption. Yet, relative to the general population, a considerable group still engages in unfavourable behaviors, particularly regarding physical activity and dieting.

1.6 Medication adherence within patient self-management

As a core characteristic of self-management, medication adherence, i.e., the process by which patients take their medications as prescribed [79], has been studied extensively in various chronically ill populations. Conversely, medication nonadherence (MNA) is defined as "a deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect" [80], Evidence on the overall population is disturbing: up to 50% of patients take their medications other than as prescribed [81, 82] .

Medication adherence starts with the ***initiation*** of treatment, when the patient takes the first dose of a prescribed medication. It continues with ***implementation*** of the dosing regimen, i.e., the extent to which a patient's actual taking behaviour corresponds to the prescribed dosing regimen. ***Discontinuation*** refers to a patient terminating a treatment earlier than recommended and not restarting. Nonadherence can involve any or all of these: late or non-initiation of the prescribed treatment, sub-optimal implementation of the dosing regimen, or early discontinuation.[79]

Nonadherence to immunosuppressant medication is particularly problematic. As observed in solid organ transplant recipients [83-86], incorrect intake can seriously affect outcomes, resulting in higher rates of hospitalization, avoidable use of multiple other services, and higher healthcare costs.[87, 88] Unfortunately, while more than a third of SCT patients are prescribed a wide array of medications, including immunosuppressants [89], no study has yet evaluated the prevalence, determinants and consequences of medication nonadherence in this population.

Chapter 7 contains the manuscript "Medication nonadherence in long-term survivors taking

immunosuppressants after allogeneic stem cell transplantation (PROVIVOmed): a multicentre cross-sectional study". This paper reports the target group's prevalence of MNA to immunesuppressants, examining its correlates and exploring its association with cGVHD.

1.7 Healthcare professionals' practice patterns for supporting medication adherence

Healthcare professionals have a duty to assess, monitor and support patients' medication management. Regarding adherence enhancing interventions, however, the extent and content of adherence support varies tremendously between clinical settings, often falling short of the state-of-the-art [90, 91]. Important first steps include routinely assessing patients' adherence and screening them for nonadherence risk factors. For those identified as non-adherent or at risk of nonadherence, three types of adherence enhancing interventions are available, all of which can quickly be integrated into normal healthcare practice: *Educational/cognitive interventions* present information or knowledge individually or in a group setting verbally, in a written format, or audio-visually; *counselling/behavioural interventions* reduce, shape or reinforce specific behaviours, empowering patients to participate in their own care, while improving their skill levels or normal routines; and *psychological/affective interventions* focus on patients' feelings and emotions or relationships and social support[92].

However, even for apparently direct needs such as patient education, no individual intervention type offers a definitive solution. A 2009 meta-analysis showed that educational interventions, which are most frequently used, actually have limited efficacy, as substantial learning requires the development of knowledge-building behaviours [93]. As an alternative, *mixed interventions* combine the benefits of any or all of the basic types to overcome their individual weaknesses [94]. For medication taking, a compelling range of evidence indicates that mixed multi-level interventional approaches, typically including multiple potentially interacting techniques, improve patient behaviour more efficiently than individual methods [93-97].

With the increasing use of such mixtures comes the need for understandable methods of analysing them. To allow clear and accurate reporting of the behavioural content of interventions described in protocols and study reports on healthy eating, physical activity, alcohol use, and smoking cessation, Michie and colleagues developed a taxonomy of 93 behaviours change techniques (BCT), clustered in 16 groups. Along with criteria for the operationalization of each BCT, clear labels are supplied to categorize and report each intervention component [98]. Elsewhere, a recent meta-analysis by Dusseldorp et al. provided evidence for effective combinations of BCTs, finding that providing information about healthy and unhealthy behaviours and their likely outcomes, encouraging prompt formation of intentions, and using follow-up prompts were particularly effective [99].

Still, a considerable gap always exists between current knowledge and clinical practice. With no information available on which patterns of practice are congruent with state-of-science adherence enhancing interventions in the field of SCT, then, it must be assumed that their actual use is lacking; and where such interventions are used, their relative efficiencies remain to be seen.

C**hapter 8** presents "Nurses' practice patterns in relation to adherence enhancing interventions in stem cell transplant care: a survey from the Nurses' Group of the European Group for Blood and Marrow Transplantation".

1.8 References

1. Gratwohl A, Baldomero H, Passweg J. Hematopoietic stem cell transplantation activity in Europe. *Curr Opin Hematol* 2013; **20:** 485-93.
2. American Society of Hematology. *50 years in HematologyResearch that revolutionized patient care*, American Society of Hematology: Washington DC, 2009.
3. Bouchardy C, Lutz JM, Kühni C. *Krebs in der Schweiz, Stand und Entwicklung von 1983 bis 2007*, Bundesamt für Statistik, National Institute for Cancer Epidemiology and Registration, Schweizer Kinderkrebsregister, 2010.
4. Passweg JR, Baldomero H, Bargetzi M, Bucher C, Chalandon Y, Duchosal MA *et al.* Haematopoietic stem cell transplantation: activity in Switzerland compared with surrounding European countries. *Swiss Med Wkly* 2013; **22:** 13757.
5. Pallua S, Giesinger J, Oberguggenberger A, Kemmler G, Nachbaur D, Clausen J *et al.* Impact of GvHD on quality of life in long-term survivors of haematopoietic transplantation. *Bone Marrow Transplant* 2010; **45:** 1534-9.
6. Wood WA, Chai X, Weisdorf D, Martin PJ, Cutler C, Inamoto Y *et al.* Comorbidity burden in patients with chronic GVHD. *Bone Marrow Transplant* 2013; **48:** 1429-36.
7. Tichelli A, Rovo A, Passweg J, Schwarze CP, Van Lint MT, Arat M *et al.* Late complications after hematopoietic stem cell transplantation. *Expert Rev Hematol* 2009; **2:** 583-601.
8. Tichelli A, Rovo A, Gratwohl A. Late pulmonary, cardiovascular, and renal complications after hematopoietic stem cell transplantation and recommended screening practices. *Hematology Am Soc Hematol Educ Program* 2008**:** 125-133.
9. Socie G, Salooja N, Cohen A, Rovelli A, Carreras E, Locasciulli A *et al.* Nonmalignant late effects after allogeneic stem cell transplantation. *Blood* 2003; **101:** 3373-85.
10. Socié G, Rizzo JD. Second Solid Tumors: Screening and Management Guidelines in Long-Term Survivors After Allogeneic Stem Cell Transplantation. *Semin Hematol* 2012; **49:** 4-9.
11. Tichelli A, Rovo A, Socie G. Late effects after hematopoietic stem cell transplantation--critical issues. *Curr Probl Dermatol* 2012; **43:** 132-49.
12. Wingard JR, Majhail NS, Brazauskas R, Wang Z, Sobocinski KA, Jacobsohn D *et al.* Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *J Clin Oncol* 2011; **29:** 2230-9.
13. Bhatia S. Long-term health impacts of hematopoietic stem cell transplantation inform recommendations for follow-up. *Expert Rev Hematol* 2011; **4:** 437-52.
14. Lof CM, Winiarski J, Giesecke A, Ljungman P, Forinder U. Health-related quality of life in adult survivors after paediatric allo-SCT. *Bone Marrow Transplant* 2009; **43:** 461-468.
15. Bresters D, van Gils IC, Kollen WJ, Ball LM, Oostdijk W, van der Bom JG *et al.* High burden of late effects after haematopoietic stem cell transplantation in childhood: a single-centre study. *Bone Marrow Transplant* 2010; **45:** 79-85.

16. Grulke N, Albani C, Bailer H. Quality of life in patients before and after haematopoietic stem cell transplantation measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C30. *Bone Marrow Transplant* 2012; **47:** 473-82.
17. Martin PJ, Counts GW, Jr., Appelbaum FR, Lee SJ, Sanders JE, Deeg HJ *et al.* Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. *J Clin Oncol* 2010; **28:** 1011-6.
18. Syrjala KL, Langer SL, Abrams JR, Storer B, Sanders JE, Flowers ME *et al.* Recovery and long-term function after hematopoietic cell transplantation for leukemia or lymphoma. *Jama* 2004; **291:** 2335-43.
19. Herzberg PY, Heussner P, Mumm FH, Horak M, Hilgendorf I, von Harsdorf S *et al.* Validation of the human activity profile questionnaire in patients after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2010; **16:** 1707-17.
20. Lee SJ, Kim HT, Ho VT, Cutler C, Alyea EP, Soiffer RJ *et al.* Quality of life associated with acute and chronic graft-versus-host disease. *Bone Marrow Transplant* 2006; **38:** 305-10.
21. Xiao C, Polomano R, Bruner DW. Comparison Between Patient-Reported and Clinician-Observed Symptoms in Oncology. *Cancer Nurs* 2013; **36**: E1-E16.
22. Lipscomb J, Gotay CC, Snyder CF. Patient-reported outcomes in cancer: a review of recent research and policy initiatives. *CA Cancer J Clin* 2007; **57:** 278-300.
23. Kirsch M., Halter J., De Geest S. Self-reported symptoms and concerns in long-term survivors attending follow-up visits after Haematopoietic Stem Cell Transplantation: A cross-sectional single centre evaluation. *Journal of Nursing & Care* 2012; **1:** doi: 10.4172/2167-1168.1000116.
24. Syrjala KL, Langer SL, Abrams JR, Storer BE, Martin PJ. Late effects of hematopoietic cell transplantation among 10-year adult survivors compared with case-matched controls. *J Clin Oncol* 2005; **23:** 6596-6606.
25. Baker KS, Ness KK, Weisdorf D, Francisco L, Sun CL, Forman S *et al.* Late effects in survivors of acute leukemia treated with hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. *Leukemia* 2010; **24:** 2039-47.
26. Leventhal H, Brissette I, Leventhal EA. The common-sense model of self-regulation of health and illness. In: Florence K, Cameron LD, Leventhal H (eds). *The Self-regulation of Health and Illness Behaviour*. Routledge, 2003, pp 43-65.
27. Andrykowski MA, Lykins E, Floyd A. Psychological health in cancer survivors. *Semin Oncol Nurs* 2008; **24:** 193-201.
28. Leventhal H, Diefenbach M, Leventhal EA. Illness cognition: Using common sense to understand treatment adherence and affect cognition interactions. *Cognitive Therapy and Research* 1992; **16:** 143-163.
29. Kugler C, Geyer S, Gottlieb J, Simon A, Haverich A, Dracup K. Symptom experience after solid organ transplantation. *Journal of psychosomatic research* 2009; **66:** 101-10.

30. Bevans MF, Mitchell SA, Barrett J, Bishop MR, Childs R, Fowler D *et al.* Symptom Distress Predicts Long-Term Health and Well-Being in Allogeneic Stem Cell Transplantation Survivors. *Biol Blood Marrow Transplant* 2014; **20:** 387-95.
31. Anderson KO, Giralt SA, Mendoza TR, Brown JO, Neumann JL, Mobley GM *et al.* Symptom burden in patients undergoing autologous stem-cell transplantation. *Bone Marrow Transplantion* 2007; **39:** 759-66.
32. Bevans MF, Mitchell SA, Marden S. The symptom experience in the first 100 days following allogeneic hematopoietic stem cell transplantation (HSCT). *Supportive Care in Cancer* 2008; **16:** 1243-54.
33. Larsen J, Nordstrom G, Bjorkstrand B, Ljungman P, Gardulf A. Symptom distress, functional status and health related quality of life before highdose chemotherapy with stem cell transplantation. *European Journal of Cancer Care* 2003; **12:** 71-80.
34. Larsen J, Nordstrom G, Ljungman P, Gardulf A. Symptom occurrence, symptom intensity, and symptom distress in patients undergoing highdose chemotherapy with stem cell transplantation. *Cancer Nursing* 2004; **27:** 55-64.
35. Schoulte JC, Lohnberg JA, Tallman B, Altmaier EM. Influence of coping style on symptom interference among adult recipients of hematopoietic stem cell transplantation. *Oncol Nurs Forum* 2011; **38:** 582-6.
36. Cohen MZ, Rozmus CL, Mendoza TR, Padhye NS, Neumann J, Gning I *et al.* Symptoms and Quality of Life in Diverse Patients Undergoing Hematopoietic Stem Cell Transplantation. *J Pain Symptom Manage* 2012; **44:** 168-80.
37. Larsen J, Nordstrom G, Ljungman P, Gardulf A. Factors associated with poor general health after stem cell transplantation. *Supportive Care in Cancer* 2007; **15:** 849-57.
38. Edman L, Larsen J, Hagglund H, Gardulf A. Health related quality of life, symptom distress and sense of coherence in adult survivors of allogeneic stem cell transplantation. *European Journal of Cancer Care* 2001; **10:** 124-30.
39. Molassiotis A, Van Den Akker OB, Milligan DW, Goldman JM. Symptom distress, coping style and biological variables as predictors of survival after bone marrow transplantation. *Journal of Psychosomtic Research* 1997; **42:** 275-85.
40. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M *et al.* Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer* 2000; **89:** 1634-46.
41. Velikova G, Weis J, Hjermstad MJ, Kopp M, Morris P, Watson M *et al.* The EORTC QLQ-HDC29: a supplementary module assessing the quality of life during and after highdose chemotherapy and stem cell transplantation. *European Journal of Cancer* 2007; **43:** 87-94.

42. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E *et al.* Content validity-establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force report: part 2 assessing respondent understanding. *Value Health* 2011; **14:** 978-88.
43. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E *et al.* Content validity establishing and reporting the evidence in newly developed patient outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1 eliciting concepts for a new PRO instrument. *Value Health* 2011; **14:** 967-77.
44. Lee S, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graftversus-host disease. *Biology of Blood and Marrow Transplantation* 2002; **8:** 444-52.
45. Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims Federal Register, 2009.
46. Beavers J, Lester J. Survivorship care for adult recipients of hematopoietic cell transplantations. *Clin J Oncol Nurs* 2010; **14:** 136-9.
47. Trotti A, Colevas AD, Setser A, Basch E. Patient-reported outcomes and the evolution of adverse event reporting in oncology. *J Clin Oncol* 2007; **25:** 5121-7.
48. Stromgren AS, Groenvold M, Sorensen A, Andersen L. Symptom recognition in advanced cancer. A comparison of nursing records against patient selfrating. *Acta Anaesthesiol Scand* 2001; **45:** 1080-5.
49. Lipscomb J, Reeve BB, Clauser SB, Abrams JS, Bruner DW, Burke LB *et al.* Patient-reported outcomes assessment in cancer trials: taking stock, moving forward. *J Clin Oncol* 2007; **25:** 5133-40.
50. Wu AW, Snyder C, Clancy CM, Steinwachs DM. Adding the patient perspective to comparative effectiveness research. *Health Aff (Millwood)* 2010; **29:** 1863-71.
51. Basch E. The missing voice of patients in drugsafety reporting. *N Engl J Med* 2010; **362:** 865-869.
52. Basch EM, Reeve BB, Mitchell SA et al. Development of the National Cancer Institute's PatientReported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J Natl Cancer Inst* In Press.
53. Basch E. Technical Proposal: Development of the PRO-CTCAE. In: York N, (ed), 2008.
54. Syrjala KL, Martin PJ, Lee SJ. Delivering care to long-term adult survivors of hematopoietic cell transplantation. *J Clin Oncol* 2012; **30:** 3746-51.
55. Lee SJ, Fairclough D, Parsons SK, Soiffer RJ, Fisher DC, Schlossman RL *et al.* Recovery after stem cell transplantation for hematologic diseases. *J Clin Oncol* 2001; **19:** 242-252.
56. Bieri S, Roosnek E, Helg C, Verholen F, Robert D, Chapuis B *et al.* Quality of life and social integration after allogeneic hematopoietic SCT. *Bone Marrow Transplant* 2008; **42:** 819-27.
57. Nutbeam D. Health promotion glossary. *Health Promotion International* 1998; **13:** 349-364.

58. Bishop MM, Lee SJ, Beaumont JL, Andrykowski MA, Rizzo JD, Sobocinski KA *et al.* The preventive health behaviors of long-term survivors of cancer and hematopoietic stem cell transplantation compared with matched controls. *Biol Blood Marrow Transplant* 2009; **16:** 207-214.
59. Cavalier M, Shmalo JA, Yu M, Billings SD, Abonour R, Nelson RP, Jr. Skin cancer after non-myeloablative hematopoietic cell transplantation. *Bone Marrow Transplant*; **37:** 11031108.
60. Kolb HJ, Socie G, Duell T, Van Lint MT, Tichelli A, Apperley JF *et al.* Malignant neoplasms in long-term survivors of bone marrow transplantation. Late Effects Working Party of the European Cooperative Group for Blood and Marrow Transplantation and the European Late Effect Project Group. *Annals of internal medicine* 1999; **131:** 738-44.
61. Skoczen S, Surmiak M, Strojny W. Survivors of acute lymphoblastic leukemia and body mass changes. *Expert Opin Drug Saf* 2010; **9:** 65-77.
62. Doyle C, Kushi LH, Byers T, Courneya KS, Demark-Wahnefried W, Grant B *et al.* Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin* 2006; **56:** 323-53.
63. Toles M, Demark-Wahnefried W. Nutrition and the cancer survivor: evidence to guide oncology nursing practice. *Semin Oncol Nurs* 2008; **24:** 171-9.
64. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *Jama* 2005; **293:** 2479-86.
65. Barrera S, Demark-Wahnefried W. Nutrition during and after cancer therapy. *Oncology (Williston Park)* 2009; **23**(2 Suppl Nurse Ed)**:** 15-21.
66. van Weert E, HoekstraWeebers JE, May AM, Korstjens I, Ros WJ, van der Schans CP. The development of an evidence-based physical self-management rehabilitation programme for cancer survivors. *Patient Educ Couns* 2008; **71:** 169-90.
67. Wiskemann J, Huber G. Physical exercise as adjuvant therapy for patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2007; **41:** 321-329.
68. Schmitz KH, Holtzman J, Courneya KS, Masse LC, Duval S, Kane R. Controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2005; **14:** 1588-95.
69. Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. *J Nutr* 2002; **132:** 3456S-3464S.
70. Baumann FT, Kraut L, Schule K, Bloch W, Fauser AA. A controlled randomized study examining the effects of exercise therapy on patients undergoing haematopoietic stem cell transplantation. *Bone Marrow Transplant* 2009; **45:** 355-362.
71. Danaher EH, Ferrans C, Verlen E, Ravandi F, van Besien K, Gelms J *et al.* Fatigue and physical activity in patients undergoing hematopoietic stem cell transplant: The symptom experience in the first 100 days following allogeneic hematopoietic stem cell transplantation. *Oncol Nurs Forum* 2006; **33:** 614-24.

72. Hovi L, Kurimo M, Taskinen M, Vettenranta J, Vettenranta K, Saarinen-Pihkala UM. Suboptimal long-term physical performance in children and young adults after pediatric allo-SCT. *Bone Marrow Transplant*; **45:** 738-45.
73. Armenian SH, Sun CL, Francisco L, Baker KS, Weisdorf DJ, Forman SJ *et al.* Health behaviors and cancer screening practices in long-term survivors of hematopoietic cell transplantation (HCT): a report from the BMT Survivor Study. *Bone Marrow Transplant* 2012; **47:** 283-290.
74. Marks DI, Ballen K, Logan BR, Wang Z, Sobocinski KA, Bacigalupo A *et al.* The effect of smoking on allogeneic transplant outcomes. *Biol Blood Marrow Transplant* 2009; **15:** 1277-87.
75. Ehlers SL, Gastineau DA, Patten CA, Decker PA, Rausch SM, Cerhan JR *et al.* The impact of smoking on outcomes among patients undergoing hematopoietic SCT for the treatment of acute leukemia. *Bone Marrow Transplant* 2011; **46:** 285-90.
76. Brown JK, Byers T, Doyle C, Courneya KS, DemarkWahnefried W, Kushi LH *et al.* Nutrition and Physical Activity During and After Cancer Treatment: An American Cancer Society Guide for Informed Choices. *CA Cancer J Clin* 2003; **53:** 268-291.
77. Chang G, Orav EJ, McNamara TK, Tong MY, Antin JH. Psychosocial function after hematopoietic stem cell transplantation. *Psychosomatics* 2005; **46:** 34-40.
78. Frobisher C, Lancashire ER, Reulen RC, Winter DL, Stevens MC, Hawkins MM. Extent of alcohol consumption among adult survivors of childhood cancer: the British Childhood Cancer Survivor Study. *Cancer Epidemiol Biomarkers Prev* 2010; **19:** 1174-84.
79. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T *et al.* A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012; **73:** 691-705.
80. Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Evans R *et al.* Nonadherence consensus conference summary report. *Am J Transplant* 2009; **9:** 35-41.
81. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care* 2004; **42:** 200-9.
82. Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Arch Intern Med* 2007; **167:** 540-50.
83. Schafer-Keller P, Garzoni D, Dickenmann M, De Geest S. [Medication non adherencepredictive factors and diagnostics]. *Ther Umsch* 2010; **67:** 283-8.
84. Denhaerynck K, Steiger J, Bock A, SchaferKeller P, Kofer S, Thannberger N *et al.* Prevalence and risk factors of nonadherence with immunosuppressive medication in kidney transplant patients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2007; **7:** 108-16.
85. Schmid-Mohler G, Thut MP, Wuthrich RP, Denhaerynck K, De Geest S. Nonadherence to immunosuppressive medication in renal transplant recipients within the scope of the Integrative Model of Behavioral Prediction: a cross-sectional study. *Clin Transplant* 2010; **24:** 213-22.

86. De Geest S, Dobbels F, Fluri C, Paris W, Troosters T. Adherence to the therapeutic regimen in heart, lung, and heartlung transplant recipients. *J Cardiovasc Nurs* 2005; **20:** S88-98.
87. Fuji S, Kapp M, Einsele H. Challenges to preventing infectious complications, decreasing re-hospitalizations, and reducing cost burden in long-term survivors after allogeneic hematopoietic stem cell transplantation. *Semin Hematol* 2012; **49:** 10-4.
88. Khera N, Zeliadt SB, Lee SJ. Economics of hematopoietic cell transplantation. *Blood* 2012; **120:** 1545-51.
89. Bishop MM, Rodrigue JR, Wingard JR. Mismanaging the gift of life: noncompliance in the context of adult stem cell transplantation. *Bone Marrow Transplantion* 2002; **29:** 875-80.
90. Berben L, Bogert L, Leventhal M, Fridlund F, Jaarsma T, Norekvål T *et al.* Which interventions are used to enhance medication adherence in cardiovascular patients? A survey of current practice. *Eur J Cardiovasc Nurs* 2011a; **10:** 14-21.
91. Berben L, Dobbels F, Kugler C, Russell CL, De Geest S. Interventions used by health care professionals to enhance medication adherence in transplant patients: a survey of current clinical practice. *Prog Transplant* 2011; **21:** 322-31.
92. De Bleser L, Dobbels F, Berben L, Vanhaecke J, Verleden G, Nevens F *et al.* The spectrum of nonadherence with medication in heart, liver, and lung transplant patients assessed in various ways. *Transpl Int* 2011; **24:** 882-91.
93. Conn VS, Hafdahl AR, Cooper PS, Ruppar TM, Mehr DR, Russell CL. Interventions to improve medication adherence among older adults: meta-analysis of adherence outcomes among randomized controlled trials. *Gerontologist* 2009; **49:** 447-62.
94. De Bleser L, Matteson M, Dobbels F, Russell C, De Geest S. Interventions to improve medicationadherence after transplantation: a systematic review. *Transplant International* 2009; **22:** 780-797.
95. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane database of systematic reviews* 2008; (2)**:** CD000011.
96. Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. Interventions to enhance medication adherence. *Cochrane database of systematic reviews* 2005; (4)**:** CD000011.
97. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *Jama* 2002; **288:** 2868-79.
98. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W *et al.* The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 2013; **46:** 81-95.
99. Dusseldorp E, van Genugten L, van Buuren S, Verheijden MW, van Empelen P. Combinations of Techniques That Effectively Change Health Behavior: Evidence From Meta-CART Analysis. *Health Psychol* 2013; **25:** 25.

CHAPTER 2:

AIMS

Given the gaps in the evidence regarding symptom experience of late effects, self-management, health behaviours and in particularly medication adherence in survivors after allogeneic SCT, the aims of this dissertation were following:

1. To develop a patient-reported outcome (PRO) instrument measuring symptom experience of late effects after SCT and to test the initial content validity
2. To validate the newly developed PRO instrument and assess its psychometric properties
3. To determine the prevalence of eight health behaviours in SCT survivors (i.e., physical activity, dietary habits and weight control, alcohol intake, smoking, influenza vaccination, sun protection, and medication adherence) and to compare survivors' health behaviours with those of matched controls from the general population
4. To determine prevalence and correlates of medication nonadherence to immunosuppressants in allogeneic SCT patients and to explore the association between patient-reported medication nonadherence to immunosuppressants and cGVHD
5. To assess practice patterns of assessment/screening methods and interventions used to enhance medication adherence and to determine nurses' perceived efficacy of used assessment/screening methods and adherence-enhancing interventions

CHAPTER 3:

UNDERSTANDING THE IMPORTANCE OF USING PATIENT REPORTED OUTCOME MEASURES IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA

Monika Kirsch[1, 2]; Robert Klaassen [3] ; Sabina De Geest [1, 3]; Axel Matzdorff [5]; Tatyana Ionova [6], Fabienne Dobbels [4]

[1] *Institute of Nursing Science, University of Basel, Switzerland*

[2] *Department of Hematology, University Hospital Basel, Switzerland*

[3] *Department of Pediatrics, Division of Hematology/Oncology, University of Ottawa, Children's Hospital of Eastern Ontario, Ottawa, Canada*

[4] *Health Services and Nursing Research, Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium*

[5] *Department of Hematology and Oncology, Oncology Center Saarbruecken, Germany*

[6] *North-Western Branch of Pirogov National Medical Surgical Center, St. Petersburg, Russia*

[7] *Multinational Center for Quality of Life Research, St.Petersburg, Russia*

Published in

Seminars in Hematology 2013; 50 Suppl 1: 39-42

Modified version

3.1 Abstract

Incorporating patient-reported outcomes (PRO) when studying patients with immune thrombocytopenia (ITP) is essential since treatment decisions are complex and using platelet count only partly explains disease burden. Since most symptoms are only experienced subjectively and are seldom captured during clinician-based evaluations, using self-report is crucial for early symptom detection. Capturing the patient's illness experience, however, necessitates using well-developed and validated instruments. This article provides insight on the importance of using PROs in ITP, summarizes the methodological steps to develop PRO instruments and discusses challenges related to integrating PROs into research and clinical practice.

3.2 Background

Immune thrombocytopenia (ITP) affects between 26 people per 100.000 per year[1]. While the disease in children generally has a sudden onset but a good prognosis, ITP in adults often presents gradually, but tends to be chronic in nature. Choosing the right therapy at the right time is the most challenging task for clinicians. Treatment side effects can be substantial, and are often perceived by patients as worse than the symptoms of the disease [2]. Traditionally, the assessment of a patient's response to the chosen treatment has been exclusively made by clinicians based on platelet count and clinical bleeding [3]. Given, however, that many patients with very low platelet counts do not bleed, it is emphasized that treatment choice should rely more on symptoms[4], underscoring the importance of incorporating the patient's perspective by using patient reported outcomes (PROs). A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. Examples include quality of life (QoL), symptom experience, treatment satisfaction, and adherence [5].

The importance of PROs in drug development is currently acknowledged worldwide, with the requirement that the PRO instruments are created and validated according to well-described standards outlined in the US Food and Drug Administration (FDA) guidance and the reflection paper on the measures of health-related QoL of the European Medicines Agency [5, 6]. This article summarizes the advantages of using PROs in ITP, provides insight into the different methodological steps involved in developing or modifying instruments, and provides examples of how they can be incorporated into research and clinical practice.

3.2.1 Advantages of the use of PROs in ITP

First of all, PROs facilitate better understanding of the impact of the disease and treatment on the patients' life. Assessing the patient's perspective may reveal valuable information that would be missed when relying exclusively on clinician report[7]. For example, current ASH treatment guidelines focus on corticosteroids' medical side effects including hyperglycemia and osteoporosis, whereas weight gain, mood swings and puffy face are most bothersome to patients[8]. Secondly, the patients' perspective might provide unique insights on treatment effectiveness. Directly asking the patient about adherence in the situation of nonresponse to steroids, for instance, might facilitate a deeper understanding why the drugs are not working. Thirdly, PROs can be relevant in decision making processes. Two drugs can have similar effectiveness, but different side effect profiles. In particular, patients report higher treatmentbother with corticosteroids than with other ITP therapies[9]. Patients' preferences might therefore guide treatment choice.

Because of these recognized values, the European Hematology Association Scientific Working Group "Quality of Life and Symptoms" developed the "Patient-Reported Outcomes in Hematology"

guidelines which cover conceptual, methodological and practical issues surrounding PRO measurement. They provide an overview of existing instruments, and describe state-of-the-art studies incorporating PROs of which some key insights are discussed below[10].

3.2.2 What constitutes a good PRO?

Developing a PRO is not a "do it yourself" project. It is labourintensive, necessitating meticulous methodology, and requires a collaborative team of clinicians, scientists, statisticians and patients. Excellent methodological guidance is offered by the article series published in "Value in Health"[11]. Before developing a new PRO, clinicians should consider using existing ones. Electronic databases, such as PROQOLID or PROMIS offer a quick and comprehensive overview of existing instruments. So far, however, instruments capturing the patient's experience of ITP almost exclusively focus on QoL, often applying generic instruments such as the Short Form36 and the EQ5D in adults, and the PedsQL and KINDL in children[10]. Three diseasespecific QoL measures are also available: the ITP-patient administered questionnaire for adults, the Kids' ITP Tool and the ITP-Quality of Life for children [12].

If a PRO instrument is available, each clinician should answer five key methodological questions [5, 11] before adopting it in research or practice.

3.2.3 Does the instrument provide a conceptual definition?

Several PRO instruments are published that do not describe what the instrument aims to measure, or do not provide the conceptual framework that is underpinning the items. One should check that what you are trying to measure fits well with the concept and items outlined in existing PRO instruments. For instance, if you would like to understand the impact of ITP on a person's social and professional functioning you should check whether the PRO you are considering addresses these issues. If that is not the case, the search for a more appropriate instrument should continue.

3.2.4 For which patient population was the PRO instrument developed?

Instead of hastily choosing a self-report instrument off the shelf, one should carefully look at the sample characteristics: for whom was the questionnaire designed? Are these patients similar to the study population one has in mind? Even if the concept measured is the same, a PRO instrument measuring side effects of immunosuppressive drugs in transplantation might not be applicable to patients taking immunosuppressive drugs for rheumatic conditions. Also, will subjects be able to complete the questionnaire? Think of vision problems, cognitive impairments or literacy levels. If questionnaires are designed in a different language, culturally sensitive translations, following rigorous protocols are mandatory, to make sure items and instructions are clear to patients with a different geographical or cultural background.

3.2.5 Was there sufficient patient input in the PRO instrument development process?

Strictly speaking, if no patients were involved in the development process, it is not really a PRO instrument. Patient involvement is recommended at three possible occasions[5]. First of all, if no conceptual definition exists, qualitative interviews with the patient group of interest, are helpful to understand how, for instance, patients conceptualize side effects of pharmacological treatment (e.g. patients might talk about frequency of occurrence, distress experienced and impact on their daily functioning as dimensions of the concept 'side effects'). Also, interviewing patients allows to identifying the symptoms which they deem to be important. Secondly, interviews with patients can be conducted to define items in line with the conceptual definition. An instrument on side effect experience, for instance, would not be a good instrument if it only assesses the occurrence of side effects but not the severity, or if the list of side effects measured is incomplete. When developing items, it is recommended that instrument developers stay as close as possible to the patients' wordings. Patients will for instance talk about wind or gas and not flatulence, or hair growth and not hirsutism. Finally, once the instrument is drafted, the appropriateness of recall period and response options, as well as the clarity of instructions and items needs to be evaluated with patients (also called cognitive debriefings).

3.2.6 Is the instrument's reliability and validity well established?

Validity and reliability testing is an ongoing process which involves many different test procedures that need to be conducted in the study population of interest. When selecting an instrument, one should ask if and to what extent it has been validated in a population that is similar to the one of interest. If treatment related improvement of PROs is a primary research goal, it is also good to know if the instrument is responsive to change. Many types of validity (e.g., content, concurrent, construct) and reliability (e.g., internal consistency, testretest) can be tested. The interested reader can find an overview of terminology related to psychometric testing in the paper of Kimberlin and colleagues[13].

3.2.7 How to interpret the collected PRO data?

Interpretability means the degree to which one can assign easily understood meaning to an instrument's quantitative score, and represents one of the most complicated challenges in PRO measurement[14]. Optimally, test developers give clear information about scoring and interpretation and if not there exists evidence guiding scoring interpretation[15]. Even more important is the distinction between "statistically significant" and "clinically relevant" differences. For instance, differences in QoL between stable chronic ITP patients taking romiplostim therapy and those with no treatment might be statistically significant, but an individual patient might not actually feel a '2 points scale difference' in daily life.

3.2.8 Integrating PROs in clinical research and practice

At present, the systematic use of PRO instruments in clinical care and research is rare, because of both clinician and patient factors. Although most clinicians agree that PROs are important to capture the patient's experience, their integration in clinical workflows is thought to be burdensome, labor-intense or will increase administrative costs. However, PRO instruments can be successfully implemented in clinical processes by using thorough planning, training of personnel and pilot-testing. They can present clinicians with real-time information that are relevant for patient communication, decision making, and interdisciplinary collaboration. There is also a concern about patients' willingness and ability to fill out questionnaires. In particular, the longitudinal use of PROs decreases patients' motivation to engage actively, especially if they do not get adequate feedback. The easier to complete and interpret, and the more relevant the PRO assessed, the higher the likelihood that both clinicians and patients will benefit of it. As a future trend, several institutions facilitate real-time electronic PRO (e-PRO) symptom reporting and combine them with electronic health records[16]. Features of these e-PRO reporting systems include simple interfaces for patients, automated reminders, clear reports for clinicians that illustrate longitudinal illness trajectories, and real-time alerts when alarming symptoms are reported. The routine use of e-PRO data in the ITP setting could create a rich data source to enable understanding of the patient experience and link this to clinical and economic outcomes.

3.3 Conclusions

The use of PROs adds to the understanding how patients are affected by ITP and of the treatment and health care provided. PROs can help in deciding whether to modify specific treatment elements such as medications, consultant care, patient education, or support services. The purpose of including PROs in clinical studies is to understand the patient's perspective on what is gained or lost from treatment. Optimally, clinical practice and research should combine objective diagnostics with PRO instruments. This approach will contribute to patient care quality by detecting health changes and nascent problems undetectable via clinical observations, leading to early treatment and hence to improved patient outcomes.

3.4 References

1. Terrell DR, Beebe LA, Vesely SK, et al. The incidence of immune thrombocytopenic purpura in children and adults: A critical review of published reports. Am J Hematol 2010; 85: 174-80.
2. George JN, Vesely SK. Immune thrombocytopenic purpuralet the treatment fit the patient. N Engl J Med 2003; 349: 903-5.
3. Blanchette V, Imbach P, Andrew M, et al. Randomised trial of intravenous immunoglobulin G, intravenous anti-D, and oral prednisone in childhood acute immune thrombocytopenic purpura. Lancet 1994; 344(8924): 703-7.
4. Matzdorff A, Giagounidis A, Greinacher A, et al. Diagnosis and therapy of autoimmune thrombocytopenia. Recommendations of a joint Expert Group of DGHO, DGTI, DTH. Onkologie 2010; 33: 2-20.
5. Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims . Available from: www.fda.gov (Accessed on 10 October 2012).
6. European Medicines Agency. Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. Available from: www.ema.europa.eu (Accessed on 10 October 2012).
7. Basch E, Jia X, Heller G, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst 2009; 101: 1624-32.
8. Berti D, Moons P, Dobbels F, et al. Impact of corticosteroid-related symptoms in patients with immune thrombocytopenic purpura: results of a survey of 985 patients. Clin Ther 2008; 30: 1540-52.
9. Brown TM, Horblyuk RV, Grotzinger KM, et al. Patient-reported treatment burden of chronic immune thrombocytopenia therapies. BMC Blood Disord 2012; 12: 2.
10. European Hematology Association Scientific Working Group “Qaulity of life and Symptoms”. Guidelines: Patient Reported Outcomes In Hematology. 1st edn. Forum Service Editore: Genoa, 2012.
11. International Society for Pharmacoeconomics and Outcomes Research. Value in Health 2007; 10: 59-147.
12. Klaassen RM, Young NL. Health related quality of life outcomes for patients with immune thrombocytopenic purpura. Ann Hematol 2010; 89: 51-54.
13. Kimberlin CL, Winterstein AG. Validity and reliability of measurement instruments used in research. American journal of health-system pharmacy 2008; 65: 2276-84.
14. Revicki D, Hays RD, Cella D, et al. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol 2008; 6: 102-9.
15. Schunemann HJ, Akl EA, Guyatt GH. Interpreting the results of patient reported outcome measures in clinical trials: the clinician's perspective. Health Qual Life Outcomes 2006; 4: 62.
16. Basch E, Abernethy AP. Supporting clinical practice decisions with realtime patientreported out

CHAPTER 4:

LINGUISTIC AND CONTENT VALIDATION OF A GERMAN-LANGUAGE PRO-CTCAE-BASED PATIENT-REPORTED OUTCOMES INSTRUMENT TO EVALUATE THE SYMPTOM EXPERIENCE IN SURVIVORS OF ALLOGENEIC HAEMATO-POIETIC STEM CELL TRANSPLANTATION

Monika Kirsch [1, 2], Sandra A. Mitchell[3], Fabienne Dobbels [4], Georg Stussi [5], Ethan Basch [6], Jorg P Halter [2], Sabina De Geest [1, 4]

[1] *Institute of Nursing Science, University of Basel, Switzerland*

[2] *Department of Haematology, University Hospital Basel, Switzerland*

[3] *Outcomes Research Branch, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, United States*

[4] *Health Services and Nursing Research, Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium*

[5] *Department of Haematology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland*

[6] *Cancer Outcomes Research Program, Lineberger Comprehensive Cancer Center, University of North Carolina, United States*

Accepted by
European Journal of Oncology Nursing

Modified version

4.1 Abstract

Purpose: The aim of this sequential mixed methods study was to develop a PRO-CTCAE (Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events)-based measure of the symptom experience of late effects in German speaking long-term survivors of allogeneic stem cell transplantation (SCT), and to examine its content validity.

Methods: The US National Cancer Institute's PRO-CTAE item library was translated into German and linguistically validated. PRO-CTCAE symptoms prevalent in ≥50% of SCT survivors (n=15) and identified as important by SCT experts (n=9) were identified. Additional concepts relevant to the symptom experience and its consequences were elicited. Content validity of the PROVIVO (Patient-Reported Outcomes of long-term survivors after allogeneic SCT) instrument was assessed through an additional round of cognitive debriefing in 15 patients, and item and scale content validity indices by 9 clinical experts.

Results: PROVIVO is comprised of 49 items capturing the experience of physical, emotional and cognitive symptoms. To improve the instrument's utility for clinical decision-making, questions soliciting limitations in activities of daily living, frequent infections, and overall well-being were added. Cognitive debriefings demonstrated that items were well understood and relevant to the SCT survivor experience. Scale CVI (0.94) and item CVI (median = 1; range 0.75-1) were very high.

Conclusions: Qualitative and quantitative data provide preliminary evidence supporting the content validity of PROVIVO and identify a PRO-CTCAE item bundle for use in SCT survivors. Studies to evaluate the measurement properties of PROVIVO, and to examine its capacity to improve survivorship care planning, is underway.

4.2 Introduction

Allogeneic hematopoietic stem cell transplantation (SCT) has become a standard therapy for patients with a variety of hematologic disorders [1]. However, its adverse symptom profile is prominent due to the use of high-dose chemotherapy and/or radiotherapy and high prevalence of acute and chronic graft-versus-host disease (cGVHD). With improved survival, there has been increased attention given to late post-transplant adverse effects (effects that develop or persist one year and beyond post-transplant), including major organ system dysfunction, secondary malignancy, side effects of immunosuppression required to treat cGVHD, and infections related to delayed or abnormal immune reconstitution [2]. These complications can cause substantial morbidity, adversely affect quality of life, and contribute to late mortality [3]. Tailored and targeted preemptive and supportive care management based on a patient-centered comprehensive assessment can favorably affect clinical outcomes and the survivorship experience [4, 5]. Systematic use of PROs in clinical practice can strengthen care-planning [6], facilitate communication between patients and health care workers [7], and optimize symptom management [8].

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) in the internationally accepted system for grading transplant-related adverse effects in trials [9], and may also be used in clinical settings [10]. Although the CTCAE provides a standard method for clinician grading of treatment-related adverse effects, additional evaluation from the patient perspective is warranted since approximately 10% of the adverse effects listed in the CTCAE are subjective symptoms that can be best evaluated by gathering information directly from patients. A recent systematic review confirms that clinicians often underestimate the incidence, severity and distress of the symptoms experienced by cancer patients [11]. Patient-reported outcomes (PROs) capture the patient's perspective directly and have had increasing use in both research and clinical practice [12].

To better capture symptomatic adverse treatment effects from the patients' perspective, the US National Cancer Institute (NCI) has developed the Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE). It is designed to complement the CTCAE and to improve precision and reliability in gaging symptomatic toxicities of cancer treatment [13]. The PRO-CTCAE item library is comprised of 124 PRO items reflecting 78 symptom terms, with each term assessed relative to one or more attributes, including presence/absence, frequency, severity, and/or interference with usual or daily activities. It includes items that capture the full range of symptomatic treatment effects that may be experienced across a variety of disease sites and cancer treatment modalities, however to date PRO-CTCAE has had limited testing in SCT settings.

SCT-specific PRO measures include the MDASI-BMT[14], FACT-BMT[15], and EORTC-HDC29 [16], however these instruments focus on the acute phase, measure a broad range of HRQoL constructs, and address only a subset of the symptoms that can occur in long-term SCT survivors. For instance, none of these instruments captures symptoms such as muscle cramping, blurred vision or skin rash, symptoms that are common in long-term post-transplant survivors. Similarly, while the Lee Chronic

GVHD Symptom Scale has demonstrated validity for the assessment of cGVHD symptoms [17], symptoms caused by late effects other than cGVHD (for example palpitations and sensory neuropathy) are not addressed by this measure. Wood et al (2013) determined that PRO-CTCAE is feasible for evaluating SCT-related symptomatic toxicities in the early post-transplant setting; however it is not currently known which items are most suitable to capture symptoms in the later post-transplant period [18]. In addition, while the PRO-CTCAE item bank has been developed in English and translated into Spanish, no German translation currently exists.

Therefore, the objectives of this study were to: (I) translate and linguistically validate the PRO-CTCAE item library in the German language; (II) identify a PRO-CTCAE-based item bundle relevant for survivors ≥1 year after allogeneic SCT and elicit additional concepts that should be incorporated into PROVIVO, a new measure of the symptom experience designed to improve supportive care management in SCT survivors; and (III) evaluate the comprehensibility and content validity of the PROVIVO measure using mixed methods.

4.2.1 Design and Methods

This sequential mixed methods study 19 is the first phase of a larger PROVIVO project that will investigate Patient-Reported Outcomes of long-term survivors after allogeneic SCT (NCT01275534). The three specific aims of the present study were accomplished, using a sample of 30 SCT survivors and 18 haematology experts. As shown in Figure 1, the PRO-CTCAE items were translated into German in accordance with recommended approaches [20, 21]. Mixed methods were used to identify a bundle of PRO-CTCAE symptoms relevant for survivors ≥1 year after allogeneic SCT, and these items were supplemented to create the PROVIVO instrument, a new measure of the symptom experience of late effects and their impact on daily life. Human subject approval was provided by the Ethics Committees of the cantons Zurich and Basel.

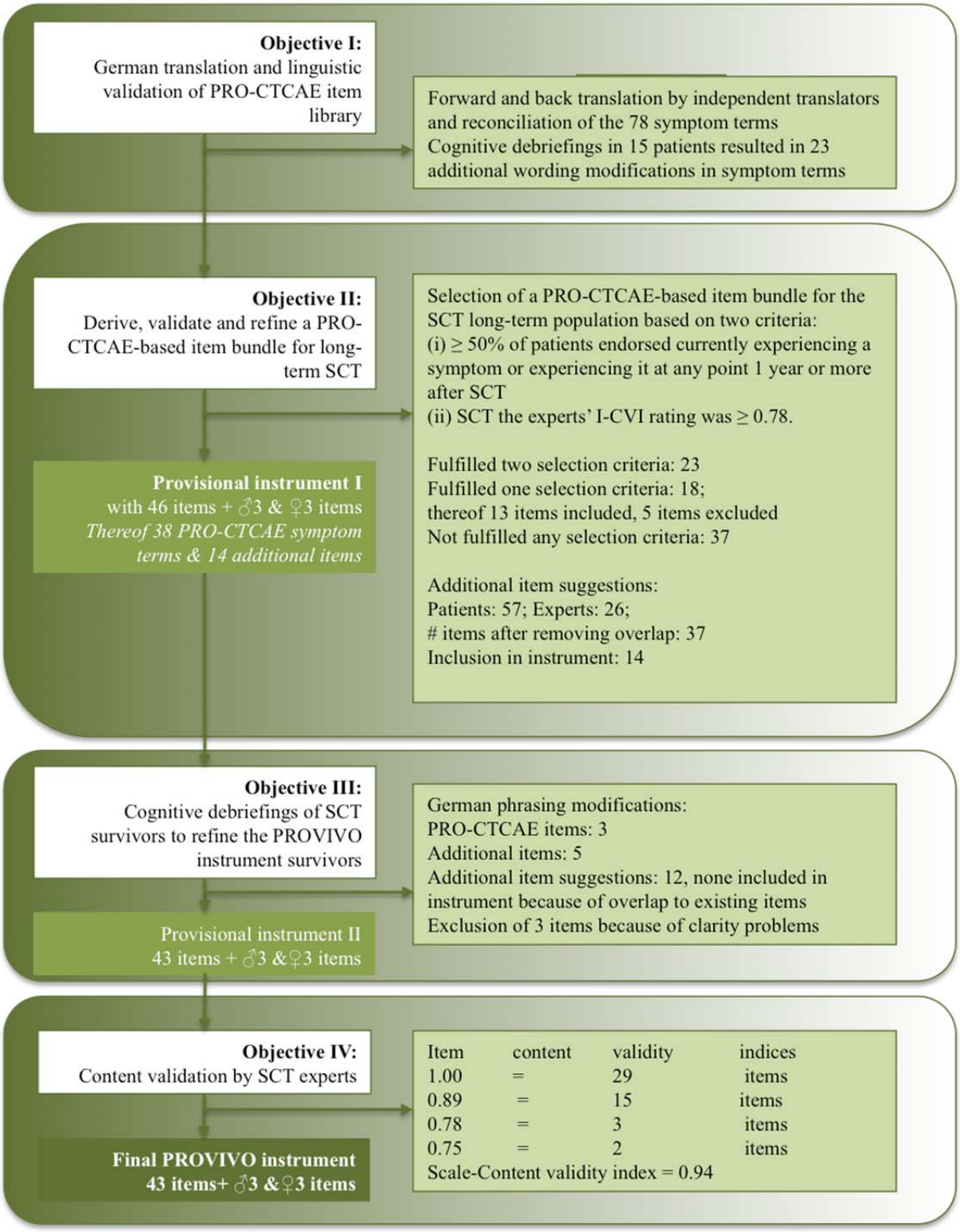


Figure 1: Study proces

4.3 Aim I: German translation and linguistic validation of PRO-CTCAE item library

Authorization was received from the US National Cancer Institute to translate the PRO-CTCAE item library into German. Two bilingual translators independently translated the 78 PRO-CTCAE symptom terms and response options into German. Translations were compared to detect literal and conceptual inconsistencies. Reconciliation of terms resulted in one final translation of each item, which was used for the conceptual back translation carried out by a third translator. Subsequently, the first two translators reviewed the back translation, discussed inconsistencies and refined some translations. All documentation pertaining to the translation, including item history, cognitive debriefing and decisions made, were provided to the National Cancer Institute Outcomes Research Branch for review, and the final version of the PRO-CTCAE-German was approved by the US National Cancer Institute. The German language PRO-CTCAE items were subsequently examined through cognitive debriefing, an interview method that evaluates respondents' comprehension of terminology, phrasing, response options, and format of a PRO measure [22]. Maximum variation sampling [23] was used to select two heterogeneous samples each comprised of 15 adults post-allogeneic SCT based on following variables (1) wide age range (2) gender; (3) different time points after SCT (1-2, 3-5, ≥6 years); (4) educational level; and (5) presence/absence of cGVHD which is known to be a main cause for worsening chronic health conditions after SCT [24]. Excluded participants were those who were younger than 18 years of age, did not speak German, had visual and/or hearing impairment, were currently hospitalized, had a life expectancy <4 weeks, or suffered from a psychiatric illness that in the opinion of the treating haematologist prevented them from participating meaningfully in the study. Eligible participants were identified by physicians and nurses working at two outpatient clinics. The investigators contacted eligible patients by phone to explain the study aims and procedures, and those willing to participate signed an informed consent document. Interviews took place either in the outpatient clinic or at the patient's home and were audiotaped and transcribed. Participant characteristics are summarized in Table 1.

Characteristics	**Interview group 1* n=15 (%) ±**		**Interview group 2+ n=15 (%)**	
Age in years, mean (SD; range)	**49.7 (11.4; 34-66)**		**48.6 (13.6; 23-69)**	
Male gender, (n, %)	**8**	**(47%)**	**7**	**(53%)**
Native Language (n, %)				
German	13	(87%)	12	(80%)
Other	2	(13%)	3	(20%)
Marital status (n, %)				
Married/cohabiting	10	(67%)	14	(93%)
Single/widowed/separated	5	(33%)	1	(7%)

Education (n, %)				
Compulsory school or less	4	(27%)	3	(20%)
Upper secondary school/high school	10	(67%)	5	(33%)
University or corresponding level	1	(7%)	7	(47%)
Current working status (n, %)				
Full time	2	(13%)	4	(27%)
Part-time	5	(33%)	5	(33%)
Not working	6	(40%)	3	(20%)
Retired	2	(13%)	3	(20%)
Diagnosis (n, %)				
Acute myeloid leukemia	5	(33%)	4	(27%)
Acute lymphoblastic leukemia	1	(7%)	3	(20%)
Chronic myeloid leukemia	1	(7%)	2	(13%)
Chronic lymphoblastic leukemia	1	(7%)	1	(7%)
Hodgkin or Non-Hodgkin Lymphoma	5	(33%)	3	(20%)
Myelodysplastic syndrome	1	(7%)	1	(7%)
Myeloproliferative disease	1	(7%)	2	(13%)
Years after SCT (n, %)				
1-2 years	7	(47%)	4	(27%)
3-5 years	5	(33%)	4	(27%)
6-9 years	2	(13%)	3	(20%)
≥ 10 years	1	(7%)	4	(27%)
NIH Chronic GVHD Global Severity Score[#] (n, %)				
None	5	(33%)	8	(53%)
Mild	7	(47%)	4	(27%)
Moderate	2	(13%)	2	(13%)
Severe	1	(7%)	1	(7%)
Duration of interviews in minutes, mean (SD)	**86 (38)**		**62 (18)**	

Table 1: Participant characteristics

A semi-structured interview guide was used to evaluate patients' comprehension of the translated PRO-CTCAE symptom terms and response options Patients were provided with a stack of cards, each listing one of the 78 translated symptom terms, and asked to perform the following tasks. First, they were encouraged to 'think aloud' and describe the meaning of each symptom in their own words. If patients believed that the symptom phrasing was not accurate, they were asked to suggest a better term. Next, they sorted each symptom card into one of the following categories: 1) "I presently have this symptom"; 2) "I had this symptom in the past"; 3) "I never experienced this symptom". Feedback concerning the clarity and comprehensiveness of the response options was also elicited. Because the PRO-CTCAE uses four different question types (severity, occurrence, frequency and interference with daily activities) patients were asked whether the response options were understandable to them.

Finally, patients were asked to list any other symptoms they had experienced that were not mentioned on the cards. Field notes were taken and a report summarizing the interview topics and the difficulties participants had in responding to PRO-CTCAE items was prepared for each interview.

Continuous content analysis was used to evaluate the clarity of the symptom terms on an item-by item basis [22]. SCT survivors' descriptions of the meaning of each symptom term were summarized and problems with comprehension were flagged. Based on these summaries, translations and potential refinements were re-evaluated after the fifth, tenth and last interview. Additionally, the occurrence of symptoms (present now or had in the past ≥1 year after SCT) was documented. Additional symptoms experienced by SCT survivors but not represented in the PRO-CTCAE item library were captured.

4.3.1 Results

The comparison of the two independent forward translations revealed literal ('same words') and conceptual equivalence ('same conceptual meaning') for 21 of the 78 PRO-CTCAE symptom terms [25]; conceptual agreement was reached for 51/78 terms. For 6 symptom terms there was minor conceptual disagreement. Reconciliation through translator discussion resulted in one final translation of each term, which was used for the back translation. The back translation resulted in 26 symptom terms with complete literal and conceptual equivalence to the original English language source, and 52 symptom terms with conceptual equivalence. The translators examined the 52 terms where there was conceptual equivalence only, and either improved the translation or proposed alternative terms that were comparatively tested in the subsequent cognitive debriefing.

Cognitive debriefing revealed that participants were generally satisfied with the proposed German language phrasing of PRO-CTCAE symptom terms; feedback prompted adjusted phrasing of 23 terms. The PRO-CTCAE response categories were generally perceived as easy to understand. However, four patients indicated a preference to use numerical response categories (e.g. 1-2 times a week, 3-4 a week) instead of labels (e.g. rarely or frequently) for frequency questions.

Symptom prevalence in the sample is displayed in Table 3. Of the 78 symptom terms, 27 were experienced by more than 50% of the patients. Respondents suggested 57 additional topics which were not covered by the PRO-CTCAE, but were thought to be important for the SCT-survivor population.

4.4 Aim II: Derive, validate and refine a PRO-CTCAE-based item bundle for long-term SCT survivors

To address this aim, we derived a PRO-CTCAE-based item bundle for SCT survivors, evaluated the content validity of the proposed bundle in a sample of patients and experts, and elicited additional concepts important to the provision of follow-up care to SCT survivors and that should be incorporated into the PROVIVO instrument.

4.4.1 Materials and methods

A convenience sample of 9 multidisciplinary experts in SCT follow-up care were surveyed to assess the relevance of the 78 PRO-CTCAE symptom terms to late effects assessment and management and survivorship care delivery for patients ≥1 year post-SCT. Participating experts (nurses and physicians) were required to have ≥5 years of experience in SCT, including a minimum of 3 years in outpatient care, and be proficient in both German and English. The chairpersons of the European Group for Blood and Marrow Transplantation (EBMT) national nurses groups of Switzerland, Germany and Austria suggested names of eligible expert nurses. Senior physicians were identified based on their active participation in the EBMT and their scientific contributions to SCT research. Ten experts were invited to participate; informed consent to participate was obtained from nine, and surveys were distributed by surface mail with an enclosed postage-paid return envelope. All nine experts who agreed to participate returned the questionnaire within four weeks. Characteristics of the experts are summarized in Table 2.

Characteristics	Expert group 1 N=9; n. (%)*		Expert group 2 N=9; n (%)	
Profession; (n, %)				
Physician	5	(56%)	5	(56%)
Nurse	4	(44%)	4	(44%)
Male gender; (n, %)	**4**	**(44%)**	**5**	**(56%)**
Age				
30-39	2	(22%)	3	(33%)
40-59	7	(78%)	4	(44%)
≥ 60			2	(22%)
Years of working experience in follow-up care (mean, SD)	**12.2**	**5.9**	**12.9**	**7.6**
Total work load; (n, %)				
60-75	2	(22%)	1	(11%)
80-100	7	(78%)	8	(89%)
Workload in direct clinical follow-up care; (n, %)				
75% or less	2	(22%)	1	(11%)
80-100%	7	(78%)	7	(78%)
Not indicated			1	(11%)
Number of allogeneic SCT done at the centre per year; (n, %)				
20-39	2	(22%)	1	(11%)
40-79	5	(56%)	5	(55%)
≥80	2	(22%)	3	(33%)

Table 2: Demographic characteristics of the two expert panels

Experts were asked to rate the relevance of each PRO-CTCAE symptom term for the care of patients who are ≥1 year after SCT using a four-point Likert scale (1 = not relevant, 2= rather not relevant, 3= relevant, 4 = highly relevant). They had the option to provide additional comments regarding the terminology used and to suggest additional symptoms and topics believed to be important for a clinically useful PRO measure designed to evaluate the symptom experience in SCT recipients with and without cGVHD. Topics mentioned within the free text responses were summarized using content analysis; The Item Content Validity Index (I-CVI) was computed as the number of experts giving a rating of either 3 or 4 divided by the total number of experts. According to Polit & Beck (2006) items with an I-CVI of ≥.78 are considered to have good content validity. 38 items of the PRO-CTCAE symptom terms received an I-CVI ≥ 0.78 establishing them as relevant for SCT survivors. Experts suggested 26 additional topics (see Figure 1).

Items to comprise a PRO-CTCAE item bundle for SCT survivors were included if two a priori criteria were met: (i) at least 50% of the patient sample (used to accomplished Aim 1) endorsed currently experiencing a symptom or experiencing it at any point 1 year or more after SCT; and (ii) SCT experts' I-CVI rating of that item was ≥0.78. If neither criterion was met an item was excluded. If one criterion was met, a decision whether to include or exclude the symptom was made by two senior hematologists (JH & GS) and one expert nurse scientist (MK). Decisions about including a symptom were made based on these experts' opinions about the clinical meaningfulness of the symptom in the post-transplant setting, and relevant literature.

4.4.2 Results

Twenty-three symptom terms met both selection criteria and were incorporated into the PRO-CTCAE SCT item bundle. Thirty-seven symptoms did not meet either of the two selection criteria and were excluded. Of the remaining 18 symptoms, the research team retained 13 symptoms. Ten out of these 13 symptoms had a prevalence ≤50%, yet a high clinical relevance, meaning that they are potentially related to less common but important late effects (e.g. *Unexpected or excessive sweating during the day or night-time* may reflect infection or relapse) Three symptoms (*anxiety, insomnia including difficulty falling asleep, staying asleep or waking up early* and *pounding or racing heartbeat*) had a prevalence ≥50%, but an I-CVI <0.78 suggesting that experts may have underestimated the importance of these symptom concerns for patients. Given that more than 50% of the SCT survivors indicated that they were experiencing or had previously experienced these symptoms, they were retained within the SCT survivor item bundle. Five items were excluded from the PRO-CTCAE SCT item bundle because of insufficient relevance for SCT follow-up care (e.g. *frequent urination*) or conceptual overlap with other included items (e.g. *headache* overlapping with *pain*).

The 57 additional topics suggested by patients and the 26 topics suggested by experts were compared using content analysis. After removing conceptual overlap, 37 additional candidate topics remained (see Box 1). These topics were considered for inclusion in the draft PROVIVO instrument. Experts were asked to rate the relevance of each PRO-CTCAE symptom term for the care of patients

Physical Symptoms	**Comorbidities**
Photosensitivity (light sensitivity of the eyes)	**Frequent infections**
Dry eyes	Osteoporosis
Joint stiffness	Osteonecrosis
Teeth problems	Joint replacement
Muscle cramps	Occurrence of skin tumours / changes in moles
Tremors	Solid tumours
Decreased flexibility of muscles and skin (e.g. problems to stretch muscles)	**Functional problems**
Speech problems (e.g. problems with word finding)	**Social problems**
Urgent need for defecation	**Problems in work life**
Cellulite-like changes to the skin and soft tissues	**Problems in family life, marriage and relationship**
Runny nose	**Fertility concerns**
Sensitivity of the gums / mouth	**Financial problems**
Hearing loss	**Social support problems**
Weight loss	Help for self-help
Skin changes	Problems with medications
Males: Change in the skin of the penis	
	General condition
Emotional symptoms	**Overall well-being**
Stress	Self-perceived physical fitness and endurance
Frustration	
Changes in body image	

Topics in bold were included in the PROVIVO instrument

Box 1: Additional topic suggestions by experts and patients

Seven physical symptom terms (muscle cramps, light sensitivity of the eyes, dry eyes, joint *stiffness, teeth problems (such as cracking, caries, and tooth sensitivity*), *tremors*; and *changes in the skin of the penis*) were incorporated into the PROVIVO instrument, based on the authors' clinical expertise and relevant literature. Eight additional items reflecting the effects of symptoms on daily living (*partner–ship and family, professional life/education/school, financial issues, social contacts (e.g. friends,*

public), family planning/fertility concerns); frequent infections, and two open-ended questions asking about current well-being and *concerns the patient would like to discuss at the annual follow-up visit* were also included in the PROVIVO instrument to inform follow-up care planning. Although these items address concerns beyond symptoms, both patients and experts perceived that the issues were salient to a full understanding of the symptom experience.

4.5 Aim III: Evaluate the comprehensibility and content validity of the PROVIVO instrument

Based on data derived from Aims I and II, the 52-items PROVIVO instrument was drafted. Self-regulation theory was chosen as the underlying conceptual framework for the PROVIVO instrument, and shaped investigators' decisions that items should capture both symptom occurrence (measured in terms of frequency or severity) and the associated symptom distress [26]. The frequency response options (Never/Rarely/Occasionally/Frequently/Almost constantly) and severity response options (None/Mild/Moderate/Severe/Very severe) were derived from PRO-CTCAE. An additional set of response options were developed to gauge how much distress (Not at all/A little bit/Somewhat/Quite a bit/Very much) was experienced in association with each symptom. To diminish respondent burden, PRO-CTCAE interference items were not included in the PROVIVO instrument. The PROVIVO measure incorporated the 7-day recall period used by PRO-CTAE.

4.5.1 Materials and methods

The comprehensibility of the 52 items, response options and instructions for the PROVIVO measure were evaluated in cognitive debriefings with 15 additional SCT survivors. Sample selection and recruitment procedures were comparable to those described previously.

For this second round of debriefing, survivors first completed the PROVIVO instrument on their own. Subsequently, the interviewer instructed them to read aloud the introduction, the instructions and the items with their respective answers. Participants were then debriefed using a semi-structured interview that focused on four aspects of comprehension:

1. Are the introduction and the instructions clear? (e.g. Could you please repeat the instructions in your own words?)
2. Are the items understood? (e.g. Could you please explain in your own words what this question means to you?)
3. Are the response options well chosen? (e.g. *Do these response options make sense to you*?)
4. Is item concept saturation reached? (e.g. Are there any items missing which should have been included in the questionnaire?)

Content analysis was used to summarize comprehension difficulties with the questionnaire introduc–tion and instructions, and the items and response options.

To evaluate the content validity of the PROVIVO items and the overall instrument, 9 additional experts were recruited using previously described eligibility criteria. Experts rated the relevance of each symptom term using a four-point Likert scale, and indicated any concerns about the questionnaire layout, introduction, instructions, items, and response options. Two CVI parameters were calculated: the previously described I-CVI, and the content validity index of the overall scale (S-CVI/Ave), which is computed by summing the I-CVI's from all items and dividing this sum by the number of items. I-CVI ≥0.78 and S-CVI/ave ≥0.90 are considered to reflect acceptable content validity [27].

4.5.2 Results

Most PROVIVO items were well understood, although for 8 items minor adjustments to phrasing of the symptom terms were suggested, mostly with regard to word order. Five of these 8 were symptom terms that were added based on the unique symptom concerns experienced by SCT survivors (e.g. muscle cramping, dry eyes, light sensitivity of the eyes). Three PRO-CTCAE items (increased sun-sensitivity of the skin, aching muscles and aching joints) were not well understood, and these items were eliminated from the final PROVIVO instrument. Specifically, respondents were unsure if increased sun-sensitivity referred to having a higher risk for developing skin cancer because of previous cancer treatment or if it was the increased risk of getting a sunburn even with minimal sun exposure. Other patients stated that they did not test their skin's sun-sensitivity, but endorsed the presence of sun sensitive skin because they were aware that they were at risk for photoxicity due to medications and GVHD. Given these perspectives, the research team decided to exclude this item from the PROVIVO measure because it was felt that photosensitivity reflects a toxicity that is best identified by a clinician. With regard to *aching muscles* and *aching joints (such as elbows, knees, shoulders)* several respondents experienced difficulty answering these questions because they could not distinguish the discomfort caused by aching muscles vs. aching joints. For the PROVIVO measure, the investigators elected to gather information about pain more generally using the PRO-CTCAE pain item, and to provide a free text option for the patient to specify the quality of the pain and a figure to mark the location.

Although the chosen recall period of 7 days was well-accepted by a majority of the respondents, some indicating that they would have liked the option of a longer recall period in order to be able to communicate their past experiences. Because the PROVIVO measure is intended to capture the current symptom experience, and supported by evidence that there is an inverse relationship between length of recall period and accuracy of recall [28], the 7-day recall period was retained. Favourable feedback on the instructions for self-administration and the layout was received, suggesting that no changes were needed. Slight adjustments were made to the phrasing of the questionnaire introduction.

Themes/Item[†]	Symptom prevalence (%)[±] in patient interview round I: (n=15)	I-CVI in expert group I*	I-CVI in expert group II
Physical symptoms			
Pounding or racing heart beat (palpitations)	9 (60%)	0.67	0.78
Vomiting	8 (53%)	0.78	0.89
Nausea	11 (73%)	0.78	1.00
Loose or watery stools (diarrhea)	6 (40%)	0.78	1.00
Arm or leg swelling	7 (47%)	0.89	0.89
Unexpected or excessive sweating during the day or	6 (40%)	0.67	0.75
Fatigue, Tiredness, or lack of energy	15 (100%)	0.89	1.00
Shortness of breath	13 (87%)	1.00	1.00
Cough	11 (73%)	1.00	0.89
Blurred vision	11 (73%)	1.00	1.00
Watery eyes (tearing)	5 (33%)	1.00	1.00
Decreased appetite	13 (87%)	0.78	1.00
Problems with tasting food or drinks	14 (93%)	0.78	1.00
Difficulty swallowing	12 (80%)	0.78	0.89
Mouth or throat sores	13 (87%)	1.00	0.89
Dry mouth	12 (80%)	0.89	1.00
Dry skin	12 (80%)	1.00	1.00
Rash	9 (60%)	1.00	1.00
Unusual darkening of the skin	7 (47%)	0.89	0.89
Itchy skin	7 (47%)	1.00	1.00
Numbness or tingling in your hands or feet	10 (67%)	0.89	1.00
Insomnia including difficulty falling asleep, staying	10 (67%)	0.67	1.00
Increased skin sensitivity to sunlight#	12 (80%)	0.89	-
Pain	11 (73%)	1.00	1.00
Aching joints#	10 (66%)	0.89	-
Aching muscles#	7 (47%)	0.89	-
Muscle cramps	/	/	0.89
Tremors	/	/	0.89
Photo sensitivity (Light sensitivity of the eyes)	/	/	0.78
Dry eyes	/	/	1.00
Teeth problems (such as	/	/	0.89
Stiffness of joints	/	/	1.00

Emotional & cognitive symptoms			
Sad or unhappy feelings/Feeling that nothing could	9 (60%)	0.89	1.00
Anxiety or worry	11 (73%)	0.67	1.00
Problems with concentration	12 (80%)	0.89	1.00
Problems with memory	10 (67%)	0.89	1.00
Male & female urogenital symptoms			
Male (n=7)			
Change in the skin of the penis	/	/	0.75
Ejaculation problems	4 (57%)	0.78	0.78
Difficulty getting or keeping an erection	3 (43%)	0.89	0.89
Female (n=8)			
Vaginal dryness	9 (100%)	1.00	1.00
Unusual vaginal discharge	2 (25%)	0.78	0.89
Pain during vaginal sex	4 (50%)	1.00	1.00
Both genders			
Decreased sexual interest	13 (87%)	0.89	0.89
Pain or burning with urination	2 (13%)	0.78	0.89
Additional items for follow-up care planning			
Partnership and family	/	/	1.00
Professional life/ education / school	/	/	1.00
Financial concerns	/	/	1.00
Social contacts (e.g. friends, public)	/	/	1.00
Family planning /fertility concerns	/	/	1.00
General well-being	/	/	0.89
Frequent infections	/	/	0.89
Current main concerns to discuss at next follow-up visit	/	/	1.00

± Prevalences are rounded

† Cell colours indicate whether the item was retrieved from the PRO-CTCAE or if it was added

PRO-CTCAE additional item

* Item Content Validity Index

Excluded items in revised questionnaire version

Table 3: Prevalence of symptoms in patients and CVI ratings of included items during the instrument development

Twenty-nine of 49 PROVIVO items received an I-CVI of 1.00 indicating that all experts found these items to be quite or very relevant. Fifteen items received I-CVIs of 0.89 and three items received an I-CVI of 0.78. Two items, specifically pounding or racing heartbeat and light sensitivity of the eyes had an I-CVI of 0.75. Despite their slightly suboptimal CVI, it was decided to retain these two items

as both reflect symptom concerns identified by SCT survivors as important. The overall PROVIVO instrument received a S-CVI/Average of 0.94, indicating strong content validity as perceived by experts. The layout, introduction and respondent instructions were viewed favorably, and judged to be easy to comprehend. A majority expressed no concerns about the response options, although three experts mentioned that different response scales (e.g. Visual analogue scales, numeric scales) could have been considered. Since the team wished to incorporate the validated response options provided in PRO-CTCAE, no changes to the response options were made.

4.6 Discussion

We report the German language translation and linguistic validation of the PRO-CTCAE item bank, and describe the evidence supporting the content validity of a new measure designed to assess the symptom experience of allogeneic SCT survivors who are a year or more post-transplant. A subset of the PRO-CTCAE symptom terms were identified by patients and clinician experts as relevant for symptom surveillance in SCT survivors. Additional symptom domains important to SCT survivors were identified by a panel of clinician experts, and through cognitive debriefing of SCT survivors, and included symptoms such as muscle cramping, joint stiffness, and dry eyes. Debriefing interviews confirm that the item phrasings, response choices, and general instructions are clear and comprehensible. All items but two exceeded an I-CVI >0.78, consistent with high relevance to SCT survivors. Data substantiate an empirically-derived PRO-CTCAE SCT survivor item bundle that can be used in prospective studies, and support the content validity of the German language PROVIVO instrument.

Given the multifactorial etiology of late effects and the need to screen for a variety of symptoms with overlapping causes, the broad range of included symptoms is a particular strength of the newly developed PROVIVO instrument. It reflects symptoms that may be related to the underlying disease, persistent and late treatment effects, and comorbid conditions. Our goal with PROVIVO was to construct a PRO measure that predominantly focuses on symptom experience and to augment it with questions guiding survivorship care planning. Using the PRO-CTCAE item library was an efficient approach for the identification of an SCT-specific item bundle broadly applicable for symptom screening, and the resultant data are immediately actionable. As an alternative, an existing SCT-specific PRO measure (e.g. FACT-BMT, EORTC-HDC29 and the MDASI symptom burden scale (BMT & cGVHD versions) [14-16, 29, 30] could have been tailored to for use in the PROVIVO instrument. However, these instruments have had limited testing in long-term SCT survivors, and to our knowledge only, Velikova and colleagues involved survivors ≥1 year after SCT in the development of the EORTC-HDC-29, as is recommended [31, 32]. Furthermore, the items included in these QoL instruments reflect only a narrow range of common symptoms (such as nausea, pain, and fatigue) and may neglect a number of the important and clinically actionable symptoms that can occur in long-term SCT survivors.

cGVHD and the immunosuppressive agents used to treat it may cause a wide range of complications that can amplify symptom distress and impair functional performance [33]. Since the PROVIVO instrument, however, was not specifically created to identify and grade cGVHD, in patients with cGVHD, we recommend that the PROVIVO measure be used in conjunction with the Lee cGVHD scale [17]. To avoid overlap in the content of these two measures, electronic reporting systems using conditional branching could be applied to customize assessment pathways based on respondents' answers.

Several limitations should be considered in interpreting our findings. We recognized that the two criteria defined a priori for the inclusion of items were relaxed in making the final selection of items. Decisions about the topics included in the PROVIVO instrument reflect triangulation of the mixed methods data sources, including patient and clinician perspectives concerning the topics that are important to optimize the delivery of SCT survivorship care. It is possible that our results were influenced by our small sample size or by socio-linguistic factors. Although standard German is the official language in Switzerland, the Swiss-German dialect is commonly spoken in everyday life [34]. Validity testing of the PRO-CTCAE German item library in a large sample of patients recruited from cancer treatment centres in Germany is ongoing to establish the generalizability of these linguistic validation findings[35]. The validity and responsiveness of the PROVIVO measure are also being examined in a study of approximately 300 Swiss-German speaking SCT survivors, with diverse characteristics with respect to age, underlying diagnosis, and severity of cGVHD manifestations.

With additional testing in both the German language and in other languages, the PROVIVO instrument and the empirically derived PRO-CTCAE item bundle offer promising tools to improve the delivery of SCT survivorship care. Our findings provide preliminary evidence supporting an SCT survivor-specific PRO-CTCAE item bundle, and identify additional PRO-CTCAE symptom terms such as muscle cramping and tremor that should be included in future versions of the NCI PRO-CTCAE item library. PROs may have utility to direct follow-up care delivery and can help survivors and their clinicians efficiently identify symptoms and other concerns that are actionable during clinic visits. Prospective studies are warranted to define the sensitivity of PROVIVO and the PRO-CTCAE SCT survivor item bundle to detect late effects such as avascular necrosis and new onset of pulmonary compromise, particularly in long-term survivors who may be seen less frequently at their transplant centre yet require life-long surveillance for a range of chronic health concerns [36]. Additional research is needed to determine how to incorporate the information derived from PROs to inform the development of survivorship care plans, strengthen care delivery, and improve outcomes for this vulnerable group of survivors.

4.7 References

1. Passweg JR, Baldomero H, Gratwohl A, Bregni M, Cesaro S, Dreger P et al. The EBMT activity survey: 1990-2010. *Bone Marrow Transplant* 2012; 47: 906-923.
2. Tichelli A, Rovo A, Socie G. Late effects after hematopoietic stem cell transplantation-critical issues. *Curr Probl Dermatol* 2012; 43: 132-49.
3. Majhail NS, Rizzo JD. Surviving the cure: long term follow up of hematopoietic cell transplant recipients. *Bone Marrow Transplant* 2013; 48: 1145-51.
4. Syrjala KL, Martin PJ, Lee SJ. Delivering care to long-term adult survivors of hematopoietic cell transplantation. *J Clin Oncol* 2012; 30: 3746-51.
5. Couriel D, Carpenter PA, Cutler C, Bolanos-Meade J, Treister NS, Gea-Banacloche J *et al.* Ancillary therapy and supportive care of chronic graft-versus-host disease: national institutes of health consensus development project on criteria for clinical trials in chronic Graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. *Biol Blood Marrow Transplant* 2006; 12: 375-96.
6. Beavers J, Lester J. Survivorship care for adult recipients of hematopoietic cell transplantations. *Clin J Oncol Nurs* 2010; 14: 136-9.
7. Berry DL, Blumenstein BA, Halpenny B, Wolpin S, Fann JR, Austin-Seymour M *et al.* Enhancing Patient-Provider Communication With the Electronic Self-Report Assessment for Cancer: A Randomized Trial. *Journal of Clinical Oncology* 2011; 29: 1029-1035.
8. Velikova G, Keding A, Harley C, Cocks K, Booth L, Smith AB *et al.* Patients report improvements in continuity of care when quality of life assessments are used routinely in oncology practice: Secondary outcomes of a randomised controlled trial. *European Journal of Cancer* 2010; 46: 2381-2388.
9. Martin PJ, Antin JH, Weisdorf DJ, Paton V, Horowitz MM. Reporting of adverse event data in hematopoietic stem cell transplantation clinical trials involving investigational new drugs or devices: A report from the William Guy Forbeck Foundation 2001 focus meeting on clinical trials in hematopoietic stem cell transplantation. *Biology of Blood and Marrow Transplantation* 2002; 8(6): 295-302.
10. Trotti A, Colevas AD, Setser A, Basch E. Patient-reported outcomes and the evolution of adverse event reporting in oncology. *J Clin Oncol* 2007; 25: 5121-7.
11. Xiao C, Polomano R, Bruner DW. Comparison Between Patient-Reported and Clinician-Observed Symptoms in Oncology. *Cancer Nurs* 2013; 36: E1-E16.
12. Basch E. New Frontiers in Patient-Reported Outcomes: Adverse Event Reporting, Comparative Effectiveness, and Quality Assessment. *Annual Review of Medicine* 2014; 65: 307-317.
13. Basch EM, Reeve BB, Mitchell SA et al. Development of the National Cancer Institute's PatientReported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J Natl Cancer Inst* In Press.

14. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M *et al.* Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer* 2000; 89: 1634-46.
15. Cohen MZ, Rozmus CL, Mendoza TR, Padhye NS, Neumann J, Gning I *et al.* Symptoms and Quality of Life in Diverse Patients Undergoing Hematopoietic Stem Cell Transplantation. *J Pain Symptom Manage* 2012; 44: 168-80.
16. Velikova G, Weis J, Hjermstad MJ, Kopp M, Morris P, Watson M *et al.* The EORTC QLQ-HDC29: a supplementary module assessing the quality of life during and after highdose chemotherapy and stem cell transplantation. *European Journal of Cancer* 2007; 43: 87-94.
17. Lee S, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. *Biology of Blood and Marrow Transplantation* 2002; 8: 444-52.
18. Wood WA, Deal AM, Abernethy A, Basch E, Battaglini C, Kim YH *et al.* Feasibility of frequent patient-reported outcome surveillance in patients undergoing hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2013; 19: 450-9.
19. Creswell JW. Mixed methods procedures. In: London (ed) *Research Design: qualitative, quantitative and mixed methods approaches*, 2 edn. Thousand Oaks: Sage Publishing, 2003, pp 208-227.
20. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A *et al.* Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health* 2005; 8: 94-104.
21. Wild D, Eremenco S, Mear I, Martin M, Houchin C, Gawlicki M *et al.* Multinational trials-recommendations on the translations required, approaches to using the same language in different countries, and the approaches to support pooling the data: the ISPOR Patient-Reported Outcomes Translation and Linguistic Validation Good Research Practices Task Force report. *Value Health* 2009; 12: 430-40.
22. Willis GB. *Cognitive Interviewing: A Tool for Improving Questionnaire Design*, Sage Publications: Thousand Oaks, 2005.
23. Patton MQ. *Qualitative Research & Evaluation Methods*, Sage Publications: Thousand Oaks, 2002.
24. Pallua S, Giesinger J, Oberguggenberger A, Kemmler G, Nachbaur D, Clausen J *et al.* Impact of GvHD on quality of life in long-term survivors of haematopoietic transplantation. *Bone Marrow Transplant* 2010; 45: 1534-9.
25. Acquadro C, Conway K, Hareendran A, Aaronson N. Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials. *Value Health* 2008; 11: 509-21.

26. Leventhal H, Brissette I, Leventhal EA. The common-sense model of self-regulation of health and illness. In: Florence K, Cameron LD, Leventhal H (eds). *The Self-regulation of Health and Illness Behaviour*. Routledge, 2003, pp 43-65.
27. Polit D, Beck C. The content validity index: are you sure you know what's being reported? Critique and recommendations. *Research in Nursing and Health* 2006; 29: 489-497.
28. Stull DE, Leidy NK, Parasuraman B, Chassany O. Optimal recall periods for patient-reported outcomes: challenges and potential solutions. *Current medical research and opinion* 2009; 25: 929-42.
29. McQuellon RP, Russell GB, Cella DF, Craven BL, Brady M, Bonomi A *et al.* Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. *Bone Marrow Transplant* 1997; 19: 357-68
30. Williams LA, Couriel DR, Mendoza TR ea. A new measure of symptom burden in chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2010; 16 (Suppl 2).
31. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E *et al.* Content validity-establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force report: part 2-assessing respondent understanding. *Value Health* 2011; 14: 978-88.
32. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E *et al.* Content validity-establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1-eliciting concepts for a new PRO instrument. *Value Health* 2011; 14: 967-77.
33. Mitchell SA, Leidy NK, Mooney KH, Dudley WN, Beck SL, LaStayo PC *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: 762-9.
34. Lüdi G, Werlen I. *Sprachenlandschaft in der Schweiz: Eidgenössische Volkszählung 2000*, Bundesamt für Statistik, 2005.
35. Wilmer A, Tasar A, Fleckenstein K, Hack C, Ruberg K, Ko Y *et al.* Evaluation of a best-practice model for multiprofessional medication management in cancer patients. *International Journal of Clinical Pharmacy* 2013; 35: 492.
36. Gifford G, Sim J, Horne A, Ma D. Health status, late effects and long-term survivorship of allogeneic bone marrow transplantation: a retrospective study. *Intern Med J* 2014; 44: 139-47.

CHAPTER 5:

SYMPTOM EXPERIENCE OF LATE EFFECTS AFTER ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION: REFINEMENT AND PRELIMINARY VALIDITY TESTING OF THE PROVIVO INSTRUMENT FOR CONSTRUCT VALIDITY AND RELATIONS TO OTHER VARIABLES

Monika Kirsch [1, 2], Jorg P. Halter [2], Gayathri Nair [3], Georg Stussi [4], Fabienne Dobbels [5], Sabina De Geest [1, 5]

[1] *Institute of Nursing Science, University of Basel, Switzerland*
[2] *Department of Haematology, University Hospital of Basel, Switzerland*
[3] *Division of Haematology, University Hospital of Zurich, Switzerland*
[4] *Department of Haematology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland*
[5] *Health Services and Nursing Research, Department of Public Health and Primary Care, KU Leuven, Belgium*

Will be submitted to
Supportive Care in Cancer

5.1 Abstract

Background: Following allogeneic haematopoietic stem cell transplantation (SCT), patients remain permanently at risk of late effects, many of which manifest as symptoms. To measure patients' symptom experiences, the PROVIVO instrument (**P**atient **R**eported **O**utcomes of long-term SCT sur**VIVO**rs) was developed. This paper describes several refinements to the initial version, followed by validity and reliability testing.

Objective: To refine the newly developed PROVIVO instrument and examine its validity and reliability.

Methods: A cross-sectional study was performed using a 376-patient convenience sample ≥1 year after allogeneic SCT in two Swiss university hospitals. Following American Educational Research Association guidelines, we tested the questionnaire on three evidence levels: construct validity based on internal structure was tested by an exploratory factor analysis; and Cronbach's alphas and inter-item correlations were calculated to examine internal consistency reliability. Relations to other variables were tested based on a set of evidence-based hypotheses.

Results: Based on performance testing, four original PROVIVO items were dropped. The exploratory factor analysis revealed an eight-factor model explaining 57.05% of variance. Internal consistency reliability was good for the entire scale (Cronbach's alphas .90), but only acceptable for the eight factor scores. Additional evidence supports relations between variables, e.g., between the number of symptoms and cGVHD occurrence, number of late and performance status.

Conclusion: Initial evidence for the validity of the PROVIVO symptom experience scale was provided. The PROVIVO questionnaire may be useful to identify late effect symptoms warranting further testing.

5.2 Background

Allogeneic hematopoietic stem cell transplantation (SCT) is an intensive curative treatment for many haematological diseases. However, patients remain at a life-long increased risk of developing various adverse side effects. These "late effects" [1] may appear months or years after treatment has ended, can persist chronically and may be experienced as distressing and burdensome symptoms [2]. Therefore, it is essential to assess symptom experience. According to Leventhal's self-regulation theory, symptoms can be adequately assessed on two dimensions: the cognitive, i.e., symptom occurrence (frequency and severity), and the emotional, i.e., symptom distress [3]. Thus, it is necessary to measure, document, and monitor symptom experience based on patient-reported outcomes (PROs). As a data collection method, PROs have become increasingly important to both clinical research and practice over the last decades. For example, before approving new therapeutic agents, the US Food and Drug Administration (FDA) and the European Medicines Agency recommend that research provides ample patient-reported evidence of their benefits [4, 5].

As few long-term post-SCT studies have simultaneously measured symptom occurrence and distress, little is known of patients' symptom experiences [6-8]. However, it has been shown that vision problems, sexual dysfunction, tiredness, anxiety and changes of taste are experienced by more than 50% of survivors and can be very distressing [7]. Also, as may be expected, patients who have chronic graft versus host disease (cGVHD) suffer more distressing symptoms than those who have no cGVHD [9-11]. Greater symptom distress has been associated with worse psychological functioning, i.e., greater degrees of depression and anxiety [12-14], worse post-transplant physical functioning [15-17], and more post-transplant comorbid conditions (≈late effects) [18]. Most importantly, lower symptom distress is a positive predictor of survival [8]. Figure 1 illustrates the interplay between this study's theoretical framework of symptom experience and the current evidence presented in the literature.

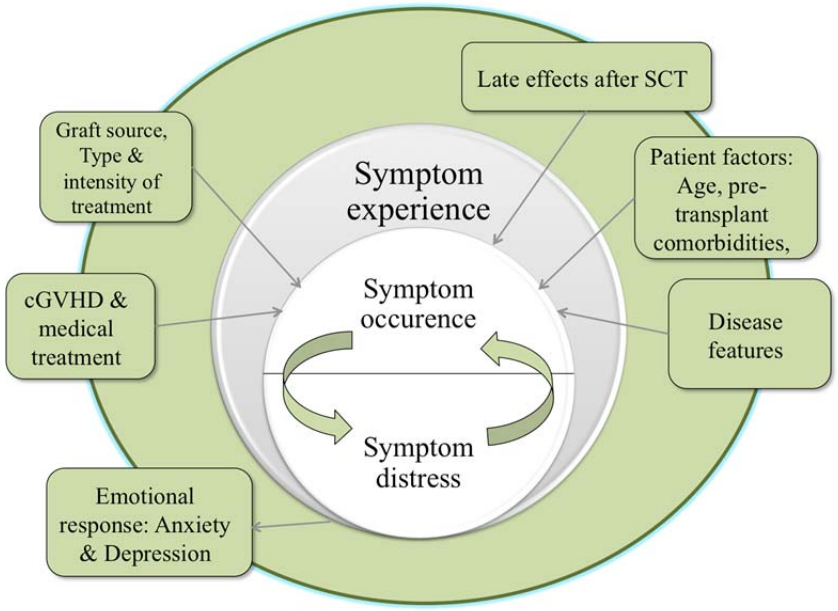


Figure 1. Symptom experience of late effects

Optimally, research on late effects should be based on a combination of PRO data and objective diagnostics. However, to date, most studies on late effects have relied only on clinician-rated adverse event forms or checklists [19, 20]. Full assessment of late effect symptom experiences requires the development of a valid and reliable PRO instrument. Although various SCT-specific PRO instruments, including the MDASI-BMT [21], FACT-BMT [22], and EORTC-HDC29 [23] already exist, these were specifically designed either for the acute treatment phase, or, in the case of the Lee Chronic GVHD scale [24], for the assessment of cGVHD symptoms. Similarly, generic instruments such as the Rotterdam Symptom Checklist [25] or the Symptom Distress Scale [26] may only address subsets of the symptoms that can occur in long-term SCT survivors.

Consequently, to assess specific symptom experiences relating to post-SCT late effects, we followed FDA state-of-the-art PRO guidelines to develop the PROVIVO questionnaire [5]. As a basis for symptom selection we used the U.S. National Cancer Institute's PRO-CTCAE – an item library comprised of 78 symptom terms relevant to all types of cancer treatment. The iterative development process involved both quantitative and qualitative research methods, and included two rounds of patient cognitive debriefings (n=30) and clinical expert review (n=18). Preliminary content validity testing revealed excellent content validity in both the scale (scale-CVI: 0.94) and its individual items (median item-CVI= 1; range 0.75-1) [27]. However, as a subsequent step, instrument refinement and psychometric testing in a larger sample of long-term SCT survivors is warranted.

Level of evidence		Hypothesis or research question
Evidence on construct validity based on internal structure	**H1**	The symptom occurrence items build a meaningful symptom structure in the exploratory factor analysis.
Internal consistency reliability	**H2**	The PROVIVO instrument shows good internal consistency.
	H3	Symptom occurrence items of the PROVIVO instrument show high correlations within its respective factor
Relation to other variables	**H4**	Symptom occurrence items of the PROVIVO instrument show high correlations within its respective factor
	H5	Having depressive symptomatology based on the HADS (score>8) is related to higher symptom occurrence and symptom distress. [12-14]
	H6	Having a lower performance status (Karnofsky <80) is associated with higher symptom occurrence [15-17]
	H7	Having more late effects is associated with higher symptom occurrence and symptom distress.

Abbreviations:
H = Hypothesis, cGVHD = chronic Graft versus Host Disease, according to the National Institute of Healtth criteria (I-III)

Table 1: Hypotheses of the validation study

As cancer patients usually simultaneously experience multiple disease- and treatment-related symptoms, many of which also influence each other, the validation of a symptom experience scale is especially complex 28. The standards for educational and psychological testing set by the American Educational Research Association (AERA) define validation as the process of developing a sound argument for how to interpret scores on a test and the relevance of the test to its proposed use 29. The purpose of this validation study was (1) to describe preliminary data of the newly developed PROVIVO instrument, (2) refine the newly developed instrument and (3) to explore its psychometric properties based on the AERA Standards. Hypotheses to rigorously check the validity and reliability of the instrument are listed in Table 1.

5.3 Methods

5.3.1 Design, sample, setting

To validate the PROVIVO instrument we used data collected for a cross-sectional study using a convenience sample of 376 patients ≥1 year after allogeneic SCT at the Basel and Zürich University Hospital outpatient clinics (NCT01275534). Inclusion criteria were a minimum age of 18 years and the ability to read and write German. Patients who were hospitalized or in a terminal illness state were excluded, as were those with psychiatric disorders that, in the opinion of the treating haematologist, would prevent them from participating in the study.

5.3.2 Variables and measurement

Symptom experience

The PROVIVO instrument measures 31 physical symptoms, 4 emotional and cognitive symptoms, three gender-specific symptoms for women (vaginal dryness, unusual vaginal discharge, pain during vaginal sex), and three more for men (difficulty getting or keeping an erection, ejaculation problems, changes in the skin of the penis). The reporting period for each is the last 7 days. Each symptom is scored in view of symptom occurrence (severity or frequency) and distress. For symptom severity, a 5-point rating scale ranging from 0 (none) to 4 (very severe) is used. Frequency is assessed from 0 (never) to 4 (nearly every time), and distress from 0 (not at all distressing) to 4 (extremely distressing). For follow-up care planning at the survivorship clinic, 5 additional items reflect the symptoms' effects on aspects of daily life (partnership and family, professional life/education/school, financial issues, social contacts (e.g., friends, public), family planning/fertility concerns). Each of these effects is also assessed regarding severity and distress, using the above-mentioned Likert scale responses. To further facilitate follow-up care planning, one item asking about frequency of infections, and two open-ended questions asking about current well-being and supportive care needs/topics the patient would like to

discuss at the annual follow-up consultation. Because these items are primarily aimed at enhancing care planning and do not strictly belong to the concept of symptom experience, they are not included in the psychometric testing procedures; still, the current report gives descriptive results for the 5 items reporting influence on daily living. Results of the two open-text items are reported elsewhere [30]. The time frame of all items is the last seven days.

Anxiety and depression

Anxiety and depression were measured using the Hospital Anxiety Depression Scale (HADS) [31], consisting of 14 items evaluated on a 4-point Likert scale. The HADS is divided into two separately-summed scales, i.e., 7 items measure anxiety and 7 measure depression. On the anxiety scale, a total score of greater than 10 indicates a clinical diagnosis of anxiety, scores of 8 to 10 are borderline, and those below 8 are interpreted as clinically insignificant or normal. Similar interpretations apply to the depression scale. Both scales can be interpreted independently of one other. The HADS is widely validated in diverse populations [32]. The German language version (HADS-D) is validated in the general German-speaking population [33].

Demographic and clinical variables

Patients provided information about marital status (married or living with partner; not married or ed), education (no completed school or professional education; mandatory school; apprenticeship or full-time vocational school; higher professional education; university degree) and employment (full-time (working ≥80%), part-time, or not employed).

Clinical data were retrieved from the transplant database and patient records. Variables included: age; years after transplantation; haematological diagnosis; transplant source (peripheral stem cells, bone marrow, cord blood); total body irradiation (yes/no); number of transplantations; donor relationship (related matched, related mismatched, syngeneic, unrelated), status of haematological disease at annual control (remission, not in remission/relapse); grade of cGVHD (none, mild, moderate, severe) [34]; and Karnofsky index (physician's rating of an individual's health and well-being, based on a criteria-related performance index of physical ability rated from 100% (normal function) to 10% (moribund)) [35].

5.3.3 Data collection

In the month before their annual follow-up visits, a research assistant phoned all eligible SCT recipients, informed them about the study and inquired whether they were interested in participating. Those who were interested received the study information letter, informed consent form and questionnaire per postal mail. Patients either gave the completed materials to their treating physicians at their annual follow-up visits or via regular mail. Clinical and demographic data were collected from the transplant database and patient records. Data was anonymised and entered in a database.

5.3.4 Data analysis

For our first aim, to describe preliminary data collected by the newly developed PROVIVO instrument, we used descriptive statistics (means and standard deviations for normally distributed and interval scaled data as well as medians and interquartile ranges (IQR) for skewed interval scaled data and ordinal scaled data). For data visualisation we used a scatterplot matching mean item severity/ frequency scores and mean item distress scores.

Our analysis used all available data, handling missing data via pairwise deletion. Data were screened for outliers and normal distributions by considering boxplots and histograms. All data were analysed using IBM SPSS Statistics 21 (SPSS, Inc., Chicago, IL). Statistical significance was set at $p<0.05$.

For our second aim, the refinement of the instrument, a-priori defined criteria guided our decisions. Items with the following characteristics were considered for removal/refinement:

1. More than 5% missing responses;
2. Ceiling or floor effects (respectively, ≥80% or ≤20 of patients experiencing a symptom); and
3. Redundancy of an item as demonstrated by a strong correlation with another item ($r\geq0.70$).

A fourth criterion, useful for both item reduction and refinement, resulted from an exploratory factor analysis (EFA) with oblique rotation (Promax rotation method (assumes correlated factors)) and principal axis factoring extraction. This used all but three interval-scored symptom severity/frequency items. The exceptions were the gender-specific items. Because of their different (male vs. female) sample characteristics, these items were subjected to separate factor analyses, i.e., one for each gender. Based on the factor loadings, items were considered for deletion or refinement either if they failed to load on exactly one factor with a value of ≥0.4, i.e., they loaded on no factor with a value ≥0.4 or if they loaded on two or more factors with values of ≥0.4. For item reduction, the clinical relevance of each item was also considered.

For our third aim, the exploration of the psychometric properties based on the AERA Standards, to test the revised instrument's *internal structure* (hypotheses 1), a second EFA was conducted with the adjusted number of items.

To test hypothesis 2 and 3 (Table 1), the instrument's *internal consistency reliability* was examined. Cronbach's alpha was calculated for each factor of the PROVIVO symptom scale, with values >0.60 indicating adequate internal consistency [36]. Additionally, to confirm the internal consistency, inter-item correlations and correlations between individual items and corresponding factor scores were calculated. An acceptable coefficient for item-total correlations, indicating that the item contributes significantly to the measure, is >0.30. For interitem correlations, coefficients of >0.30 and <0.70 are acceptable. An item coefficient of ≤0.30 indicates no significant contribution; a coefficient of ≥0.70 indicates redundancy.

Evidence concerning relations to other variables was assessed with Spearman correlations. Based on the evidence from the literature, we proposed hypotheses 3-7 (displayed in Table 1).

5.4 Results

5.4.1 Demographics

A total of 376 completed questionnaires were returned (overall response rate: 61.6%). On average, patients were 50.3 (SD 12.7) years old, with a median post-SCT follow-up period of 7.1 years (IQR 8.9). Most had been treated for an acute or chronic myeloid leukaemia. Detailed socio-demographic and clinical characteristics are shown in Table 2.

Characteristics	n	%
Gender, male (%)	**207**	**(55.1%)**
Age in years, mean (s.d.)	**50.3(12.7)**	
Initial Diagnosis (%)		
Acute & chronic myeloid leukemia	180	(47.8%)
Acute & chronic lymphoid leukemia	73	(19.4%)
Plasma cell disorder	21	(5.6%)
Hodgkin or Non Hodgkin lymphoma	40	(10.6%)
Myelodysplastic or Myeloproliferative syndrome	44	(11.7%)
Non-malignant haematologic disease	18	(4.9%)
Years after transplantation, median	**7.1 (IQR 8.9, range 1-33)**	
Source of transplant (%)		
Bone marrow	117	(31.1%)
Peripheral blood	258	(68.6%)
Umbilical cord blood	1	(0.3%)
Conditioning regimen (%) [a]		
Myeloablative	286	(76.9%)
Reduced intensity	86	(23.1%)
Total Body Irradiation with ≥12 Gray (%)	**220**	**(58.5%)**
Donor relationship (%)		
Matched related	226	(60.1%)
Syngen	8	(2.1%)
Mismatched related	9	(2.4%)
Unrelated	133	(35.4%)

Current stage of disease (%) [b]		
Complete remission	347	(94.8%)
Not in remission/Relapse	19	(5.2%)
Chronic GVHD (%)		
None	206	(54.8%)
Mild	101	(26.8%)
Moderate	36	(9.6%)
Severe	12	(3.2%)
No information available	21	(5.6%)
Karnofsky Score (%) [c]		
100 - 90%	297	(84.2%)
<90 - 80	35	(9.9%)
<80	21	(5.9%)
Education (%) [d]		
Compulsory schooling	52	(14.1%)
Secondary education	204	(55.3%)
Tertiary education	113	(30.6%)
Partnership (%) [e]		
Married or cohabiting	292	(78.3%)
Single, not cohabiting	81	(21.7%)
Employment (%)		
Full-time (≥80%)	130	(34.6%)
Part-time	127	(33.8%)
Not working	119	(31.6%)

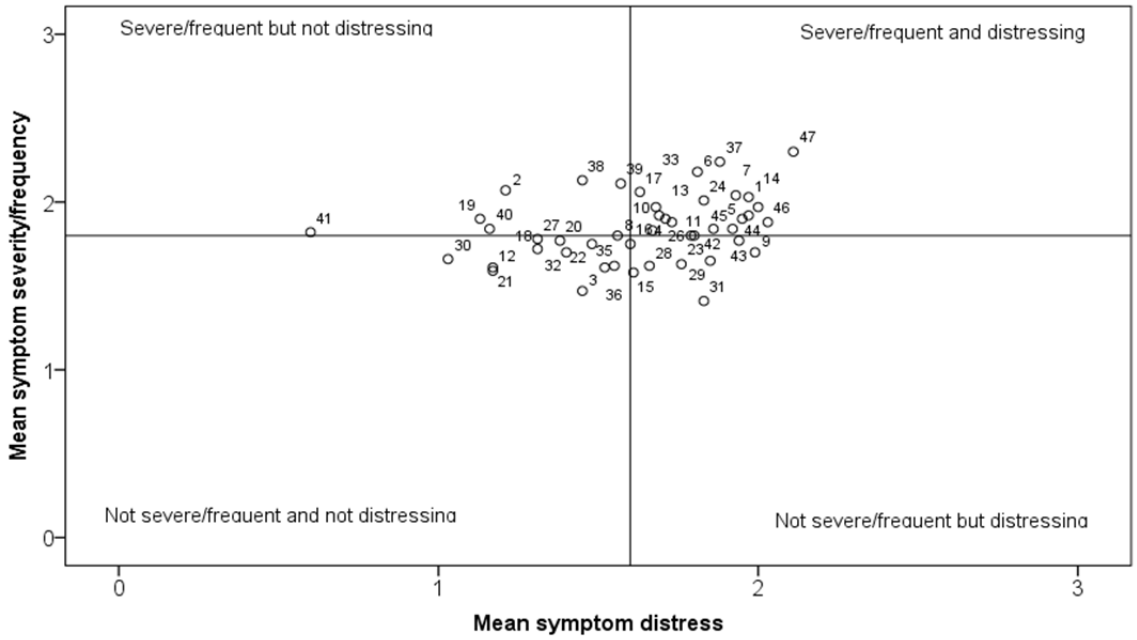
[a] missing n = 4; [b] missing n = 10; [c] missing n = 23; [d] missing = 7; [e] missing= 3;

Table 2: Sample characteristics (N=376)

5.4.2 Results for aim 1: Preliminary description of results of the newly developed PROVIVO instrument

The median number of symptoms/problems per patient was 13 (IQR 13; range: 0-36). The most often reported symptom was fatigue, tiredness or lack of energy (74.2%) followed by problems with memory (68.8%) and dry skin (67.8%). Six more symptoms were reported by more than 50% of all patients: pain (58.0%), problems with concentration (54.8%), light-sensitivity of the eyes (54.0%), muscle cramps (51.6%), dry eyes (51.1%), and insomnia (50.0%). While no items showed ceiling effects, i.e., prevalences above 80%, six showed floor effects, i.e., prevalences below 10%: vomiting (9.8%), pain or burning with urination (2.7%), ejaculation problems (8.5%), change in the skin of the penis (2.4%), unusual vaginal discharge (2.9%) and pain during vaginal sex (6.6%). Distributions of symptom occurrence and distress items were skewed.

Median occurrence scores ranged from 1.89 (vomiting) to 3.47 (child wish/family planning) while median distress scores ranged from 1.25 (unusual vaginal discharge) to 3.14 (family planning/ child wish). A scatter plot of mean symptom severity/frequency scores (Figure 2) shows the classification of symptoms into four categories. Symptoms in the lower left quadrant are both less severe/ frequent and less distressing (n=13); those in the upper left quadrant are more severe/frequent but less distressing (n=6); in the upper right quadrant they are both more severe/frequent and more distressing (n=19), and symptoms in the lower right quadrant are less severe/frequent but more distressing (n=9).



Legend

Physical symptoms

1 Fatigue, tiredness, or lack of energy
2 Dry skin
3 Pain
4 Light sensitivity of the eyes
5 Muscle cramps
6 Dry eyes
7 Insomnia including difficulty falling, asleep, staying asleep
8 Unexpected or excessive sweating during the day or night time
9 Blurred vision
10 Dry mouth
11 Shortness of breath
12 Cough
13 Numbness or tingling in hands or feet
14 Stiffness of joints
15 Itchy skin
16 Loose or watery stools (diarrhea)
17 Arm or leg swelling
18 Pounding or racing heart beat
20 Tremors
21 Teeth problems
22 Watery eyes (tearing)
23 Nausea
24 Problems with tasting food/drinks
26 Rash
27 Decreased appetite
28 Mouth or throat sores
29 Difficulty swallowing
30 Unusual darkening of the skin
31 Vomiting
32 Pain or burning with urination

Emotional/cognitive symptoms

33 Problems with memory
34 Problems with concentration
35 Sad or unhappy feelings
36 Anxiety or worry

Gender symptoms

19♂♀ Decreased sexual interest
37♂ Difficulty getting or keeping an erection
38♂ Ejaculation problemserection
39♂ Change in the skin of the penis
40♀ Vaginal dryness
41♀ Unusual vaginal discharge
42♀ Pain during vaginal sex

Influence on daily life

43 Partnership and family
44 Professional life/education/school
45 Financially
46 Social contacts (e.g. friends, public)
47 Family planning /child wish

Figure 2: Mean symptom severity/frequency and distress score per item (N = 376)

	Frequency		Symptom occurrence	Symptom distress
	n	%	Median (IQR)	Median (IQR)
Physical symptoms				
Fatigue, Tiredness, or lack of energy	279	74.2%	2.85 (1.70)	3.00 (2.08)
Dry skin	255	67.8%	2.88 (1.68)	1.94 (1.62)
Pain	218	58.0%	3.31 (1.55)	2.83 (2.72)
Light sensitivity of the eyes	203	54.0%	2.70 (1.61)	2.60 (1.89)
Muscle cramps	194	51.6%	2.63 (1.47)	2.89 (1.90)
Dry eyes	192	51.1%	3.12 (1.91)	2.76 (1.95)
Insomnia including difficulty falling asleep, staying asleep, or waking up early)	188	50.0%	2.86 (1.70)	2.94 (2.04)
Unexpected or excessive sweating during the day or night time (not related to hot flashes)	143	38.0%	2.51 (1.44)	2.32 (1.67)
Blurred vision	143	38.0%	2.36 (2.36)	2.96 (1.95)
Dry mouth	139	37.0%	2.78 (1.66)	2.57 (1.85)
Shortness of breath	138	36.7%	2.57 (2.57)	2.71 (1.88)
Cough	135	35.9%	2.14 (2.14)	1.84 (1.49)
Numbness or tingling in your hands or feet	133	35.4%	2.76 (1.75)	2.64 (1.94)
Stiffness of joints	124	33.0%	2.71 (1.53)	2.83 (1.70)
Itchy skin	118	31.4%	2.00 (2.00)	2.34 (1.65)
Loose or watery stools (diarrhea)	115	30.6%	2.41 (1.38)	2.57 (2.05)
Arm or leg swelling	112	29.8%	2.81 (1.55)	2.57 (1.89)
Pounding or racing heart beat (palpitations)	110	29.3%	2.37 (1.34)	1.96 (1.43)
Decreased sexual interest	101	26.9%	2.62 (1.43)	2.00 (1.80)
Tremors	91	24.2%	2.42 (1.35)	2.17 (1.79)
Teeth problems	89	23.7%	2.16 (2.16)	2.56 (1.73)
Watery eyes (tearing)	87	23.1%	2.50 (2.50)	2.23 (1.72)
Nausea	86	22.9%	2.23 (2.23)	2.56 (1.72)
Problems with tasting food or drinks	76	20.2%	2.83 (1.70)	2.93 (2.21)
Rash	75	19.9%	2.55 (2.55)	2.74 (1.98)
Decreased appetite	69	18.4%	2.52 (2.52)	2.03 (1.71)
Mouth or throat sores	68	18.1%	2.23 (2.23)	2.5 (1.73)
Difficulty swallowing	52	13.8%	2.28 (2.28)	2.79 (1.92)
Unusual darkening of the skin	41	10.9%	2.32 (2.32)	1.82 (1.72)
Vomiting	37	9.8%	1.89 (1.89)	2.91 (2.2)
Pain or burning with urination	10	2.7%	2.40 (1.40)	2.50 (2.17)
Emotional and cognitive symptoms				
Problems with memory	258	68.6%	2.58 (1.42)	2.78 (2.14)
Problems with concentration	206	54.8%	2.52 (1.42)	2.66 (2.03)
Sad or unhappy feelings	172	45.7%	2.19 (2.19)	2.30 (1.69)
Anxiety or worry	118	31.4%	2.18 (2.18)	2.23 (1.57)

Male symptoms				
Difficulty getting or keeping an erection	81	21.5%	2.92 (1.62)	2.50 (1.87)
Ejaculation problems	32	8.5%	2.83 (1.43)	2.53 (1.96)
Change in the skin of the penis	9	2.4%	2.95 (1.43)	2.7 (1.57)
Female symptoms				
Vaginal dryness	159	42.3%	2.57 (1.43)	2.13 (1.95)
Unusual vaginal discharge	11	2.9%	2.58 (1.52)	1.25 (1.25)
Pain during vaginal sex	25	6.6%	2.61 (1.53)	2.80 (1.80)
Influence on daily life				
Partnership and family	117	31.1%	2.51 (2.51)	2.90 (1.89)
Professional life/ education / school	105	27.9%	2.75 (1.72)	2.90 (1.87)
Financially	86	22.9%	2.58 (1.52)	2.76 (1.72)
Social contacts (e.g. friends, public)	72	19.4%	2.65 (1.64)	3.02 (1.99)
Family planning /child wish	40	10.6%	3.47 (2.27)	3.14 (2.14)

Heat intensity mapping was used to represent the median scores for symptom occurrence and distress varying from light to dark grey (i.e., the darker the grey colour the larger the median score, the lighter the grey color the lower the mean score).

≥75 Percentile ≥ 50 percentile < 50 percentile

Abbreviations: IQR = Interquartile range

Table 3: Symptom prevalence, median symptom occurrence and distress scores (N=376)

5.4.3 Aim 2: Refinement of the scale

A missing value analysis indicated 4-items with more than 5% missing values (range: 0–7.2%): "decreased sexual interest", "pain or burning during urination", "problems at work/training/school", and "problems with child wish/family planning"

The item-to-item correlations were all below 0.80, with the closest association indicated was between nausea and vomiting (r=0.624), indicating a conceptual similarity. Subsequently, the EFA was conducted including all 35 non-gender-specific physical and emotional/cognitive symptom items. This yielded 10 factors with eigenvalues ranging from 8.301 to 1.012, explaining 59.4% of the variance. Twenty-seven items clearly loaded on one of the 10 factors, with loadings ranging from .403 to .903. Of the remaining 8, two cross-loaded: *blurred vision*, with factor loadings of .587 on factor 2 (*dry eyes, light-sensitivity*) and .517 on factor 10 (*watery eyes*); and *problems with tasting food or drinks,* with factor loadings of .480 on factor 3 (*cough, numbness or tingling in your hands or feet, shortness of breath*) and .485 on factor 7 (*vomiting, nausea, decreased appetite*). Six items failed to load significantly on any factor.

Based on these preliminary results, we adapted the PROVIVO scale according to our pre-defined criteria for item retention and clinical meaningfulness. As the *vomiting* item had a floor effect and a high item-to-item correlation with *nausea*, we combined the two items into *nausea or vomiting*.

Also, we observed double loadings in two factors related to eye problems, *watery eyes* and *dry eyes.* As both are manifestations for abnormal tearing production (potentially related to a damage of the conjunctivas or cataract) we also combined them into a single item, *abnormal tearing (too dry or watery eyes)*. Further, we changed one item, *skin rash* into *changes of the skin (including skin rash)* and deleted two others entirely – *unusual darkening of the skin*, which showed a floor effect, and *pain or burning with urination*, which had both 5.6% missing data and a floor effect. Other items with floor effects were left unchanged, as, from a clinical point of view, they would prevent errors in the detection of clinically important symptoms.

5.4.4 Construct validity and internal consistency reliability

	Factor							
	1	2	3	4	5	6	7	8
Decreased appetite	.750							
Nausea & vomiting	.741							
Loose or watery stools (diarrhea)	.404							
Pounding or racing heartbeat (palpitations)	.402							
Abnormal tearing of eyes (too dry or watery)		.795						
Eye sensitivity to light		.745						
Blurred vision		.714						
Cough			.711					
Numbness or tingling in your hands or feet			.618					
Problems with tasting food or drinks			.567					
Shortness of breath			.468					
Skin rash or abnormal changes of skin				.836				
Itchy skin				.767				
Dry skin				.553				
Arm or leg swelling					.672			
Muscle cramps					.611			
Stiffness of joints					.514			
Pain					.486			
Mouth or throat sores						.636		
Dental problems						.635		
Dry mouth						.403		
Difficulty swallowing						.401		
Sad feelings							-.722	
Problems concentrating							-.708	
Problems with memory							-.682	
Anxiety							-.663	
Decreased sexual interest								.844
Fatigue, tiredness, or lack of energy								
Tremors								
Insomnia (including difficulties falling asleep, or waking up early)								
Unexpected or excessive sweating during the day or nighttime (not related to hot flashes)								

Table 4: exploratory factor analysis

After reducing the number of items as described above, the EFA of the adjusted 34-item instrument yielded 8 factors explaining 57.05% of the total variance. The Kaiser-Meyer-Olkin measure of sampling adequacy produced a figure of 0.824, showing that the data are suitable for factor analysis. Eigenvalues ranged from 8.069 to 1.103. Factor loadings are presented in Table 4. Five items did not load adequately on any factor. The EFA for the male symptoms yielded one factor with an eigenvalue of 1.785, explaining 59.52% of the variance; the factor loadings ranged from .483 to .883. The female symptoms yielded one factor with an eigenvalue of 1.936, explaining 64.42% of the variance; loadings ranged from .568 to .926.

As predicted in hypothesis 1, the 8-factor model yielded acceptable/good reliability values, with Cronbach's alphas varying from 0.53 to 0.82 (Table 5). For the male and female symptom factors, Cronbach's alphas were respectively 0.65 and 0.72.

Factors of PROVIVO	Eigenvalue	Cronbach's alpha	Inter-item correlation	Item to factor correlation, range
Ingestion symptoms (4 items)	8.069	0.66	.340	.368–.599
Eye symptoms (3 items)	1.885	0.72	.465	.538–.545
Symptoms of neurological & pulmonary toxicity/morbidity (4 items)	1.695	0.62	.295	.348–.454
Skin symptoms (3 items)	1.462	0.67	.428	.457–.575
Skeletal, connective tissue symptoms & pain (4 items)	1.348	0.66	.333	.366–.477
Symptoms of the mouth & dental problems (4 items)	1.117	0.53	.230	.284–.355
Emotional & cognitive symptoms (4 items)	1.103	0.82	.526	.564–.736
Decreased sexual interest	1.015	n.a	n.a.	n.a.

Table 5: Reliability characteristics of the eight factors

5.4.5 Relations to other variables

Testing evidence based on relations to other variables confirmed four literature-based hypotheses. As hypothesized, any grade of cGVHD was associated with a higher number of physical symptoms (r =.304; p<=0.00); depressive symptomatology was related to both higher number of emotional/ cognitive symptoms (r=.474; p=.000) and higher emotional/cognitive symptom distress (r=.596; p=.000). Also more anxiety symptomatology was related to more emotional/cognitive symptoms (r=.595; p=.000) and higher emotional/cognitive symptom distress (r=.527; p=.000). Symptom occurrence was higher both in patients with lower performance status (Karnofsky <80) (r=-.417; p=.000) and in those with more late effects (r=.189; p=.000).

5.5 Discussion

The PROVIVO instrument appears to be a useful measure of late effect symptom experience following SCT. In this initial psychometric evaluation, item refinement and reduction resulted in the final 34-item symptom experience scale including three gender specific items each for women and men. Eight additional items are included to guide follow-up care planning. The questionnaire's measurement properties were supported, with findings suggesting good internal structure, adequate consistency, and reliability, along with evidence for validity related to other variables. This study provides initial evidence regarding measurement of long-term allogeneic SCT survivors late effect symptom experiences. The minimal incidence of missing data from the submitted PROVIVO questionnaires suggests ease of use and comprehensibility.

From our factor analysis examining construct validity, logical patterns of symptoms emerged, i.e., symptoms which typically occur frequently in combination also loaded together [37]. For instance, as *abnormal tearing of eyes, light-sensitivity of the eyes* and *blurred vision* might appear more frequently in patients with eye-related problems such as cataract or sicca syndrome of the conjunctivas [38, 39]. However, five items did not load on any factor: *fatigue, tiredness or lack of energy, tremors, insomnia, unexpected or excessive sweating during the day or night.* Since inter-item correlations of these symptoms showed relations to various symptoms, a possible explanation for their failure to load significantly is that they co-appear with a variety of conditions and therefore cannot be clearly related to any single symptom factor. As an example, while fatigue is a symptom very commonly related to numerous co-morbidity conditions after SCT [40-42], it did not load significantly on any specific factor.

It is acknowledged that performing factor analyses on a symptom questionnaire is a difficult undertaking [43, 44]. Regarding the current study, any of a number of particularities, including the heterogeneity of symptom profiles, differences in the occurrence and severity of symptoms, or the overall heterogeneity of the study sample could have skewed the results. This may also explain our low Cronbach alphas and item to factor correlations. In contrast to scales measuring very distinct constructs such as anxiety, "late effect symptom experience" is more manifold on a patient level and therefore more difficult to assess.

Further research should therefore examine the eight revealed factors in view of their predictive validity for specific late effects. For example, it would be useful to investigate whether the factor including *arm or leg swelling, muscle cramps, stiffness of joints and pain* predicts late skeletal system effects. This information would be particularly valuable to determine the PROVIVO's predictive validity for specific late effects' symptom factor scores, and to determine whether sub-scores can be calculated for the PROVIVO instrument. Currently we recommend scoring the instrument using two separate sum scores – one for the number of symptoms (physical and emotional/cognitive) and one for symptom distress. Regarding symptom occurrence and distress, scores can also be calculated on the item level.

Moreover, as the current study's patients reported a high number of symptoms (median 13 (IQR 13) – considerably more than those in previous studies (median <10) [6, 18] – the PROVIVO instrument's preliminary results underscore the importance of symptom assessment in long-term survivors. Differences may be related to the researchers' choices of measures, or to variations in sample characteristics, or even data collection time points. Bevans et al.'s prospective study of 171 patients (minimum post-SCT follow-up time 3 years) reported an average of 8 (SD 5) to 10 symptoms (SD 6.6) across time. For Larsson et al., one year after transplantation, patients evaluating their health status reported symptoms with an adapted 23-item version of the symptom distress scale. Based on this self-evaluation, patients were divided into those with poor health status (n=9), with a median of 10 symptoms (range: 6-14) and those with good health status (n=21), with a median of 3 symptoms (range 0-10) [6]. The differences between our results and previous studies might result from the difference in sample size and/or the measurements used.

Other long-term post-SCT studies used health related quality of life questionnaires to survey patients' perspectives. However, symptom assessment is only one aspect of these questionnaires, and not be well captured. Therefore, evidence on the symptom experience for SCT recipients is often extrapolated from broader HRQoL instruments which use only limited subsets of items with a unidimensional question format (e.g., "Do you have nausea?"). Although symptoms are embedded in the common HRQoL dimensions of a questionnaire, a more comprehensive assessment is required before suggesting interventions. This seems obvious for the physical symptoms routinely assessed in allogeneic SCT follow-up, wherein a healthcare provider would immediately expand assessment of nausea if reported by a patient (e.g., "How much does it distress you?"). The PROVIVO instrument systematizes this process, minimizing response biases to compile a full list of symptoms, their incidence and the distress they cause. Given the clear need for patient reports of their symptom experiences, then, the PROVIVO instrument is a promising tool for the development and evaluation of symptom management interventions

This study has to be viewed in the light of following limitations. First, our sample size might have been underpowered [45]. Along with the heterogeneity of our patient sample characteristics, this may have contributed to our moderate results in terms of internal structure. Second, our study included only one measurement point; therefore, future longitudinal studies are suggested.

The validation of PRO instruments is an on-going process, and confidence in a questionnaire develops based on the long-term accumulation of psychometric data[46]. Therefore, despite encouraging preliminary results, the current study should be considered only as an initial step in validating the PROVIVO instrument. Subsequent steps should include examining the instrument's responsiveness to change over time and developing interpretation guidelines such as the minimally important difference [47].

In sum, the refined PROVIVO demonstrated reliability and validity as a PRO measure that allows for a brief yet comprehensive assessment of symptom experience from the patient perspective.

5.6 References

1. Tichelli A, Rovo A, Passweg J, Schwarze CP, Van Lint MT, Arat M *et al.* Late complications after hematopoietic stem cell transplantation. *Expert Rev Hematol* 2009; **2:** 583-601.
2. Tichelli A, Socie G. Considerations for adult cancer survivors. *Hematology Am Soc Hematol Educ Program* 2005**:** 516-522.
3. Leventhal H, Brissette I, Leventhal EA. The common-sense model of self-regulation of health and illness. In: Florence K, Cameron LD, Leventhal H (eds). *The Self-regulation of Health and Illness Behaviour*. Routledge, 2003, pp 43-65.
4. European Medicines Agency. Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. London, 2005; www.emea.eu.int.
5. Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims Federal Register, 2009.
6. Larsen J, Nordstrom G, Ljungman P, Gardulf A. Factors associated with poor general health after stem-cell transplantation. *Supportive Care in Cancer* 2007; **15:** 849-57.
7. Edman L, Larsen J, Hagglund H, Gardulf A. Health-related quality of life, symptom distress and sense of coherence in adult survivors of allogeneic stem-cell transplantation. *European journal of cancer care* 2001; **10:** 124-30.
8. Molassiotis A, Van Den Akker OB, Milligan DW, Goldman JM. Symptom distress, coping style and biological variables as predictors of survival after bone marrow transplantation. *Journal of Psychosomtic Research* 1997; **42:** 275-85.
9. Lee SJ, Kim HT, Ho VT, Cutler C, Alyea EP, Soiffer RJ *et al.* Quality of life associated with acute and chronic graft-versus-host disease. *Bone Marrow Transplant* 2006; **38:** 305-10.
10. Pallua S, Giesinger J, Oberguggenberger A, Kemmler G, Nachbaur D, Clausen J *et al.* Impact of GvHD on quality of life in long-term survivors of haematopoietic transplantation. *Bone Marrow Transplant* 2010; **45:** 1534-9.
11. Mitchell SA, Leidy NK, Mooney KH, Dudley WN, Beck SL, LaStayo PC *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:** 762-9.
12. Artherholt SB, Hong F, Berry DL, Fann JR. Risk Factors for Depression in Patients Undergoing Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant* 2014; **18:** 00159-1.
13. Mosher CE, Redd WH, Rini CM, Burkhalter JE, DuHamel KN. Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: a review of the literature. *Psychooncology* 2009; **18:** 113-27.
14. Gruber U, Fegg M, Buchmann M, Kolb HJ, Hiddemann W. The long-term psychosocial effects of haematopoetic stem cell transplantation. *Eur J Cancer Care* 2003; **12:** 249-256.

15. Mosher CE, Duhamel KN, Rini C, Corner G, Lam J, Redd WH. Quality of life concerns and depression among hematopoietic stem cell transplant survivors. *Support Care Cancer* 2010; **19:** DOI 10.1007/s00520-010-0958-y.
16. Artz AS, Pollyea DA, Kocherginsky M, Stock W, Rich E, Odenike O *et al.* Performance status and comorbidity predict transplant-related mortality after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2006; **12:** 954-64.
17. Sorror M, Storer B, Sandmaier BM, Maloney DG, Chauncey TR, Langston A *et al.* 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.
18. Bevans MF, Mitchell SA, Barrett J, Bishop MR, Childs R, Fowler D *et al.* Symptom Distress Predicts Long-Term Health and Well-Being in Allogeneic Stem Cell Transplantation Survivors. *Biol Blood Marrow Transplant* 2014; **20:** 387-95.
19. Trotti A, Colevas AD, Setser A, Basch E. Patient-reported outcomes and the evolution of adverse event reporting in oncology. *J Clin Oncol* 2007; **25:** 5121-7.
20. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG *et al.* Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* 2005; **106:** 2912-9.
21. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M *et al.* Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer* 2000; **89:** 1634-46.
22. McQuellon RP, Russell GB, Cella DF, Craven BL, Brady M, Bonomi A *et al.* Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. *Bone Marrow Transplant* 1997; **19:** 357-68.
23. Velikova G, Weis J, Hjermstad MJ, Kopp M, Morris P, Watson M *et al.* The EORTC QLQ-HDC29: a supplementary module assessing the quality of life during and after high-dose chemotherapy and stem cell transplantation. *European Journal of Cancer* 2007; **43:** 87-94.
24. Lee S, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. *Biology of Blood and Marrow Transplantation* 2002; **8:** 444-52.
25. de Haes JC, van Knippenberg FC, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. *Br J Cancer* 1990; **62:** 1034-8.
26. McCorkle R, Cooley ME, Shea JA. The user's manual for the symptom distress scale. *Instrument manual* 1994.

27. Kirsch M, Halter JP, Stussi G, Nair G, Dobbels F, De Geest S. Symptom experience of late effects after allogeneic haematopoietic stem cell transplantation: Refinement and preliminary validity testing for construct validity and relation to other variables of the PROVIVO instrument *Support Care Cancer* accepted.
28. Kim JE, Dodd MJ, Aouizerat BE, Jahan T, Miaskowski C. A review of the prevalence and impact of multiple symptoms in oncology patients. *J Pain Symptom Manage* 2009; **37:** 715-36.
29. American Educational Research Association. Standards for educational and psychological testings. Washington; DC: AERA, 1999.
30. Gerwig N, Kirsch M, Fierz K, De Geest S. Self-reported Well-being and Supportive Care Needs among long-term Survivors after Haematopoietic Stem Cell Transplantation attending a follow-up clinic – a secondary mixed methods data analysis of the PROVIVO study. University Basel, Basel, 2014.
31. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67:** 361-70.
32. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. *Journal of psychosomatic research* 2002; **52:** 69-77.
33. Hermann C, Buss U. HADS-D. Hospital anxiety and depression scale-Deutsche Version. In: *Testdokumentation und Handanweisung*. Huber, Bern, 1995.
34. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ *et al.* National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant* 2005; **11:** 945-56.
35. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. *Cancer* 1984; **53:** 2002-2007.
36. Hays RD, Anderson R, Revicki D. Psychometric considerations in evaluating health-related quality of life measures. *Qual Life Res* 1993; **2:** 441-9.
37. Esther Kim J-E, Dodd MJ, Aouizerat BE, Jahan T, Miaskowski C. A Review of the Prevalence and Impact of Multiple Symptoms in Oncology Patients. *J Pain Symptom Manage* 2009; **37:** 715-736.
38. Tabbara KF, Al-Ghamdi A, Al-Mohareb F, Ayas M, Chaudhri N, Al-Sharif F *et al.* Ocular findings after allogeneic hematopoietic stem cell transplantation. *Ophthalmology* 2009; **116:** 1624-1629.
39. Daikeler T, Mauramo M, Rovo A, Stern M, Halter J, Buser A *et al.* Sicca symptoms and their impact on quality of life among very long-term survivors after hematopoietic SCT. *Bone Marrow Transplant* 2013; **48:** 988-93.

40. Solberg Nes L, Ehlers SL, Patten CA, Gastineau DA. Self-Regulatory Fatigue, Quality of Life, Health Behaviors, and Coping in Patients with Hematologic Malignancies. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 2014; **7:** 7.
41. Syrjala KL, Martin PJ, Lee SJ. Delivering care to long-term adult survivors of hematopoietic cell transplantation. *J Clin Oncol* 2012; **30:** 3746-51.
42. Clanton NR, Klosky JL, Li C, Jain N, Srivastava DK, Mulrooney D *et al.* Fatigue, vitality, sleep, and neurocognitive functioning in adult survivors of childhood cancer. *Cancer* 2011; **117:** 2559-2568.
43. Kim HJ, Abraham I, Malone PS. Analytical methods and issues for symptom cluster research in oncology. *Curr Opin Support Palliat Care* 2013; **7:** 45-53.
44. Skerman HM, Yates PM, Battistutta D. Multivariate methods to identify cancer-related symptom clusters. *Research in nursing & health* 2009; **32:** 345-60.
45. Fabrigar LR, Wegener DT, MacCallum RC, Strahan EJ. Evaluating the use of exploratory factor analysis in psychological research. *Psychological methods* 1999; **4:** 272.
46. Frost MH, Reeve BB, Liepa AM, Stauffer JW, Hays RD. What is sufficient evidence for the reliability and validity of patient-reported outcome measures? *Value Health* 2007; **10:** 94-105.
47. Revicki DA, Gnanasakthy A, Weinfurt K. Documenting the rationale and psychometric characteristics of patient reported outcomes for labeling and promotional claims: the PRO Evidence Dossier. *Qual Life Res* 2007; **16:** 717-23.

CHAPTER 6:

DIFFERENCES IN HEALTH BEHAVIOURS BETWEEN RECIPIENTS OF ALLOGENEIC HAEMATOPOIETIC STEM CELL PLANTATION AND THE GENERAL POPULATION: A MATCHED CONTROL STUDY

Monika Kirsch[1, 2], Anna Götz [3], Jorg P. Halter [2],
Urs Schanz [3], Georg Stussi [4], Fabienne Dobbels [5],
Sabina De Geest [1, 5]

[1] *Institute of Nursing Science, University of Basel, Switzerland*

[2] *Department of Haematology, University Hospital of Basel, Switzerland*

[3] *Division of Haematology, University Hospital of Zurich, Switzerland*

[4] *Department of Haematology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland*

[5] *Health Services and Nursing Research, Department of Public Health and Primary Care, KU Leuven, Belgium*

In press:
Bone Marrow Transplantation
Modified version

6.1 Abstract

Little is known of health-relevant behaviours among long-term survivors of haematological disorders treated with haematopoietic stem cell transplantation. This comparative cross-sectional multicentre study aimed (1) to explore the prevalence of selected behaviours in this group and (2) to compare them with those of the general population. Self-reported data of 376 survivors (mean age: 50.4 (s.d.=12.8); median 7 years post-allogeneic SCT (IQR=8.9; range 1-33) were compared with controls derived from the Swiss Health Survey 2007 by propensity score matching. Survivors were more physically inactive (26.8% vs. 12.5%; p=<.001) and consumed fewer portions of vegetables (≥ 3 pieces: 10% vs. 21.6%; p<.001), fruits (≥ 3 pieces: 6.5% vs. 10.6%; p<.001), and fish (31.2% vs. 60.9% weekly fish dish; p<.001). More consumed dairy products daily (92.5% vs. 62.9%; p<.001), used sun protection regularly (94.5% vs. 85.3%, p<.001) and had received influenza vaccinations in the last year (58.4% vs. 21.5%; p<.001); fewer smoked (13.4% vs. 35.4%; p<.001). Survivors' weekly alcohol consumption was lower (median 1.5 servings (IQR 4) vs. median 4.5 (IQR 10.3); p<.001). Of those taking immunosuppressants, 65.7% were non-adherent. Similar to the general population, survivors experience problems executing several health-enhancing behaviours, warranting corrective interventions.

6.2 Introduction

Haematopoietic stem cell transplantation (SCT) is an established treatment for patients with severe disorders of the haematopoietic system. Although many patients can be cured of their initial disease, up to two-thirds develop chronic conditions, including cGVHD, heart problems, endocrine disorders, neurocognitive impairment, musculoskeletal disorders and secondary malignancies [1]. Since these conditions require life-long management [2] the majority of SCT survivors can be regarded being chronically ill. Research in chronic illness patients as well as in the general population indicates that favourable health behaviours prevent some chronic illnesses, delay progression of existing conditions and decrease mortality rates [3]. In particular, four health behaviours – adequate physical activity, healthy diet, non-smoking, and moderate alcohol consumption – contribute to a longer, healthier life [4]. Ford's large prospective study in the general population (N= 23.125) linked engagement in these behaviours with a reduced risk for early death from cancer and cardiovascular diseases [3]. In Switzerland, cancer survivors, including SCT recipients, are therefore encouraged to follow the same national health recommendations for these four key health behaviours [5-9]. Additional recommendations include sun protective measures [10], scheduled vaccinations [11, 12] and close adherence to any medication regimen [13] (see also table 1 for overview).

While the literature on health behaviours in cancer survivors is growing [14,15], little is known about how many SCT survivors succeed in following a healthy lifestyle. Studies from the United States show that 29-36% of survivors exercised for at least 20-30 minutes three times per week compared to 30-45% of matched controls [16, 17]. Overweight was observed 52% of survivors and 47% of controls; and only 5% of survivors reported eating a healthy diet, i.e., one low in fat and high in fruits and vegetables [17]. Survivors

were also less likely than controls to drink more than 2 servings of alcohol per day (15% vs 25%) [17], and high-risk drinking was less prevalent in survivors (9.5%) than in controls (13.3%) [18]. In the reported studies 7 to 14% of survivors currently smoked [16-18]. Survivors were more likely than controls to have received seasonal influenza vaccinations (59.7% vs. 32.7%), especially those aged over 65 years (95% vs. 73%) [17].

To date no study has examined sun-protective behaviours and medication intake in the long term following SCT. Further, knowledge is lacking as to whether health behaviours among European SCT survivors differ from those of the general population; and previous research focused on small sets of behaviours. Therefore, the present study aimed

1. to determine the prevalence of 8 health behaviours in Swiss SCT survivors (i.e., physical activity, dietary habits and weight control, alcohol intake, smoking, influenza vaccination, sun protection, and medication adherence)
2. to compare Swiss SCT survivors' health behaviours with those of matched controls from the general population

6.3 Subjects and methods

6.3.1 Design

This cross-sectional comparative observational study is part of the mixed-methods multicentre PROVIVO project investigating Patient Reported Outcomes of long-term survivors after allogeneic SCT (NCT01275534). Data from the PROVIVO study and the 2007 Swiss Health Survey (SHS) were used. The PROVIVO study was approved by the Basel and Zurich ethical committees.

6.3.2 Setting, sample and data collection procedures

Convenience sampling was used to recruit allogeneic SCT recipients from the University Hospitals of Basel and Zurich from November 2011 until November 2012. Inclusion criteria were at least one year post-transplantation and an age of at least 18 years. Exclusion criteria were an inability to read German, current hospitalization or a diagnosed end-of-life stage. Patients with visual and/or hearing impairment or severe psychiatric disorders (e.g., suicidal tendencies, acute psychosis) were also excluded. In the month before their annual follow-up visits, a research assistant phoned all eligible SCT recipients, informed them about the study and inquired whether they were interested in participating. They were also asked if they were taking any type of immunosuppression medication. Those who were interested received the study information letter, an informed consent form and an appropriate questionnaire (version A for patients with immunosuppressants or version B for patients without) per postal mail. Patients returned the completed study materials to their treating physician at their annual follow-up visit or returned them via post. Clinical and demographic data were collected from the transplant database and patient records. Data was anonymised and entered in a database.

6.3.3 Selection of case-matched controls from the SHS sample

Controls were selected from the 2007 dataset of the Swiss Health Survey (SHS). The national representative health survey is repeated in 5-year intervals and consists of a telephone interview and a written questionnaire. In addition to questions about physical, mental and social health, symptoms, co-morbidities, accidents, and disabilities, participants were asked about their health behaviours, living conditions and resources which would potentially affect their health. The 2007 survey involved a sample of 30.179 Swiss households with telephone landlines. From each participating household, one person aged over 15 years was randomly chosen. With a response rate of 66%, the final sample included 18.760 participants [19].

Propensity score (PS) matching was used to match each survivor with one control from the SHS. The following covariates were matched: gender, age, education, and residence, i.e., the Swiss region (7 regions) and urbanisation zone (9 types) of residence [20]. Each PS value was allocated a score between 0 and 1 to express the probability of one participant having a perfect match when their observable characteristics are given. Using the minimum distance method, each patient was linked with the control group subject with the nearest PS value.[21] The area under the curve (c-statistic) of the logistic model to calculate the propensity scores was 0.74 (95%; CI=0.72-0.76), indicating appropriate matching.

6.4 Variables and measurement

6.4.1 Socio-demographic and clinical data

The following socio-demographic variables were documented for both patients and controls: gender, age, education (compulsory schooling, secondary education, tertiary education), Swiss living region and urbanisation zone (not displayed in this article), partnership (married or cohabiting/single or not cohabiting), and employment (full time (working ≥80%), part-time, or not employed). Table 2 gives an overview about the clinical characteristics of SCT survivors.

Health behaviours assessed in survivors and in SHS population

To allow comparison with the general population, health behaviours were measured with standardised questions, almost all of which were drawn from the SHS. On-going data quality controls concerning item clarity and validity were performed by the Swiss Federal Statistical Office [19]. Table 1 displays health behaviour recommendations, variables of interest and categorizations used.

Health behaviour	Recommendations[5-13]	Study variables, measurement and categorization
Physical activity (3 items)	▪ Engage in at least 30 minutes of daily moderate activity (e.g. cycling, brisk walking) *or* a total of 2 ½ hours of moderate physical activity per week *or* 1 ¼ hours or high-intensity activity per week (e.g. jogging, playing tennis)	*Physically active* (yes/no); if yes: *frequency* (days), *duration* (minutes) and *intensity* (very easy, easy, moderate, strong, very strong). Categorization in three levels: *Inactive* (less than once weekly, 30 minutes of physical activity with moderate or strong intensity); *partially active* (at least once weekly, 30 minutes activity with a moderate intensity or once with strong intensity regardless of duration); and *active* (at least on 5 days weekly, moderate physical activity for 30 minutes each time or 3 times with strong intensity)
Dietary habits (5 items) **and weight control** (indicated by BMI)	▪ Eat 5 or more servings of a variety of vegetables and fruits each day. ▪ Limit intake of processed and red meats ▪ Eat (preferable three) dairy products daily ▪ Achieve and maintain a healthy weight (BMI 18.5-24.9)	Numbers of consumed *vegetables* and *fruits* (per day), *dairy products* (per day), *meat* and *fish servings* (per week); *frequency of weekly visits to fast food restaurants* (only survivors). Categorization: *Meeting the 5-a-day recommendation* (to consume 5 daily servings of fruits and vegetables) (yes/no). *Body mass index* (BMI) was used as an indicator for adequate weight control and was calculated based on the self-reported weight and height[22], divided into underweight (BMI <18.5 kg/m2), normal (BMI 18.5-24.9 kg/m2), overweight (BMI 25-29.9 kg/m2) and obese (BMI ≥ 30 kg/m2)
Alcohol consumption (5 items)	▪ Limit the intake to ≤ 2 drinks per day for men and ≤1 drink per day for women	*Frequency of alcohol consumption* (never, ≤ 2 times per month, 1-2 times per week, 3-6 times per week, daily); if individuals indicated drinking alcohol *average weekly amount of alcoholic* drinks (number of glasses of *beer (3dl), wine (1dl), liquor and spirits (4cl*). Categorization in critical alcoholic intake: women ≥ 1 alcoholic beverage per day, or >7 per week, and for men ≥ 2 alcoholic beverages per day or >14 per week
Smoking (2 items)	▪ Do not smoke	Smoking status (never; former or current smoker), and daily number of cigarettes for smokers (1-9 cigarettes, 10-19 cigarettes, ≥ 1 pack, not daily)
Sun protection (3 items)	▪ Protect yourself from UV light. Stay in the shade between 10 AM to 4 PM, wear protective clothes and wear sunscreen (Factor> 20)	The use of sun protective measures was assessed differently in the survivor population and the SHS; therefore, answers from survivors were recoded to allow comparison. SHS respondents were asked if they regularly apply sun protective measures (yes/no). Survivors were asked how strictly they adhere to three sun protective measures: using sunscreen, staying in shade between 10 AM and 4 PM and wearing protective clothes (never, rarely, sometimes, often, and always). Survivors' responses to the three questions were dichotomized (often and always = yes; never, rarely and sometimes = no). If at least one question was answered yes, a patient was categorised as using sun protective measures regularly.

Vaccination (1 item)	▪ Receive a yearly influenza vaccination	Received an influenza vaccination in the last year (yes/no).
Medication adherence (6 items)	▪ Adhere to your health care professionals' recommendation with respect to timing, dosage, and frequency of medication-taking during the prescribed length of time	**Basel Assessment of Adherence with Immunosuppressive Medication Scale (BAASIS©)** (only measured in survivors) During the past four weeks, the BAASIS evaluates the different dimensions of non-adherent medication taking behaviour referring to the acknowledged ABC taxonomy which is described as followed [23]: **Implementation** of medication adherence: *taking* (omission of single doses), *drug holidays* (omission of successive doses), *timing* (deviation > 2 h) on a six-point scale; and *dose reduction* (deviation from prescribed amount) (yes/no). **Discontinuation** (stopping treatment too early) is measured by one item (yes/no). **Overall medication (non-)adherence** is measured in two ways: dichotomously, i.e., any self-reported medication nonadherence on any of the five aforementioned items is considered nonadherence; and continuously, indicating self-perceived overall medication adherence on a Visual Analogue Scale (VAS) ranging from 0% (never took medications as prescribed) to 100% (always took medications as prescribed) [24]. Patients taking immunosuppressants received the full version of the BAASIS©; those taking any other medications received adapted versions, which ask the same questions for any kind of oral medications and omits the *timing* dimension of medication intake. Content, concurrent and predictive validity of the BAASIS© have been reported in solid organ transplantation [25, 26].

Table 1: Health behaviour recommendations, study variables and measurements

6.5 Data analysis

Descriptive statistics included frequencies, percentages and proportions, means and standard deviations, or medians and inter-quartile ranges (IQR). Missing data were excluded pairwise for the statistical analysis. Clinical characteristics of respondents and non-respondents in the SCT sample were compared using independent t-tests, Chi-Square tests and the Mann-Whitney-U test. In order to compare the prevalence of health behaviours in survivors to those of their matched SHS subjects, we used McNemar or Wilcoxon signed-rank paired testing methods as appropriate [27]. Influenza vaccination rates were compared between the survivor and control groups, including a subgroup analysis comparing survivors with controls over the age of 65, for whom a yearly influenza vaccine is recommended [12]. All calculated p-values were adjusted (upwards) to correct for multiple testing. To limit the expected number of false positive findings with an alpha level of 0.05 to below 5% we used the false discovery rate procedure (reported as q-values in tables) [28]. Analyses were performed with IBM SPSS software© version 21 and SAS version 9.3.1.

6.6 Results

6.6.1 Characteristics of survivors and controls

Of the 638 survivors identified as eligible, 610 (95.6%) were contacted successfully. Of these, 376 (61.6%) were included in the final sample for analysis (figure 1). Compared with all nonparticipants (those unreachable, withdrawn from the study, or declined), participants were more likely to be older at the date of transplantation (aged 41.3 (s.d. 14.5) years vs 36.9 (16.5) years; $p < .03$), and to be at an early follow-up stage (median follow-up 7.1 (range 1-33) vs 9.0 (range 1-35) years; $p < .01$).

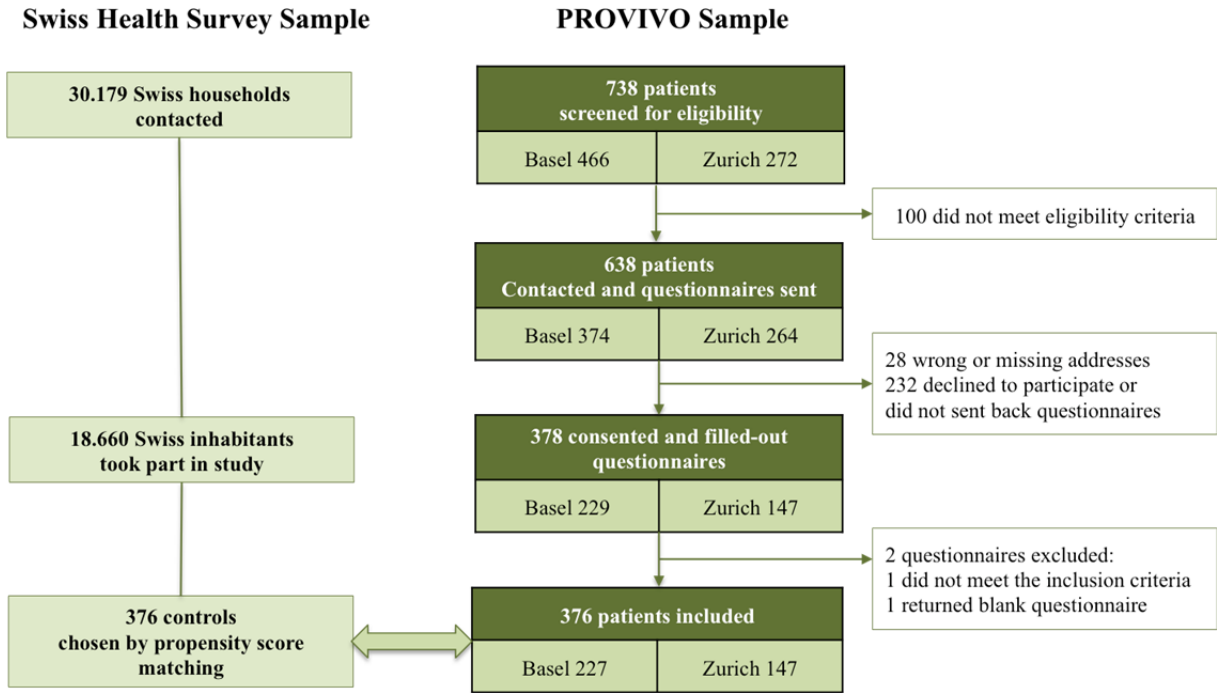


Figure 1: Flow of participants

Among survivors; 39.6% showed some form of cGVHD but most (84.2%) were highly functional (Karnofsky Index Score ≥ 90%). The primary disease was active in 5.2% (Table 2).

Characteristic		n	(%)[a]
Initial Diagnosis (%)	***(n=376)***		
AML		119	(31.6%)
ALL		58	(15.4%)
CML		61	(16.2%)
CLL		15	(4%)
Plasma cell disorder		21	(5.6%)
Hodgkin or Non Hodgkin lymphoma		40	(10.6%)
Myelodysplastic syndrome		31	(8.2%)

Myeloproliferative syndrome		13	(3.5%)
Non-malignant haematologic disease		18	(4.9%)
Years after transplantation, median	**7.1 (IQR 8.9, range 1-33)**		
Source of transplant (%)	***(n=376)***		
Bone marrow		117	(31.1%)
Peripheral blood		258	(68.6%)
Umbilical cord blood		1	(0.3%)
Conditioning regimen (%)	***(n=372)***		
Myeloablative		286	(76.9%)
Reduced intensity		86	(23.1%)
Total Body Irradiation with ≥12 Gray (%)	***(n=376)***	220	(58.5%)
No. of transplantations (%)	***(n=376)***		
1		305	(81.1%)
> 1		71	(18.9%)
Donor relationship (%)	***(n=376)***		
Matched related		226	(60.1%)
Syngen		8	(2.1%)
Mismatched related		9	(2.4%)
Unrelated		133	(35.4%)
Current stage of disease (%)	***(n=366)***		
Complete remission		347	(94.8%)
Not in remission/Relapse		19	(5.2%)
Chronic GVHD[b] (%)	***(n=376)***		
None		206	(54.8%)
Mild		101	(26.8%)
Moderate		36	(9.6%)
Severe		12	(3.2%)
No information available		21	(5.6%)
Karnofsky Score (%)	***(n=353)***		
100 - 90%		297	(84.2%)
<90 – 80		35	(9.9%)
<80		21	(5.9%)

Table 2: Clinical characteristics of survivors

Table 3 compares the demographic characteristics of survivors and controls. More survivors were married or cohabiting (78.3% vs 67.2%, p <.001); fewer had a full-time employment (34.6% vs 53.1%), and in contrast more than double a part-time job (33.8% vs 14.4%) while the proportion of individuals not working was similar in both groups.

	Survivors			Case-matched controls[b]				
	N[a]	n	%	*N*[a]	n	%	p-	q-value[c]
Gender, male (%)	*(n=376)*	207	(55.1%)	*(n=376)*	207	(55.1%)	n.a.	
Age in years, mean (s.d.)	*(n=376)*	50.3(12.7)		*(n=376)*	50.5 (12.7)		n.a.	
Education (%)	*(n=369)*			*(n=376)*			n.a.	
Compulsory schooling		52	(14.1%)		51	(13.6%)		
Secondary education		204	(55.3%)		212	(56.4%)		
Tertiary education		113	(30.6%)		113	(30.1%)		
Nationality (%)	*(n=376)*			*(n=376)*			.368	.504
Swiss		328	(87.2%)		337	(89.6%)		
Foreign nationality		48	(12.8%)		39	(10.4%)		
Partnership (%)	*(n=373)*			*(n=375)*			.001	.002
Married or cohabiting		292	(78.3%)		252	(67.2%)		
Single, not cohabiting		81	(21.7%)		123	(32.8%)		
Employment (%)	*(n=376)*			*(n=369)*			<.001	<.001
Full-time (≥80%)		130	(34.6%)		196	(53.1%)		
Part-time		127	(33.8%)		53	(14.4%)		
Not working		119	(31.6%)		120	(32.5%)		

Table 3: Demographic and clinical characteristics

6.6.2 Comparison of health behaviours between survivors and controls

Table 4 summarizes the health behaviours of survivors and their controls. Compared to the general population, survivors were more likely to report inactivity (26.8% vs. 12.5%, p <.001). Only 11.2% of survivors had the recommended 5 servings of fruits and vegetables per day–in contrast to 24.2% of controls (p <.001). Survivors were less likely to have at least one weekly serving of fish (31.2% vs. 60.9%; p<.001). Compared to controls, fewer survivors ate meat on more than 5 days per week (17.8% vs. 26.6%; p <.001) and more consumed dairy products on a daily basis (92.5% vs. 62.9%; p <.001). No significant differences arose in BMI distribution. Overweight and obesity were present in 26.4%, respectively 10.2% of survivors and 29.4%, respectively 12.4% of controls. Survivors reported consuming significantly lower numbers of alcoholic beverages per week (median 1.5 (IQR 4) vs. 4.5 (IQR 10.3); p <.001), yet critical amounts of alcohol (i.e. >21 standard beverages per week for men, 14 for women) were consumed by 14 survivors (3.7%; 8 men, 6 women). Despite reporting similar rates of ever having smoked, significantly fewer survivors currently smoked (13.4% vs. 35.4%; p <.001). Survivors made more regular use of sun protection (94.1% vs. 85.3%; p <.001) – the most common method being sunscreen (with 79.1% using it often or always), followed by staying in shaded areas between 10 AM and 4 PM (73.6%) and wearing sun-protective clothes (71.1%). Survivors (58.4%) were more likely than controls to have received influenza vaccinations

(21.5%); this was also true for the 56 survivors over the age of 65 compared to their matched controls, for whom the vaccine was also recommended (76.8% vs. 32.3%; p=.002).

Behaviour	Survivors			Controls				
	N[a]	n	%	N[a]	n	%	p-value	q-value[b]
Physical activity	***(n=354)***			***(n=376)***			**<.001**	**<.001**
Inactive		95	(26.8%)		47	(12.5%)		
Partially active		112	(31.6%)		163	(43.4%)		
Active		147	(41.5%)		166	(44.1%)		
Diet								
Number of daily fruit servings [c]	***(n=371)***			***(n=375)***			**<.001**	**<.001**
None or less than once a day		54	(14.5%)		61	(16.3%)		
1 – 2		280	(75.5%)		233	(62.1%)		
≥3		37	(10.0%)		81	(21.6%)		
Number of daily vegetable servings [c]	***(n=372)***			***(n=376)***			**<.001**	**<.001**
None or less than once a day		27	(7.3%)		54	(14.4%)		
1-2		321	(86.3%)		282	(75.0%)		
≥ 3		24	(6.5%)		40	(10.6%)		
Daily dairy products consumption [d]	***(n=374)***			***(n=375)***			**<.001**	**<.001**
Yes		346	(92.5%)		236	(62.9%)		
Number of weekly fish servings	***(n=375)***			***(n=376)***			**<.001**	**<.001**
Never		36	(9.6%)		30	(8.0%)		
Less than once a week		222	(59.2%)		117	(31.1%)		
≥1 a week		117	(31.2%)		229	(60.9%)		

Number of weekly meat servings	***(n=376)***		***(n=376)***		**<.001**	**<.001**
Never or less than once a week	47	(12.5%)	24	(6.4%)		
1-3	132	(35.1%)	152	(40.4%)		
4-5	130	(34.6%)	100	(26.6%)		
≥ 6	67	(17.8%)	100	(26.6%)		
Frequency of eating at a fast food restaurant per week	***(n=363)***				**n.a.**	
Never or less than once a week	310	(85.5%)				
≥ once a week	53	(14.5%)				
Body mass index	***(n=322)***		***(n=371)***		**.067**	**0.111**
Underweight	24	(7.5%)	12	(3.2%)		
Normal	180	(55.9%)	204	(55.0%)		
Overweight	85	(26.4%)	109	(29.4%)		
Obese	33	(10.2%)	46	(12.4%)		
Alcohol drinking	***(n=374)***		***(n=375)***		**<.001**	**<.001**
Abstinent	68	(18.2%)	48	(12.8%)		
Less than once a-week	137	(36.6%)	92	(24.5%)		
1-6 times a-week	154	(41.2%)	173	(46.1%)		
Daily	15	(4.0%)	62	(16.5%)		
Number of alcoholic beverages per week (Median; IQR) [e]	***(n=374)***	**1.5 (0-4)**	***(n=375)***	**4.5 (0.3-10.6)**	**<.001**	**<.001**
Smoking	***(n=367)***		***(n=376)***		**<.001**	**<.001**
Never	201	(54.8%)	143	(38%)		
Previous smoker	117	(31.9%)	100	(26.6%)		
Current smoker	49	(13.4%)	133	(35.4%)		
Number of cigarettes per day for smokers					*.001*	*.002*
1-9 cigarettes	22	(44.9%)	20	(16.0%)		
10-19 cigarettes	9	(18.4%)	28	(22.4%)		
≥ 1 pack	9	(18.4%)	38	(30.4%)		
Not daily	9	(18.4%)	39	(31.2%)		

Received an influenza vaccination in the last year	***(n=366)***		***(n=299)***		**<.001**	**<.001**
Yes	219	(58.4%)	64	(21.4%)		
Regular sun protective measures	***(n=375)***		***(n=374)***		**<.001**	**<.001**
Yes	353	(94.1%)	319	(85.3%)		
Yes	353	(94.1%)	319	(85.3%)		

[a] Number of survivors and controls available for analysis
[b] Q value adjustments were made for multiple comparisons
[c] 1 portion = size of a fist or circa 120 g
[d] 1 portion = 2dl milk, yoghurt, quark or 30-60g cheese
[e] One alcoholic beverage = 0.3 dl beer; or 1 dl wine; or 4 cl Spirits or liquor

Table 4: Prevalence of health behaviours among survivors and controls

6.6.3 Medication nonadherence in patients taking immunosuppressants or other medications

Of 376 participants, 107 required no medications and 170 required non-immunosuppressant medications. The remaining 99 were using immunosuppressants, of whom 65 (65.7%) reported nonadherence to at least one dimension of their medication regimens. Nonadherence in the implementation of the prescribed medical regimens was observed in 64 patients (64.6%). Thirty-three (33.3%) had failed to take at least on dose in the past four weeks and 61.2% had had timing deviations of more than two hours. Four (4.1%) reported having reduced their dosages without consulting a physician and three (3.2%) had taken drug holidays. Further three patients had stopped their immunosuppressant intake early and were therefore regarded as non-persistent with the therapy. The median self-perceived overall adherence (reported via the VAS) was 95.0% (IQR: 15).

One hundred and seventy patients took non-immunosuppressant medications. For this group, the 4-week prevalences of the 4 measured dimensions of nonadherence (taking nonadherence, dose reduction, drug holidays and non-persistence) were 37.6%, 7.3%, 12%, and 2.4%, respectively. Their average VAS rating for self-perceived adherence was 98.0% (IQR 5).

6.7 Discussion

To our knowledge, this is the first study to compare a comprehensive set of health behaviours in SCT survivors with those of matched controls. We observed that survivors were more likely to be inactive, and showed more unfavourable nutrition habits with regard to vegetable, fruit and fish consumption. However, survivors were less likely to be current smokers and drank less alcohol. They were also more likely to receive influenza vaccinations and to protect themselves from UV radiation. Our findings indicate that, overall, survivors engage less often in active health behaviours (e.g., physical activity and dieting) aimed at

preventing new diseases. However, they more often avoid health-impairing habits such as smoking and drinking. These innovative insights warrant evaluation in the light of existing evidence.

Although the proportion of active individuals is similar in both groups, twice as many patients were inactive compared to matched controls. The following hypotheses might explain these low percentages: Many survivors suffered from some form of cGVHD and certainly from various other late effects, potentially inhibiting their physical performance [29]. Moreover, many survivors complain about fatigue, which can persist far beyond treatment. Interestingly, although fatigue is a barrier to exercise, it can be reduced by regular physical activity [30]. Therefore, given that recent research has showed that regular activity not only reduced fatigue but might also attenuate the risk of developing diabetes and cardiovascular conditions (including hypertension) after SCT [31, 32], interventions are needed to improve survivors' physical activity.

Another health behaviour that might lower the risks of co-morbidities such as diabetes and dyslipidaemia is a diet rich in fruits and vegetables [32]. Although consistent with earlier reports showing that cancer survivors often fail to adhere to dietary guidelines [33], the low fruit and vegetable intake in our study is particularly worrisome. To some extent, our findings concerning dietary habits might be linked to oral cGVHD-related factors such as xerostomia, mucosal and hypopharyngeal inflammation (which cause painful burning sensations in the mucous membranes). Other late effects such as dental problems might cause problems with chewing and swallowing food, which might explain the lower meat consumption. Further reasons for dietary intolerances or aversions might be food allergies, taste changes, medication-related nausea or a low-bacteria diet (e.g., avoiding raw seafood and vegetables) [34, 35]. Mean BMIs did not differ significantly between survivors and controls, indicating that overweight and obesity in survivors are as common as in the general population. Since the 1990s, obesity has almost doubled in the Swiss population [36], and also appears problematic in the survivor group, potentially increasing the risks of several complications and non-relapse mortality [37, 38]. Using focus group interviews, Jim et al. showed that survivors desire more information regarding post-transplant quality of life aspects and in particular in regard to late complications, as these often arise unexpectedly and threaten the ongoing sense of recovery [39]. Giving information about potential benefits of healthier lifestyle choices should be also an integral part of survivor care. Admittedly, at the time of data collection, no comprehensive lifestyle counselling was included in either of the two hospitals' follow-up services. The higher dairy product consumption in our survivor sample remains difficult to explain. One possibility is that beneficial effects of dairy products on skeletal and dental health might have been delivered more frequently (although in a non-standardized manner), yet this is only a hypothesis.

More than three quarters of our participants reported regular use of sun protective measures a proportion much higher than in the matched control group. Survivors also seem to be more aware of this factor than solid organ transplant groups, among which only one-third of patients wear protective clothing and two-thirds regularly use sunscreen [40]. Also, survivors were less likely than their controls to smoke: a substantial number had quit smoking. Nevertheless, while consistent with previous research (7-13%) [16-18], the prevalence of smokers is still problematic, given the known relationship between smoking and the high risk for

malignancies due to exposure to alkylating agents, bleomycin, radiation, TBI, and cGVHD [41]. Therefore, regular smoking cessation programs should be offered.

Unfortunately, our study revealed a high rate of immunosuppressive nonadherence (65.7%). This prevalence is higher than numbers found in solid organ transplant groups, although comparisons are complicated by differences in operational definitions and measurement methods [42]. Evidence from solid organ transplantation has linked even minimal deviations from the prescribed medication schedule (>5%) to negative clinical consequences (e.g., graft loss, rejection) [43,44]. This underpins our stringently chosen cut-off for nonadherence. However, a clear need exists for further research identifying a clinically meaningful definition for medication nonadherence in SCT. Hence, a prospective study is recommended to assess the impact of subclinical medication nonadherence on clinical outcome, especially in terms of cGVHD. The influenza vaccination rate among our participants was higher than in the normal population. However, it is not yet satisfactory given that influenza may cause severe disease and mortality in SCT survivors. As patients' motivation to vaccinate might depend on the practice patterns of their transplant centres, transplant teams should actively educate them and their families.

The findings of this cross-sectional study allow no causal relationships and must be interpreted in the context of potential limitations. For example, we used survey data with the potential to underestimate true health behaviour prevalences. Socially undesirable behaviours such as smoking are prone to underreporting– particularly in a cancer survivor population, in which smoking is mostly undesirable [45]. Only German-speaking patients participated, as the questionnaire was only available in this language. In order to enhance the participation of high-risk foreign language speakers [46], we recommend using multi-lingual questionnaires and the assistance of professional translators as appropriate. Additionally, hospitalized patients were not included. Therefore it is possible that those who participated were in better physical condition, making them more likely to engage in health behaviours such as physical activity. Also, we did not ask patients taking IS about their adherence to other medications; therefore, it remains unclear whether differences exist in their taking behaviour between IS and other medication. A future study should examine medication-taking behaviour regarding the entire medical regimen, optimally triangulating patient self-report with other vigorous assessment methods such as electronic monitoring, blood assay and physician estimations.

Despite these limitations, this study had the strength of a case-match control design. Even taking into account the low prevalence (i.e., lower than the OECD average) of unhealthy behaviours in Switzerland's general population [47], this allows a sound comparison with other European populations. In the context of the growth and increasing longevity of the SCT survivor population, our work has several important clinical implications. First, given the high prevalence of suboptimal health behaviours, regular screening throughout follow-up is warranted, and preventive and remediating strategies are indicated. It is crucial to recognize this population's health behaviour practices and to use the information from this and other studies both to assist survivors with their disease self-management practices, and to allow practitioners to develop accurately-targeted behavioural interventions. In particular, physical inactivity, poor nutritional practices, medication nonadherence and lack of influenza vaccinations were problematic in our group. Interventions on physical

activity and diet have been tested in cancer survivors, including SCT recipients, resulting in observable short- and medium-term of improvements in health behaviours [48]. Further investigations are needed to examine the relationship between programs' content and delivery and their sustainable effects on clinical outcomes.

6.8 Conclusions

This study provides population-based measures of health behaviours among SCT survivors in Switzerland. Survivors are most likely to adopt beneficial health behaviours regarding not smoking and low alcohol consumption. Yet, relative to the general population, a considerable group still engage in unfavorable behaviours. Our findings indicate a need for investigating the effectiveness of interventions to increase survivors' positive health behaviours, including medication adherence.

6.9 References

1. Sun CL, Francisco L, Kawashima T, Leisenring W, Robison LL, Baker KS et al. Prevalence and predictors of chronic health conditions after hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. Blood 2010; 116: 3129-3139.
2. World Health Organization. Innovative care for chronic health conditions. Revista Panamericana de Salud Pública 2002; 12: 71-74.
3. Ford ES, Bergmann MM, Kroger J, Schienkiewitz A, Weikert C, Boeing H. Healthy living is the best revenge: findings from the European Prospective Investigation Into Cancer and Nutrition-Potsdam study. Arch Intern Med 2009; 169: 1355-1562.
4. McQueen D. Research in Health Behaviour, Health Promotion and Public Health, Edinburgh Research Unit in Health and Behavioural Change: Edinburgh, UK, 1987.
5. Majhail NS, Rizzo JD, Lee SJ, Aljurf M, Atsuta Y, Bonfim C et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. Bone Marrow Transplant 2012; 47: 337-41.
6. Federal Office for Sports. Gesundheitswirksame Bewegung bei Erwachsenen: Empfehlungen für die Schweiz, [PDF on Internet] Federal Office for sports: [updated 16 May 2013; cited 19 February 2014]. Available from: www.hepa.ch/internet/hepa/de/home/dokumentation/grundlagendokumente.html
7. Keller U, Battaglia Richi E, Beer M, Darioli R, Meyer K, Renggli A, Römer-Lüthi C, Stoffel-Kurt N. Sechster Schweizerischer Ernährungsbericht. Federal Office of Public Health: Berne, Switzerland, 2012.
8. Swiss Society for Nutrition. Alkohol, [PDF on Internet] [updated November 2011; cited 19 February 2014]. Available from: www.sge-ssn.ch/media/medialibrary/2012/10/merkblatt_-alkohol_2011.pdf
9. Tobaco Prevention Fond. Jahresbericht Tabakpräventionsfonds 2012, Federal Office for Public Health: Berne, Switzerland, 2012.
10. Federal Office of Public Health. Sonnenschutz: [updated 8 April 2011; cited 19 February 2014]. Available from: www.bag.admin.ch/uv_strahlung/10653/index.html?lang=de
11. Engelhard D, Mohty B, de la Camara R, Cordonnier C, Ljungman P. European guidelines for prevention and management of influenza in hematopoietic stem cell transplantation and leukemia patients: summary of ECIL-4 (2011), on behalf of ECIL, a joint venture of EBMT, EORTC, ICHS, and ELN. Transpl Infect Dis 2013; 15: 219-232.
12. Federal Office of Public Health and Federal Office for Vaccinations. Schweizerischer Impfplan 2013. Richtlinien und Empfehlungen, Federal Office of Public Health: Berne, 2013.
13. Sabaté E. Adherence to Long-Term Therapies: Evidence for Action, World Health Organisation: Geneva, Switzerland, 2003.

14. Mishra SI, Scherer RW, Geigle PM, Berlanstein DR, Topaloglu O, Gotay CC et al. Exercise interventions on health-related quality of life for cancer survivors. The Cochrane database of systematic reviews 2012; 8: CD007566.
15. Ligibel J. Lifestyle factors in cancer survivorship. J Clin Oncol 2012; 30: 3697-3704.
16. Syrjala KL, Langer SL, Abrams JR, Storer BE, Martin PJ. Late effects of hematopoietic cell transplantation among 10-years adult survivors compared with casematched controls. J Clin Oncol 2005; 23: 6596-6606.
17. Bishop MM, Lee SJ, Beaumont JL, Andrykowski MA, Rizzo JD, Sobocinski KA et al. The preventive health behaviors of long-term survivors of cancer and hematopoietic stem cell transplantation compared with matched controls. Biol Blood Marrow Transplant 2009; 16: 207-214.
18. Armenian SH, Sun CL, Francisco L, Baker KS, Weisdorf DJ, Forman SJ et al. Health behaviors and cancer screening practices in long-term survivors of hematopoietic cell transplantation (HCT): a report from the BMT Survivor Study. Bone Marrow Transplant 2012; 47: 283-290.
19. Federal Statistical Office. Die Schweizerische Gesundheitsbefragung in Kürze: Konzept, Methode, Durchführung. [PDF on Internet] [updated November 2011; cited 19 February 2014]. Available from: http://compass-data.unil.ch/SGB-Documentation/ESS_SGB_2007%20Konzept-%20in%20Kuerze.pdf
20. Schuler M, Dessemontet P, Joye D. Die Raumgliederungen der Schweiz, Swiss Federal Statistical Office: Neuchâtel, Switzerland, 2005.
21. Blackstone EH. Comparing apples and oranges. J Thorac Cardiovasc Surg 2002; 123: 8-15.
22. World Health Organization. Consultation on Obesity. Preventing and managing the global epidemic: report of a WHO consultation on obesity. World Health Organization technical report series: Geneva, Switzerland, 2000.
23. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T et al. A new taxonomy for describing and defining adherence to medications. British journal of clinical pharmacology 2012; 73: 691-705.
24. Leuven-Basel Adherence Research Group. The Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS© Explanation). [Manuscript] Basel, Switzerland, 2005.
25. Marsicano E, Fernandes N, Colugnati F, Grincenkov F, Fernandes N, De Geest S et al. Transcultural adaptation and initial validation of Brazilian-Portuguese version of the Basel assessment of adherence to immunosuppressive medications scale (BAASIS) in kidney transplants. BMC Nephrology 2013; 14: 108.
26. De Simone P, Ducci J, Denhaerynck K, Dobbels F, Filipponi P, De Geest S. Subclinical nonadherence to immunosuppression: correlates and clinical consequences. Liver Transplant 2013; 19: 89.

27. Breslow NE, Day NE. Statistical Methods in Cancer Research: Volume 1 - The Analysis of Case-Control Studies, International Agency for Research on Cancer: Lyon, France, 1980.
28. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B 1995; 57: 289-300.
29. Mitchell SA, Leidy NK, Mooney KH, Dudley WN, Beck SL, LaStayo PC 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.
30. Persoon S, Kersten MJ, van der Weiden K, Buffart LM, Nollet F, Brug J et al. Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: A systematic review and meta-analysis. Canc Treat Rev 2013; 39: 682-690.
31. Armenian SH, Chow EJ. Cardiovascular disease in survivors of hematopoietic cell transplantation. Cancer 2014; 120: 469-479.
32. Chow EJ, Baker KS, Lee SJ, Flowers MED, Cushing-Haugen KL, Inamoto Y et al. Influence of Conventional Cardiovascular Risk Factors and Lifestyle Characteristics on Cardiovascular Disease After Hematopoietic Cell Transplantation. J Clin Oncol 2014; 32: 191-198.
33. Blanchard CM, Courneya KS, Stein K. Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. J Clin Oncol 2008; 26: 2198-204.
34. Sakashita K, Nakazawa Y, Yanagisawa R, Tanaka M, Saito S, Yoshikawa K et al. Food allergy after cord blood transplantation in children. Br J Haematol 2012; 158: 672-676.
35. Kida A, McDonald GB. Gastrointestinal, Hepatobiliary, Pancreatic, and Iron-Related Diseases in Long-Term Survivors of Allogeneic Hematopoietic Cell Transplantation. Semin Hematol 2012; 49: 43-58.
36. Eichholzer M, Bernasconi F, Jordan P, Gutzwiller F. Nutrition in Switzerland 2002-results of the Swiss Health Survey. Praxis 2005; 94: 1713-1721.
37. Armenian SH, Sun CL, Vase T, Ness KK, Blum E, Francisco L et al. Cardiovascular risk factors in hematopoietic cell transplantation survivors: role in development of subsequent cardiovascular disease. Blood 2012; 120: 4505-4512.
38. Tomita Y, Ishiguro H, Yasuda Y, Hyodo H, Koike T, Shimizu T et al. High incidence of fatty liver and insulin resistance in long-term adult survivors of childhood SCT. Bone Marrow Transplant 2011; 46: 416-425.
39. Jim HS, Quinn GP, Gwede CK, Cases MG, Barata A, Cessna J et al. Patient education in allogeneic hematopoietic cell transplant: what patients wish they had known about quality of life. Bone Marrow Transplant 2014; 49: 299-303.
40. Donovan JC, Rosen CF, Shaw JC. Evaluation of sun-protective practices of organ transplant recipients. Am. J. Transplant 2004; 4: 1852-1858.

41. Ehlers SL, Gastineau DA, Patten CA, Decker PA, Rausch SM, Cerhan JR et al. The impact of smoking on outcomes among patients undergoing hematopoietic SCT for the treatment of acute leukemia. Bone Marrow Transplant 2011; 46: 285-290.
42. Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Evans R, Gerber R, Lapointe Rudow D, McKay D, Neu A, Nevins T, Reyes J, Wray J, Dobbels F. Non-adherence Concensus Conference Summary Report. Am J Transplant 2009; 9: 35-41.
43. De Geest S, Abraham I, Moons P, Vandeputte M, Van Cleemput J, Evers G et al. Late acute rejections and subclinical noncompliance with cyclosporine-therapy in heart transplant patients. J Heart Lung Transplant 1998; 17: 854-863.
44. Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. Transplant outcomes and economic costs associated with patient noncompliance to immuno-suppression. Am J Transplant 2009; 9: 2597-2606.
45. Connor Gorber S, Schofield-Hurwitz S, Hardt J, Levasseur G, Tremblay M. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinineassessed smoking status. Nicotine Tob Res 2009; 11: 12-24.
46. Armenian SH, Sun CL, Teh JB, Arora M, Baker KS, Francisco L et al. Ethnic differences in chronic health conditions after hematopoietic cell transplantation. Cancer 2010; 116: 4152-4159.
47. OECD. Health at a Glance: OECD Indicators [PDF on Internet] OECD Publishing: [2013; cited 19 February 2014]. Available from: http://dx.doi.org/10.1787/health_glance-2013-e
48. Alfano CM, Molfino A, Muscaritoli M. Interventions to promote energy balance and cancer survivorship: priorities for research and care. Cancer 2013; 119 Suppl 11: 2143-2150.

CHAPTER 7:

MEDICATION NON-ADHERENCE TO IMMUNO–SUPPRESSANTS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION IS ASSOCIATED WITH cGVHD: PROVIVOMED – A MULTICENTRE CROSS-SECTIONAL STUDY

Barbara Gresch [1]; Monika Kirsch [2,3]; Katharina Fierz [2];
Jörg Halter[3]; Gayathri Nair[1]; Sabina De Geest[1,4]

[1] *Department of Haematology, University Hospital Zurich, Switzerland*
[2] *Institute of Nursing Science, University of Basel, Switzerland*
[3] *Department of Haematology, University Hospital Basel, Switzerland*
[4] *Centre for Health Services and Nursing Research, Department of Public Health and Primary Care, KU Leuven, Belgium*

Will be submitted to
Bone Marrow Transplantation

7.1 Abstract

Following allogeneic stem cell transplantation (SCT), adherence to immunosuppressants (IS) is essential to prevent and treat chronic GVHD (cGVHD), which is associated with reduced quality of life and increased morbidity, mortality, and overall healthcare needs.

This secondary analysis of data from a multicentre cross-sectional study included a conve–nience sample of 99 IS-prescribed patients. Its aims were to determine the prevalence of medication nonadherence (MNA) in post-SCT patients, to examine its correlates, and to explore its associations with cGVHD. MNA measurement combined patients' and physicians' (collateral) reports. Descriptive statistics and logistic regressions were applied. Self-reported taking and timing MNA prevalences were 33.3% and 61.2%, respectively; discontinuation occurred in 3.1% of cases. Combining these data with the physicians-reported prevalence (18.9%) yielded a composite MNA rate of 68.7%. MNA correlated with higher numbers of IS [odds ratio (OR):1.42; p=0.011] and fewer co-medications (OR:0.85; p=0.02). MNA was significantly associated with higher grades of cGVHD (OR: 3.01; p = 0.012). Patients with higher grades of cGVHD were more likely to have problems in the implementation of the medication regimen (OR:2.60; CI:1.14-5.91; p=0.023); in particular regarding taking (OR:2.46; p=0.028) and self-initiated dose reduction (OR:15.57; p=0.022). This study indicates high levels of MNA in SCT patients, calling for adherence-enhancing interventions.

7.2 Introduction

For many haematological malignancies, allogeneic haematopoietic stem cell transplantation (SCT) is the only curative treatment available; the frequency of transplants continues to increase worldwide. However, while Allo-SCT usually causes a beneficial graft-versus-leukemia effect, a major source of morbidity and mortality in the long-term after treatment is chronic graft-versus-host disease (cGVHD) [1-3]. In particular, moderate and severe cGVHD are major causes of transplant-related functional impairments, reduced patient-reported quality of life [4, 5], higher morbidity [6], worse late non-relapse mortality and inferior overall survival [4]. Immunosuppressant (IS) intake is essential, but increases the risk of severe infections and reduces the graft-versus-tumour effect [7]. Therefore, taking IS as prescribed can be challenging for many patients [8]. However, significant deviations from optimal intake, i.e., medication nonadherence (MNA), may increase the risk of poor clinical outcomes, resulting in re-hospitalisation, the use of multiple services, higher medical and healthcare costs [9, 10].

MNA is defined as any deviation from the prescribed medication regimen sufficient to adversely influence the regimen's intended effect [11]. This can occur in the following situations or combinations: late- or non-initiation of the prescribed treatment; suboptimal implementation of the dosing regimen; or early discontinuation of treatment [12]. The process of medication adherence starts with ***initiation*** of the treatment, when the patient takes the first dose of a prescribed medication. It continues with ***implementation*** of the dosing regimen, i.e., the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the final dose is taken. ***Discontinuation*** means that the patient terminates the treatment earlier than recommended and does not restart [12].

Developing methods to promote adherence to complex treatment regimens demands an understanding of the reasons behind nonadherence. MNA is influenced by a number of factors recognized by the WHO's 'Five dimensions of adherence'. The PROVIVOmed study framework (see Figure 1) integrated Vrijens et al.'s taxonomy of adherence [12] as well as the risk factors of the five-dimensional WHO adherence model [13].

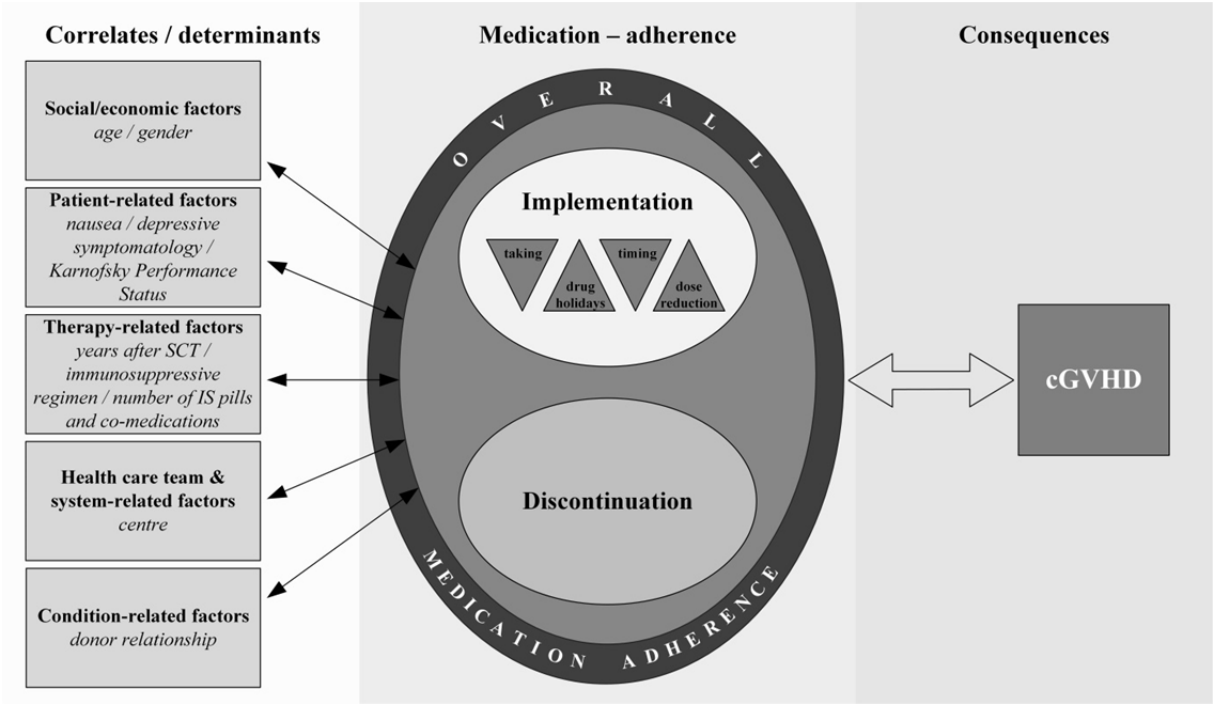


Figure 1: The PROVIVOmed adherence model (adapted from Vrijens et al., 2012 [12] and Sabaté, 2003 [13])

To date, few studies have examined MNA post-SCT. One notable exception is the cross-sectional PROVIVO study, which examined medication adherence, along with various other health behaviours. Out of 99 patients using IS, two-thirds (65.7%) reported nonadherence over the past month to at least one dimension of their medication regimens [14].

The aims of this study were (1) to describe MNA along the different dimensions of Vrijens' taxonomy, (2) to examine associations between MNA and potential influencing factors and (3) to explore the association between patient-reported immunosuppressive MNA and cGVHD.

7.3 Patients and Methods

7.3.1 Design, setting and sample

This report is a secondary data analysis of the multicentre PROVIVO study, investigating patient reported outcomes of long-term survivors after Allo-SCT (NCT01275534). Convenience sampling was used to recruit Allo-SCT recipients from the University Hospitals of Basel and Zurich (Switzerland). Inclusion criteria were an age of at least 18 years, a post-transplantation period of ≥1 year and current IS intake. Exclusion criteria were an inability to read German, current hospitalization, a diagnosed end-of-life stage, severe visual impairment or severe psychiatric disorders (e.g., suicidal tendencies, acute psychosis).

7.3.2 Variables and measurements

MNA was assessed via a combination of patient self-reports and physician collateral reports.

Patient reported MNA

The six-item "Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS©)" [15] was used to measure medication adherence to IS over the preceding four weeks. In accordance to Vrijens et al.'s taxonomy [12], the BAASIS© evaluates *implementation* of medication adherence according to four items: *taking* (omission of single doses); *drug holidays* (omission of successive doses); *timing* (deviation > 2 h) [rated on a six-point scale ranging from never (0) to more than four times or almost every day (5)]; and *dose reduction* (deviation from prescribed amount – YES/NO). *Discontinuation* (stopping treatment too early) is measured by one item (YES/NO). A patient is considered to be *overall nonadherent* if he/she has shown nonadherence on any of the five aforementioned items. Additionally, self-perceived *overall medication adherence* in the past four weeks is measured by a Visual Analogue Scale (VAS) ranging from 0% (never took medications as prescribed) to 100% (always took medications as prescribed [15]. Concurrent (r=0.65) and predictive validity of the BAASIS© have been established in kidney [16] and liver transplantation [17].

Physician reported MNA

Patients' medication adherence was also assessed by physicians' collateral reports. The treating senior physicians who were aware of the patient's GVHD symptomatology were provided with a list of all patient names and, separately, the assayed IS drug level of each. Based on this information and their personal knowledge of patient's medication intake behaviour, physicians judged each patient's medication adherence in a single dichotomous score (YES=adherent / NO=nonadherent).

7.3.3 Composite nonadherence score

In a second step, as combining reporting sources provide greater sensitivity than self-reports alone, we combined patient reported MNA with that reported by physicians [18, 19]. Patients were classified as nonadherent if they fulfilled at least one criteria of the BAASIS© and/or the physician collateral report (adherent=0 / nonadherent=1) listed them as nonadherent.

7.3.4 Adherence correlates

In order to examine associations between MNA and potential correlates we applied variables in accordance with the five dimensions of the WHO adherence model [13].

Three ***social/economic factors*** were retrieved from patient records: *nationality*, *age* and *gender*. *Marital status*, *education level* and *patients' employment status* were collected via self-report questionnaire.

For ***patient-related factors*** we included *depressive symptomatology,* measured via the sevenitem depression subscale of the German version of the Hospital Anxiety Depression Scale (HADS) [20]. The HADS uses a four-point (0-3) Likert scale. Subscale scores were calculated by summing the individual item scores. A total score of ≥8 indicates depression symptoms. The HADS is widely validated in different populations including cancer patients [21] and has been used in several SCT studies [22-25]. As an indicator for treatment side effects, i.e., potential barriers to taking IS, we included symptom intensity of *nausea* in our analysis. Nausea was assessed by a single self-report item on a five-point rating scale ranging from one (none) to five (very severe) during the last seven days [26]. The *Karnofsky Performance Status* was graded by the treating physician [27].

Therapy-related factors assessed were *treatment regimen*, *number of transplantations*, *TBI* (yes/no), *stem cell source*, *years after SCT*, and medication specific variables including *immunosuppressive regimen* (calcineurin inhibitor/steroids/others/combination), daily *number of IS pills,* as well as *number of co-medications* were retrieved from the transplant database or patient records.

As a ***health care team & system-related factor*** we considered the *treating centre* (Basel/ Zurich) in our analysis.

Condition-related factors included *haematological diagnosis*, *status of haematological disease at annual control*, *donor relationship* were extracted from participants' medical records. For the analysis, *cGVHD* was scored according to the NIH criteria (none, mild, moderate, severe) [28].

7.4 Data collection

Patients were recruited for the PROVIVO study between November 2011 and November 2012; detailed data collection procedures are described elsewhere [14]. Clinical and demographic data were collected from the transplant database and patient records. Data was anonymised and entered in a database. The PROVIVO study was approved by the Ethics Committees of Basel and Zurich.

7.5 Data analysis

Depending on measurement levels and data distributions, detailed descriptive statistics were performed using frequencies, proportions, measures of central tendency and dispersion as appropriate. For the statistical analysis, missing data were excluded pairwise.

MNA prevalence was depicted for the overall patient sample and for nonadherent patients. Correlates of the composite MNA score were initially determined using univariate binary logistic regression (see Table 5). Factors arising from the univariate analysis which revealed significant p-values (<0.05) were entered in an additional multivariate binary logistic regression model. In this second model, as no multilevel analysis was indicated for two clusters, "transplant centre" was treated as a confounding factor.

The association between the composite MNA score and cGVHD grade was assessed with an ordinal logistic regression. Here "donor relationship" and "centre" were controlled as they might be confounding factors for the occurrence of cGVHD. Additionally, we carried out a series of post-hoc sensitivity analyses to determine the impacts of the different MNA dimensions on cGVHD grade. Therefore we used again the ordinal logistic regression model with cGVHD grade as outcome variable and entered the different MNA dimensions (taking, timing, drug holidays, dose reduction, discontinuation) successively as independent variables.

Data analysis was performed using IBM SPSS® Statistics for Windows, Version 21.0 and SAS 9.1.3. Armonk, NY: IBM Corp. Statistical significance was set at alpha = 0.05 and q-values were used to control for false positive results.

7.6 Results

7.6.1 Patient characteristics

Of 638 eligible SCT recipients, 376 (58.9%) took part in the PROVIVO study. Of these, 99 (26.3%) were currently taking IS and were therefore included in the PROVIVOmed substudy (Figure 2).

Median patient age was 51 years (range: 20–72 years), with a median of 3.9 years (range: 1–29 years) post-transplant. Participants were mostly male (61.6%), were Swiss citizens (88.9%), had an average of 15.9 years of education and were predominantly married or cohabited (75.8%). Nearly half did not work professionally (46.5%). Seventy-five (77.3%) had documented diagnoses of cGVHD (40.2% mild, 27.8% moderate and 9.3% severe) according to the NIH consensus criteria. Half (50.5%) took a single calcineurin inhibitor, mostly CYA, 32.6% were receiving combined calcineurin inhibitor-steroid therapies, and 11.6% were receiving steroids alone. The total daily number of IS pills ranged from 1 to 12 and of co-medications from 1 to 22. Sample characteristics are summarized in Tables 1 and 2.

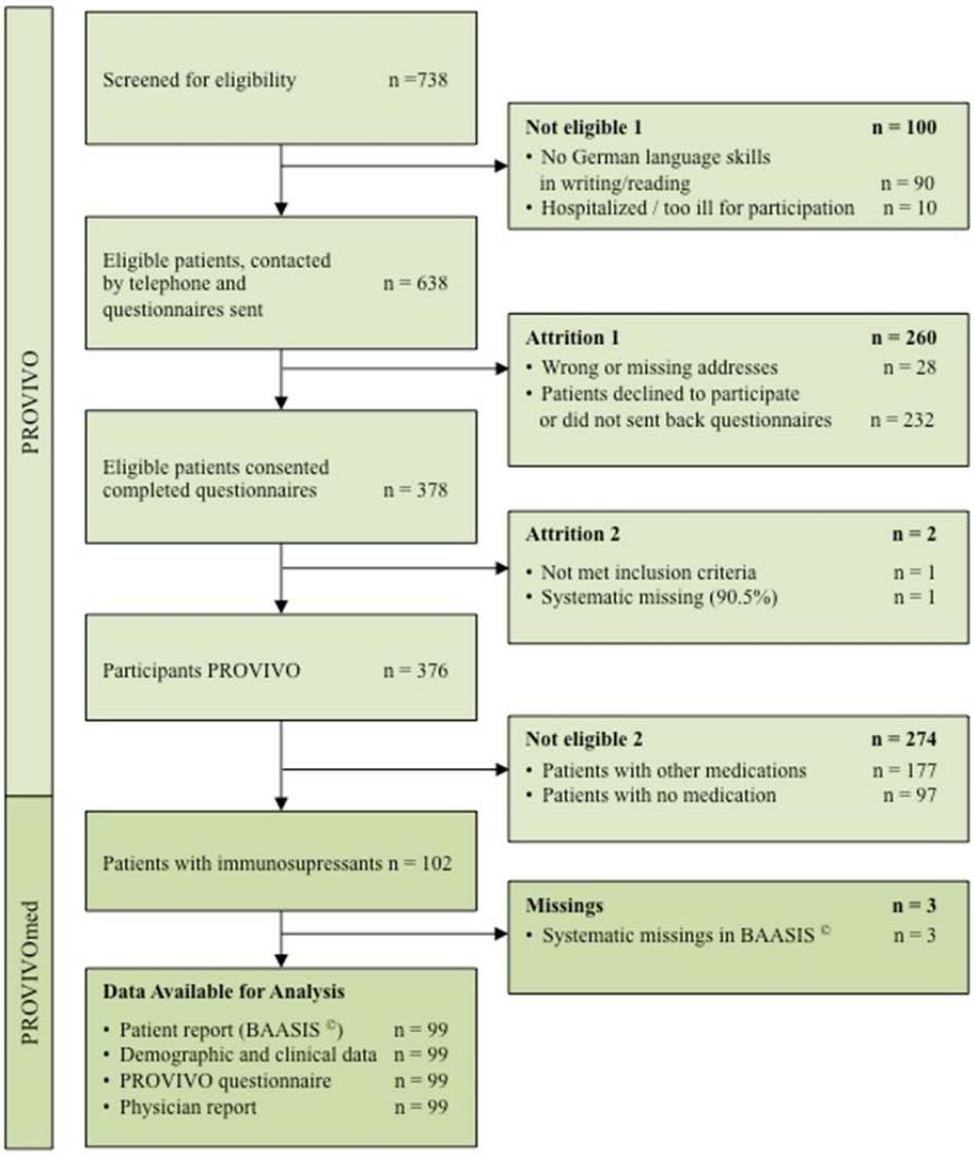


Figure 2: Flowchart for the PROVIVOmed study sample

Characteristics	Total N = 99	Non-adherent[1] n = 65	Adherent n = 34
Age, median (IQR; range)	51.0	51.0	53.0
Years after SCT, median (IQR; range)	3.9 (2.1 - 7.1; 1.0 - 29.0)	4.0 (2.3 - 7.0; 1.0 - 29.0)	3.9 (1.7 - 7.6; 1.0 - 26.0)
Gender; male, n (%)	61 (61.6)	42 (64.6)	19 (55.9)

Marital status, n (%)			
Married or cohabited	75 (75.8)	49 (75.4)	26 (76.5)
Nationality, n (%)			
Swiss	88 (88.9)	57 (87.7)	31 (91.2)
Others	11 (11.1)	8 (12.3)	3 (8.8)
Education level, n (%)			
Not completed school orcompulsory schooling	13 (13.4)	10 (15.4)	3 (9.4)
Secondary education	38 (39.2)	22 (33.8)	16 (50.0)
Tertiary education[2]	46 (47.4)	33 (50.8)	13 (40.7)
Not reported	2 (2.0)	0 (0.0)	2 (5.9)
Employment status, n (%)			
Working full-time[3]	16 (16.2)	12 (18.5)	4 (11.8)
Working part-time	37 (37.4)	23 (35.4)	14 (41.2)
Unemployed	46 (46.5)	30 (46.2)	16 (47.1)

Abbreviations: IQR = interquartile range

[1] Nonadherence is any YES answer on any of the five items.

[2] Tertiary education includes high school, higher professional education, college and university.

[3] Full-time engagement means working at least 33.6 h per week.

Table 1: Demographic data

Characteristics	Total N = 99	Non-adherent[1] n = 65	Adherent n = 34
Haematological diagnosis, n (%)			
AML	28 (28.3)	17 (26.2)	11 (32.4)
ALL	21 (21.2)	16 (24.6)	5 (14.7)
CML	10 (10.1)	6 (9.2)	4 (11.8)
CLL	8 (8.1)	4 (6.2)	4 (11.8)
Hodgkin or Non Hodgkin lymphoma	15 (15.1)	10 (15.4)	5 (14.7)
Myelodysplastic syndrome	11 (11.1)	8 (12.3)	3 (8.8)
Multiples Myeloma	4 (4.0)	3 (4.6)	1 (2.9)
Myeloproliferative syndrome	1 (1.0)	0 (0.0)	1 (2.9)
Autoimmune disease	1 (1.0)	1 (1.5)	0 (0.0)
Status of haematological disease, n (%)			
Complete remission	92 (92.9)	63 (96.9)	29 (85.3)
Treatment regimen (conditioning), n (%)			
Myeloablative	75 (76.5)	52 (81.3)	23 (67.6)
Reduced intensity	23 (23.5)	12 (18.8)	11 (32.4)
Not documented	1 (1.0)	1 (1.5)	0 (0.0)
Stem cell source, n (%)			
Peripheral blood	88 (88.9)	59 (90.8)	29 (85.3)
Bone marrow	11 (11.1)	6 (9.2)	5 (14.7)
TBI2, n (%)			
Yes	65 (66.3)	44 (68.8)	21 (61.8)
Not documented	1 (1.0)	1 (1.5)	0 (0.0)

Number of transplantations, n (%)			
1	81 (81.8)	51 (78.5)	30 (88.2)
≥ 2	18 (18.2)	14 (21.5)	4 (11.8)
Donor relationship, n (%)			
Unrelated	52 (52.5)	35 (53.8)	17 (50.0)
Identical sibling or matched related	44 (44.4)	29 (44.6)	15 (44.1)
Mismatched related	3 (3.0)	1 (1.5)	2 (5.9)
cGVHD[3], n (%)			
Yes	75 (77.3)	54 (84.4)	21 (63.6)
Mild	39 (40.2)	26 (40.6)	13 (39.4)
Moderate	27 (27.8)	20 (31.3)	7 (21.2)
Severe	9 (9.3)	8 (12.5)	1 (3.0)
No	22 (22.7)	10 (15.6)	12 (36.4)
Not documented	2 (2.0)	1 (1.5)	1 (2.9)
Karnofsky Performance Status[4], n (%)			
100%	38 (39.2)	27 (42.9)	11 (32.4)
90%	25 (25.8)	17 (27.0)	8 (23.5)
80%	17 (17.5)	11 (17.5)	6 (17.6)
< 80%	17 (17.5)	8 (12.7)	9 (26.5)
Not documented	2 (2.0)	2 (3.1)	0 (0.0)
Immunosuppressive regimen, n (%)			
Steroids5 only	11 (11.6)	3 (4.8)	8 (25.0)
CNI (CYA or tacrolimus) only	48 (50.5)	33 (52.4)	15 (46.9)
Others (mTOR inhibitor or mycophenolate)	5 (5.3)	3 (4.8)	2 (6.3)
Combination (+ steroids5)	31 (32.6)	24 (38.1)	7 (21.9)
Not documented	4 (4.0)	2 (3.1)	2 (5.9)
Number of IS pills, median (IQR; range)	2.5 (2-4.25; 1-12)	3.0 (2.0-5.0; 1-10)	2.0 (1.25-3.75;1- 2)
Not documented	5	3	2
Number of co-medications, median (IQR; range)	8.0 (5.0-10.0; 1-22)	8.0 (5.0-10.0; 1-14)	9.0 (6.0-11.0;1-22)
Not documented	3	2	1

Abbreviations: cGVHD = chronic graft-versus-host disease; CNI = calcineurin inhibitor; mTOR = mammalian target of rapamycin; IS = immunosuppressants; IQR = interquartile range

[1] Nonadherence is any YES answer on any of the five items of the BAASIS©.

[2] Prevalence of patients who had a total body irradiation in the conditioning regime with 12 Gray.

[3] cGVHD was rated by the physician with the cGVHD grading scheme recommended by the National Institutes of Health consensus development project on criteria for clinical trials in cGVHD.

[4] Karnofsky Performance Status was determined by the physician at the annual follow-up visit and comprises an individual's health and physical functionality, based on a criteria related performance index rated from 100% (normal function) to 10% (morbid).

[5] Prednisone with a dosage of at least 2.5 mg

Table 2: Clinical characteristics

7.6.2 Prevalence of MNA

MNA according to dimensions of the BAASIS©	Total sample (N = 99)	Non-adherent patients (N = 65)
Implementation, n (%)	64 (64.6)	64 (98.5)
Taking nonadherence, n (%)	33 (33.3)	33 (50.8)
Drug holidays[1], n (%)	3 (3.2)	3 (4.6)
Timing nonadherence[2], n (%)	52 (61.2)	52 (80.0)
Dose reduction[3], n (%)	4 (4.1)	4 (6.2)
Discontinuation[3], n (%)	3 (3.1)	3 (4.6)
Overall medication (non-)adherence		
Overall nonadherence on any of the 5 BAASIS© items, n (%)	65 (65.7)	n.a.
Overall adherence rated on VAS in %, median (IQR)[4]	95 (90 - 100)	90 (80 -95)
Physician-reported MNA (N = 95)[5]		
Nonadherence, n (%)	18 (18.9)	15 (23.1)
Composite adherence score (N = 99)		
Nonadherence, n (%)	68 (68.7)	n.a

Abbreviations: MNA = medication nonadherence; BAASIS© = The Basel Assessment of Adherence to Immunosuppressive Medication Scale; VAS = Visual Analogue Scale; IQR = interquartile range
[1]4 missings (4.0%), [2]14 missings (14.1%); from which 8 patients (missings) took only steroids, [3]1 missing (1.0%), [4]3 missings (3.0%), [5]4 missings (4.0%)

Table 3: Prevalence of patient- and physician-reported MNA

Table 3 shows the prevalence of patient and physician reported MNA for the overall sample as well as for patients with no/mild cGVHD and for those with moderate/severe cGVHD. Combining patients' self-reported MNA on any items of the BAASIS© with physicians assessment of MNA yielded an overall nonadherence prevalence of 68.7% across the entire sample, 62.2% in patients with no/mild cGVHD, and 80.2% in patients with moderate/severe cGVHD.

7.6.3 Correlates of MNA

The univariate binary logistic regression model (Table 4) indicates that MNA is associated with higher numbers of IS pills (p=0.022), and with immunosuppressive therapies using either CNI alone (p=0.030) or CNI-steroid combinations (p=0.011), and with lower numbers of comedications (p=0.035).

Univariate binary logistic regression(N = 99)[1]	*Adjusted model for centre*			
	OR (95% CI)	**Df**	**p-value**	**q-value**
Age	0.985 (0.952–1.019)	1	0.373	0.4747
Gender	0.533 (0.220–1.289)	1	0.162	0.2835
Time after SCT	0.984 (0.903–1.073)	1	0.714	0.7689
Number of IS pills	1.328 (1.042–1.694)	1	**0.022**	0.0672
Immunosuppressive regimen		3	0.067	
CNI (CYA or tacrolimus) only[2]	5.513 (1.175–25.857)	1	**0.030**	0.0700
Others (mTOR inhibitor or mycophenolate)[2]	2.650 (0.253–27.781)	1	0.416	0.4853
Combination (+ steroids)[3]	8.560 (1.623–45.159)	1	**0.011**	0.0560
Number of co-medications	0.871 (0.766–0.990)	1	**0.035**	0.0700
Karnofsky Performance Status[4]	1.016 (0.98–1.047)	1	0.282	0.4387
Depression	0.860 (0.271–2.733)	1	0.798	0.7980
Nausea severity	0.801 (0.519–1.235)	1	0.314	0.4396
Multivariate binary logistic regression (N =	*Adjusted model for centre*			
	OR (95% CI)	**df**	**p-value**	**q-value**
Number of IS pills	1.422 (1.083–1.867)	1	**0.011**	0.0560
Number of co-medications	0.852 (0.742–0.979)	1	**0.024**	0.0672
Centre	*0.174 (0.055–0.553)*	*1*	*0.003*	

Abbreviations: MNA = medication nonadherence; OR = odds ratio; CI= confidence interval; df = degrees of freedom; IS = immunosuppressants; CNI = calcineurin inhibitor; mTOR = mammalian target of rapamycin

[1] Outcome variable for the regression analyses were the composite MNA adherence score

For the univariate binary logistic regression correlates were selected based on the WHO adherence model and evidence of the literature from adherence research in CML patients. [29, 31, 33, 44, 46, 60-63]

[2] Reference category: Steroids

[3] Prednisone with a dosage of at least 2.5 mg

[4] Karnofsky Performance Status was determined by the physician at the annual follow-up visit and comprises an individual's health and physical functionality, based on a criteria related performance index rated from 100% (normal function) to 10% (morbid).

Table 4: Correlates of MNA in the univariate and multivariate analysis

Multivariate binary logistic regression analysis results revealed that MNA is associated with higher numbers of IS pills (odds ratio (OR):1.422; 95% confidence interval (CI):1.083-1.867; p=0.011), as well as with a lower number of co-medications (OR:0.852; CI:0.742-0.979; p=0.024). The explained variance of the adjusted model is acceptable (Nagelkerke R^2: 22.7%).

7.6.4 Association of MNA with cGVHD

The ordinal logistic regression indicated a positive association between composite MNA and higher grades of cGVHD (OR:3.01; CI:1.27-7.14; p=0.012).

Ordinal logistic regression (N = 99)	*Adjusted model for centre and donor relationship*		
	OR (95% CI)	df	p-value
Composite MNA	3.007 (1.267 - 7.135)	1	**0.012**
Centre	0.209 (0.083 - 0.526)	1	0.001
Donor relationship			
Identical sibling or matched related	1.184 (0.550 - 2.547)	1	0.666
Mismatched related	10.034 (1.047 - 96.255)	1	0.046
Unrelated[1]			

Abbreviations: MNA = medication nonadherence; cGVHD = chronic graft-versus-host disease; OR = odds ratio; CI = confidence interval; df = degrees of freedom; BAASIS© = The Basel Assessment of Adherence to Immunosuppressive Medication Scale [1]This parameter is set to zero because it is redundant.

Table 5: Association of MNA with cGVHD

Further our post-hoc sensitivity analyses revealed that, patients with higher grades of cGVHD, reported significantly more problems relating to the implementation of the medication regimen (OR:2.60; CI:1.14-5.91; p=0.023). In particular, with higher grades of cGVHD there was a higher risk for taking nonadherence (OR:2.46; CI:1.10-5.50; p=0.028) and dose reduction (OR:15.57; CI:1.49-162.72; p=0.022), respectively, see Table 6.

Ordinal logistic regression (N = 99)	*Adjusted model for centre and donor relationship*		
	OR (95% CI)	df	p-value
Implementation	2.60 (1.14 - 5.91)	1	**0.023**
Taking nonadherence	2.46 (1.10 - 5.50)	1	**0.028**
Drug holidays	1.60 (0.19 - 13.57)	1	0.667
Timing nonadherence	0.91 (0.97 - 2.10)	1	0.826
Dose reduction	15.57 (1.49 - 162.72)	1	**0.022**
Discontinuation	3.03 (0.22 - 41.18)	1	0.406

Abbreviations: MNA = medication nonadherence; cGVHD = chronic graft-versus-host disease; OR = odds ratio; CI = confidence interval; df = degrees of freedom

Table 6: Post-hoc sensitivity analyses MNA with cGVHD

7.7 Discussion

This is the first study to show a relationship between cGVHD and MNA. It also indicates a high prevalence of nonadherence, particularly regarding timing and taking. Furthermore, not only patients taking more IS agents, but also, surprisingly, those taking lower numbers of comedications were more likely to be nonadherent.

For the first time, our study showed a significant association between MNA and cGVHD as a clinical outcome. Nonadherent patients were more likely to have higher grades of MNA. More specifically taking nonadherence and dose reduction were more common in patients with higher grades of cGVHD. These results need further exploration. Research in patients with chronic myeloid leukemia showed that the consequences of MNA to Imanitinib were fatal since taking nonadherence was significantly related to poor cytogenetic and molecular response [29-32] and poor survival [32, 33].

In fact, while evidence in solid organ transplantation indicates clear associations between small deviations from prescribed medication schedules and poor clinical outcomes [34, 35] (e.g., more than 5% deviation from dosing schedules has been associated with higher incidences of graft loss or late acute rejections in renal and heart transplant recipients), however no information is available on how much timing deviation is tolerable in SCT. Further research is needed to identify a clinically meaningful definition of IS MNA in the stem cell transplant population. To develop such a definition, a prospective cohort study design assessing subclinical MNA levels and its relationship with clinical outcomes would be most appropriate.

Although extensive research has examined genetic and biophysiological factors behind cGVHD [36-39] its behavioural influences remain unexplored. To the existing knowledge base, the current study adds that MNA as a behavioural factor is linked to cGVHD. Given the increasing global number of transplantations using mobilized peripheral blood stem cells, the increasingly frequent use of reduced conditioning regimens, mismatched and unrelated donors, and older SCT recipients, larger numbers of patients with GVHD can be expected in the near future [40]. Yet, while numerous efforts have been made to improve the staging and treatment of cGVHD [28], its management remains puzzling. Challenges to clinical practice and research include the heterogeneous nature of the disease [e.g., variable organ involvement, patient risk factors (age, gender) and treatment-related factors (conditioning regimens, cGVHD treatment and SCT type)] and the absence of a clear consensus about second- and third-line management options [37, 39, 41-43]. Therefore, to clarify our understanding of cGVHD pathogenesis, it is recommended that researchers routinely combine patient reported outcome instruments (such as the BAASIS©) and objective measurements (e.g. electronic monitoring systems) in prospective multicentre studies.

In accordance with our theoretical model, we revealed that two therapy-related factors – "number of IS pills" and "number of co-medications" – are strongly associated with MNA. While we did not assess underlying reasons for patients' nonadherence, the present results are consistent with those of previous studies from hemato-oncology settings, which have associated higher numbers of

medications (≈ higher medication doses) with higher MNA [29, 31, 44-46]. Research in solid organ transplantation [47] indicates that barriers to adherence are often unintentional (e.g., *Forgetfulness/ Interruption of daily routine*) or determined by patients' attitude (e.g., the belief that *not all IS are necessary to prevent rejection*). [48] Such explanations might also be relevant to our study population. For instance, clinicians might recognize that patients consciously or unconsciously reduce or omit IS intake, potentially leading to cGVHD exacerbation. Clinical experience shows that some patients with treatment refractory disease eventually lose their belief in their medications' effectiveness ("*the drugs don't work*"). Further practical barriers to IS intake might include the unpleasant smell and taste of pills or cGVHD involvement of the mouth, which can make pill intake difficult. Surprisingly, though, while one might expect that higher numbers of co-medications would result in greater MNA, we found a negative relationship. Here a possible explanation could be that patients with fewer concomitant medications pay less attention to their medication. However, these hypotheses need to be further studied in prospective studies.

As western healthcare systems are shifting from a strictly acute treatment system to one that embraces effective long-term management of chronic conditions [49], the current study has notable clinical implications. Supporting patients' medication management is a key task for transplant teams – one for which multidisciplinary teams are under growing pressure to develop innovative solutions [50]. And while educational strategies appear to be most commonly used for medication adherence in SCT patients [51], information alone may not be sufficient. Therefore, combinations of cognitive/ behavioural and psychological interventions, drawing upon skill development and consolidation of favourable behaviours, may more effectively engage patients in their own medication management [52-55]. For example, a nurse-coordinated intervention program could offer an excellent opportunity to assess medication taking behaviours and initiate individually tailored adherence enhancing interventions with components proven effective against MNA, e.g., brief (maximum one page) written medication adherence instructions, electronic reminders to take medications regularly, dose modifications, special packaging, self-monitoring, and medication side effect management [52-55]. Additional use of electronic monitoring could provide feedback data for patients to track their medication taking progress [56, 57]. Finally, considering the overall increase of chronically ill patients on complex medication regimens, the topic of MNA demands greater awareness among healthcare professionals and should be a major component of continuous professional education.

The findings of this secondary analysis must be interpreted in the context of this study's potential limitations. The small sample size permits only low analytic sensitivity, inclusion of a small set of study variables and limited statistical power, possibly resulting in undetected reliable relationships between variables. Our ordinal regression analysis revealed a significant effect for the control variable "centre" which can be explained by the fact that one centre had considerable more patients with higher grades of cGHVD because of their higher performance in HLA-mismatched transplantations. Admittedly, our cross-sectional study design does not allow inferences of causality.

Therefore, the impact of MNA as a potential behavioural risk factor for cGVHD should be assessed as a component of prospective cohort studies. Such a longitudinal study could clarify if patients who show complete medication adherence have less cGVHD over time and therefore have to take lower IS doses for a shorter time periods. Also, although depression and illness severity are possible risk factors for MNA, patients with psychiatric disorders and in-patients were excluded [44, 58]. And concerning measurement accuracy, while combining self-report questionnaires with physicians' collateral reports results in greater sensitivity than either alone, the additional use of electronic monitoring would have provided the greatest possible sensitivity [19].

Clearly, further research will be needed to confirm and expand the current study's findings and to transpose the knowledge acquired here into clinical practice [59]. A qualitative interview study would be particularly helpful to understand patients' reasons for taking and particularly timing MNA, as well as to tailor and deliver effective individual support. Further research will then be needed to investigate the effectiveness of adherence-enhancing interventions. This will be particularly useful to assess the impact of early post-transplant interventions on the occurrence and severity of both acute and chronic GVHD. Given the knowledge that MNA is not entirely patient-driven but is also influenced by the healthcare team/system related factors (quality of patient-physician communication, reimbursement of medication costs, and regularity of follow-up) this will have to be examined in future studies.

To conclude, this is one of the first studies demonstrating the high magnitude of MNA in a SCT population. For the first time, associations clearly link MNA and cGVHD as a clinical outcome, while its associations with medication-specific variables (numbers of IS pills and co-medications) have been shown in SCT recipients. Our findings indicate a strong need for a meaningful definition of MNA regarding SCT.

7.8 References

1. Baird K, Pavletic SZ. Chronic graft versus host disease. *Curr Opin Hematol* 2006; **13:** 426-35.
2. Mohty B, Mohty M. Long-term complications and side effects after allogeneic hematopoietic stem cell transplantation: an update. *Blood Cancer J* 2011; **1:** e16.
3. Majhail NS, Rizzo JD. Surviving the cure: long term followup of hematopoietic cell transplant recipients. *Bone Marrow Transplant* 2013; **48:** 1145-51.
4. Pidala J, Kim J, Anasetti C, Nishihori T, Betts B, Field T *et al.* The global severity of chronic graft-versus-host disease, determined by National Institutes of Health consensus criteria, is associated with overall survival and non-relapse mortality. *Haematologica* 2011; **96:** 1678-84.
5. Pallua S, Giesinger J, Oberguggenberger A, Kemmler G, Nachbaur D, Clausen J *et al.* Impact of GvHD on quality of life in long-term survivors of haematopoietic transplantation. *Bone Marrow Transplant* 2010; **45:** 1534-9.
6. Wood WA, Chai X, Weisdorf D, Martin PJ, Cutler C, Inamoto Y *et al.* Comorbidity burden in patients with chronic GVHD. *Bone Marrow Transplant* 2013; **48:** 1429-36.
7. Bishop MM, Rodrigue JR, Wingard JR. Mismanaging the gift of life: noncompliance in the context of adult stem cell transplantation. *Bone Marrow Transplant* 2002; **29:** 875-80.
8. McGrady ME, Williams SN, Davies SM, Pai AL. Adherence to outpatient oral medication regimens in adolescent hematopoietic stem cell transplant recipients. *Eur J Oncol Nurs* 2014; **18:** 140-4.
9. Fuji S, Kapp M, Einsele H. Challenges to preventing infectious complications, decreasing re-hospitalizations, and reducing cost burden in long-term survivors after allogeneic hematopoietic stem cell transplantation. *Semin Hematol* 2012; **49:** 10-4.
10. Khera N, Zeliadt SB, Lee SJ. Economics of hematopoietic cell transplantation. *Blood* 2012; **120:** 1545-51.
11. Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Evans R *et al.* Nonadherence consensus conference summary report. *Am J Transplant* 2009; **9:** 35-41.
12. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T *et al.* A new taxonomy for describing and defining adherence to medications. *British journal of clinical pharmacology* 2012; **73:** 691-705.
13. Sabaté E. *Adherence to long-term therapies: evidence for action.*, World Health Organization (WHO): Geneva, 2003.
14. Kirsch M, Götz A, Halter J, Schanz U, Stussi G, Dobbels F *et al.* Differences in health behaviours between survivors after allogeneic haematopoietic stem cell transplantation and the general population: the PROVIVO study. *Bone Marrow Transplant (in press)* 2014.
15. Leuven-Basel Adherence Research Group. *The Basel Assessment of Adherence to Immuno-suppressive Medication Scale (BAASIS© Explanation)*. [Manuscript] Basel, Switzerland, 2005.

16. Marsicano Ede O, Fernandes Nda S, Colugnati F, Grincenkov FR, Fernandes NM, De Geest S *et al.* Transcultural adaptation and initial validation of Brazilian-Portuguese version of the Basel assessment of adherence to immunosuppressive medications scale (BAASIS) in kidney transplants. *BMC nephrology* 2013; **14:** 108.
17. De Simone P, Ducci J, Denhaerynck K, Dobbels F, Filipponi F, Sabina DG. Subclinical Non Adherence to Immunosuppression: Correlates and Clinical Consequences. *Liver Transplantation* 2013; **19:** 89.
18. Schafer-Keller P, Steiger J, Bock A, Denhaerynck K, De Geest S. Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. *Am J Transplant* 2008; **8:** 616-26.
19. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005; **353:** 487-97.
20. Hermann C, Buss U. HADS-D. Hospital anxiety and depression scale-Deutsche Version. In: *Testdokumentation und Handanweisung*. Huber, Bern, 1995.
21. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; **52:** 69-77.
22. Hjermstad MJ, Knobel H, Brinch L, Fayers PM, Loge JH, Holte H *et al.* A prospective study of health-related quality of life, fatigue, anxiety and depression 3-5 years after stem cell transplantation. *Bone Marrow Transplant* 2004; **34:** 257-66.
23. Gruber U, Fegg M, Buchmann M, Kolb HJ, Hiddemann W. The long-term psychosocial effects of haematopoetic stem cell transplantation. *Eur J Cancer Care* 2003; **12:** 249-56.
24. Grulke N, Larbig W, Kachele H, Bailer H. Pre-transplant depression as risk factor for survival of patients undergoing allogeneic haematopoietic stem cell transplantation. *Psychooncology* 2008; **17:** 480-7.
25. Grulke N, Larbig W, Kachele H, Bailer H. Distress in patients undergoing allogeneic haematopoietic stem cell transplantation is correlated with distress in nurses. *Eur J Oncol Nurs* 2009; **13:** 361-7.
26. Kirsch M, Mitchell S, Dobbels F, Stussi G, Basch E, Halter J *et al.* Linguistic and content validation of a German-language PRO-CTCAE-based patient-reported outcomes instrument to evaluate the symptom experience in survivors of allogeneic haematopoietic stem cell transplantation. *European Journal of Oncology Nursing* in press
27. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. *Cancer* 1984; **53:** 2002-2007.

28. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ *et al.* National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant* 2005; **11:** 945-56.

29. Marin D, Bazeos A, Mahon F-X, Eliasson L, Milojkovic D, Bua M *et al.* Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology* 2010; **28:** 2381-2388.

30. Ibrahim AR, Eliasson L, Apperley JF, Milojkovic D, Bua M, Szydlo R *et al.* Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. *Blood* 2011; **117:** 3733-3736.

31. Noens L, van Lierde MA, De Bock R, Verhoef G, Zachee P, Berneman Z *et al.* Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood* 2009; **113:** 5401-11.

32. Ganesan P, Sagar TG, Dubashi B, Rajendranath R, Kannan K, Cyriac S *et al.* Nonadherence to imatinib adversely affects event free survival in chronic phase chronic myeloid leukemia. *American Journal Of Hematology* 2011; **86:** 471-474.

33. Richardson JL, Shelton DR, Krailo M, Levine AM. The effect of compliance with treatment on survival among patients with hematologic malignancies. *J Clin Oncol* 1990; **8:** 356-64.

34. De Geest S, Abraham I, Moons P, Vandeputte M, Van Cleemput J, Evers G *et al.* Late acute rejections and subclinical noncompliance with cyclosporine-therapy in heart transplant patients. *Journal of Heart and Lung Transplantation* 1998; **17:** 854-863.

35. Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. Transplant outcomes and economic costs associated with patient noncompliance to immuno-suppression. *American journal of transplantation* 2009; **9:** 2597-606.

36. Alousi AM, Bolanos-Meade J, Lee SJ. Graft-versus-host disease: state of the science. *Biol Blood Marrow Transplant* 2013; **19:** 102-8.

37. Jaglowski SM, Devine SM. Graft-versus-host disease: why have we not made more progress? *Curr Opin Hematol* 2014; **21:** 141-7.

38. Garnett C, Apperley JF, Pavlu J. Treatment and management of graft--host disease: improving response and survival. *Therapeutic advances in hematology* 2013; **4:** 366-378.

39. Pavletic SZ, Fowler DH. Are we making progress in GVHD prophylaxis and treatment? *Hematology Am Soc Hematol Educ Program* 2012; **2012:** 251-64.

40. Lee SJ. New approaches for preventing and treating chronic graft-versus-host disease. *Blood* 2005; **105:** 4200-6.

41. Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M *et al.* Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. *Biol Blood Marrow Transplant* 2011; **17:** 1-17.

42. Duarte RF, Greinix H, Rabin B, Mitchell SA, Basak G, Wolff D *et al.* Uptake and use of recommendations for the diagnosis, severity scoring and management of chronic GVHD: an international survey of the EBMT-NCI Chronic GVHD Task Force. *Bone Marrow Transplant* 2014; **49:** 49-54.

43. El-Jawahri A, Pidala J, Inamoto Y, Chai X, Khera N, Wood WA *et al.* Impact of Age on Quality of Life, Functional Status and Survival in Patients with Chronic Graft-versus-Host Disease. *Biol Blood Marrow Transplant* 2014; 7: 285-7

44. Darkow T, Henk HJ, Thomas SK, Feng W, Baladi J-F, Goldberg GA *et al.* Treatment interruptions and non-adherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukaemia. *Pharmacoeconomics* 2007; **25:** 481-496.

45. Wu EQ, Johnson S, Beaulieu N, Arana M, Bollu V, Guo A *et al.* Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients. *Curr Med Res Opin* 2010; **26:** 61-9.

46. Feng W, Henk H, Thomas S, Baladi J, Hatfield A, Goldberg GA *et al.* Compliance and persistency with imatinib. *Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I.* 2006; **24**: 18

47. Gordon EJ, Gallant M, Sehgal AR, Conti D, Siminoff LA. Medication-taking among adult renal transplant recipients: barriers and strategies. *Transplant international : official journal of the European Society for Organ Transplantation* 2009; **22:** 534-45.

48. Schmid-Mohler G, Thut MP, Wuthrich RP, Denhaerynck K, De Geest S. Non-adherence to immunosuppressive medication in renal transplant recipients within the scope of the Integrative Model of Behavioral Prediction: a cross-sectional study. *Clin Transplant* 2010; **24:** 213-22.

49. Majhail NS, Rizzo JD. Surviving the cure: long term followup of hematopoietic cell transplant recipients. *Bone Marrow Transplant* 2013; **48:** 1145-51.

50. Dignan FL, Manwani R, Potter MN, Ethell ME, Leonard H, Brennan J *et al.* A dedicated GvHD clinic may improve the quality of life for allogeneic stem cell transplant survivors. *Clin Transplant* 2013; **27:** E1-2.

51. Kirsch M, Berben L, Johansson E, Calza S, Eeltink C, Stringer J *et al.* Nurses' practice patterns in relation to adherence-enhancing interventions in stem cell transplant care: a survey from the Nurses Group of the European Group for Blood and Marrow Transplantation. *Eur J Cancer Care 2014; **7:** 12172.*

52. De Bleser L, Matteson M, Dobbels F, Russell C, De Geest S. Interventions to improve medication-adherence after transplantation: a systematic review. *Transpl Int* 2009; **22:** 780-97.

53. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *The Cochrane database of systematic reviews* 2008**:** CD000011.

54. De Geest S. Immunosuppressive drugs and non-adherence in transplantation. *Journal of Renal Nursing* 2010; **2:** 58-63.

55. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC *et al.* Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Ann Intern Med* 2012; **157:** 785-95.

56. Demonceau J, Ruppar T, Kristanto P, Hughes DA, Fargher E, Kardas P *et al.* Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. *Drugs* 2013; **73:** 545-62.

57. Vervloet M, Linn AJ, van Weert JC, de Bakker DH, Bouvy ML, van Dijk L. The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature. *J Am Med Inform Assoc* 2012; **19:** 696-704.

58. Richardson JL, Marks G, Johnson CA, Graham JW, Chan KK, Selser JN *et al.* Path model of multidimensional compliance with cancer therapy. *Health Psychol* 1987; **6:** 183-207.

59. LoBiondo-Wood G, Brown CG, Knobf MT, Lyon D, Mallory G, Mitchell SA *et al.* Priorities for oncology nursing research: the 2013 national survey. *Oncol Nurs Forum* 2014; **41:** 67-76.

60. Mancini J, Simeoni MC, Parola N, Clement A, Vey N, Sirvent N *et al.* Adherence to leukemia maintenance therapy: a comparative study among children, adolescents, and adults. *Pediatr Hematol Oncol* 2012; **29:** 428-39.

61. Lee CR, Nicholson PW, Souhami RL, Deshmukh AA. Patient compliance with oral chemotherapy as assessed by a novel electronic technique. *Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology* 1992; **10:** 1007-1013.

62. Efficace F, Rosti G, Cottone F, Breccia M, Castagnetti F, Iurlo A *et al.* Profiling chronic myeloid leukemia patients reporting intentional and unintentional non-adherence to lifelong therapy with tyrosine kinase inhibitors. *Leuk Res* 2014; **38:** 294-8.

63. Kiguchi T, Tauchi T, Ito Y, Miyazawa K, Kimura Y, Ohyashiki K. Compliance with taking imatinib mesylate in patients with chronic myeloid leukemia in the chronic phase. *Leuk Res* 2009; **33:** 506-8.

CHAPTER 8:

NURSES' PRACTICE PATTERNS IN RELATION TO ADHERENCE ENHANCING INTERVENTIONS IN STEM CELL TRANSPLANT CARE: A SURVEY FROM THE NURSES GROUP OF THE EUROPEAN GROUP FOR BLOOD AND MARROW TRANSPLANTATION

Monika Kirsch [1, 2], Lut Berben [1], Eva Johansson [3], Simona Calza [4], Corien Eeltink [5], Jacqui Stringer [6], Sarah Liptrot [7], Sabina De Geest [1]

[1] *Institute of Nursing Science, University of Basel, Switzerland*

[2] *Department of Haematology, University Hospital Basel, Switzerland*

[3] *Department of Neurobiology, Care Sciences and Society, Division of Nursing, Karolinska Institutet, Stockholm, Sweden*

[4] *Department of Paediatric Haematology and Oncology, Gaslini Children's Hospital, Genoa, Italy*

[5] *Department of Haematology, VU University Medical Center, Amsterdam, The Netherlands*

[6] *Haematology Transplant Unit, The Christie NHS Foundation Trust, Wilslow Road, Manchester, Great Britain*

[7] *European Institute of Oncology, Milan, Italy*

Published in
European Journal of Cancer Care 2014; 7(10): 12172
Modified version

8.1 Abstract

Recipients of stem cell transplants (SCT) must accurately manage multiple medications as nonadherence jeopardizes treatment benefits. There is an evidence base for the efficacy of adherence enhancing interventions, however level of clinical implementation is unknown.

This study aimed to identify patterns of practice in assessing medication adherence, screening for risk factors of nonadherence, interventions used in SCT to improve adherence and how nurses perceive the effectiveness of such interventions.

A convenience sample of 143 European nurses completed a 29-item questionnaire measuring the frequency and perceived effectiveness of assessment/screening methods for adherence and three types of intervention (*educational/cognitive, counselling/behavioural, and psychological/affective*).

Questioning patients about adherence was the most regularly used assessment method (51.5%). Nurses used a median of 7 interventions (IQR: 6) '*frequently*', the most popular being provision of reading materials (79%). The interventions perceived as most effective were; providing individual patient/family with teaching and reading materials.

This is the first study exploring patterns of practice relating to adherence in SCT. Educational interventions were the most frequently employed style of intervention, which is at odds with recent data suggesting limited efficacy with this style of intervention. Combining educational, behavioral and psychological interventions would more accurately embrace current understanding.

8.2 Introduction

Stem cell transplantation (SCT) is routinely used as an intensive treatment for haematological malignancies as well as selected solid tumours and non-malignant diseases. It requires prolonged medication regimens and clinical follow-up [1]. Patients must take numerous oral medications, including immunosuppressing drugs and infection prophylaxis treatments for 6 months or longer depending on the type of transplant. The success of such medical treatment depends partly on patients' ability and willingness to take medications correctly. As shown in other chronically ill patient populations, not taking medications as prescribed is a major issue jeopardizing the benefits of a pharmacological treatment [2]. Medication nonadherence is defined as 'a deviation from the prescribed medication regimen sufficient to adversely influence the regimen's intended effect' [3]. While one might expect that the diagnosis of a potentially fatal illness would ensure medication adherence, the evidence indicates otherwise. Where self-administration of oral medications is required for cancer treatment, 20% to 100% of patients fail to execute their prescribed drug regimens correctly [4-8]. Given the possible magnitude of the issue and consequences of non-adherent behaviour, healthcare professionals should take advantage of their unique position to assess, monitor and support patients' management of self-medication. However, extent and content of adherence support between clinical settings varies tremendously and patterns of practice do not always reflect the state-of-science regarding adherence enhancing interventions [9, 10].

Important first steps in dealing with nonadherence include routinely assessing patients' adherence in clinical practice and screening them for nonadherence risk factors [11]. For patients identified as nonadherent or at risk of nonadherence, there are three different types of adherence enhancing interventions described in the literature, which healthcare professionals can integrate into their care practice. *Educational/cognitive interventions* present information or knowledge individually or in a group setting, delivering it verbally, in a written format, and/or audio-visually. *Counselling/ behavioural interventions* target, shape and/or reinforce behaviour, empowering patients to participate in their own care, while positively changing their skill levels or normal routines. *Psychological/ affective interventions* focus on patients' feelings and emotions or relationships and social support. *Mixed interventions* combine any two or more of these intervention types [11].

Using this terminology, Berben et al. [9, 10] have assessed healthcare professionals' patterns of practice regarding medication adherence in areas of cardiovascular care (N=137) and solid organ transplantation (N=85). In both studies, healthcare professionals relied more on educational interventions than on counselling/behavioural and psychological/affective interventions. However, a 2009 meta-analysis showed that the frequently used educational interventions have limited efficacy in bringing about behaviour change which results in substantial improvements in patients' knowledge [12]. Multi-level interventional approaches combining educational/cognitive interventions with counselling/ behavioural interventions and/or psychological/affective interventions appear to be more efficient in improving patient medication taking behaviour [11-16]. In other words, combinations of interventions appear to be more effective than single interventions. In particular, a combination of measures such as

special medication packaging, dose modifications, participant monitoring of medication effects/side effects and the use of succinct written instructions indicated considerable potential value [12]. Further promising approaches are interventions that are likely to shape behaviour by simple interactions; for instance, reminder systems (SMS, smart phone applications, alarm clocks) or direct feedback loops based on electronic monitoring (a medication bottle containing a microchip which registers the date and time of every bottle opening) [17, 18].

To date, no information is available looking at practice patterns relating to medication adherence in the field of SCT. It is unknown which interventions are perceived as most efficient. Moreover, there is no information regarding which patterns of practice are congruent with the state-of-science adherence enhancing interventions.

The aims of this study were therefore

1. To assess practice patterns of assessment/screening methods and interventions used to enhance medication adherence
2. To determine nurses' perceived efficacy of used assessment/screening methods and adherence-enhancing interventions

8.3 Materials and Methods

8.3.1 Design, setting and sample

This study survey used a methodology previously developed by Berben et al. [9, 10]. A convenience sample of nurses was recruited in April, 2011 during the Annual Conference of the European Group for Blood and Marrow Transplantation (EBMT) Nurses Group in Paris (France). The survey was approved by the EBMT General Board. Inclusion criteria were: employment as a nurse providing direct care for autologous or allogeneic SCT patients, and the ability to understand and read English. Informed consent was presumed with the return of the completed questionnaire.

8.4 Measurements and Variables

8.4.1 Demographic information

Respondents' demographic information was collected by self-report and included: gender; age in years; total years of working experience in nursing; years of clinical experience in SCT care; highest level of education (Diploma, Bachelor, Master, Doctorate/PhD); and current involvement in direct SCT patient care. Furthermore, data were collected on respondents' working environments regarding:

the age range of patients treated (children, adults, or both); the work setting (inpatient, outpatient, or both); the kind of transplants performed (allogeneic, autologous or both); and the country where the centre was located (Table 1).

	Total (N=143)	
Gender; n (%)[1]		
Female	124	(87.3)
Age; mean (SD)	**39.4**	**(8.3)**
Years of working experience as a nurse; mean (SD)	**15.9**	**(8.1)**
Years of working experience in SCT care; mean (SD)	**11.0**	**(6.6)**
Professional qualification in nurses; n (%) [2]		
Diploma	58	(41.1)
Bachelor	43	(30.5)
Master	39	(27.7)
Doctorate/PhD	1	(0.7)
Kind of transplants performed at the centre; n (%)		
Allogeneic & autologous	119	(84.4)
Autologous	11	(7.8)
Allogeneic	11	(7.8)
Primary workplace; n (%)[1]		
Inpatient	80	(55.9)
Outpatient	26	(18.2)
Inpatient and outpatient	34	(23.8)
Home care	2	(1.4)
Kinds of patients treated at the centre; n (%)		
Children	30	(21.0)
Adults	102	(71.3)
Children and adults	11	(7.7)
Region where department is located[3]		
Western Europe	62	(43.3)
Northern Europe	53	(37.1)
Southern Europe	15	(10.5)
Eastern Europe	3	(2.1)
Asia	9	(6.3)
Northern America	1	(0.7)

[1] missing n=1; [2] missing n=2; [3] Classification according United Nations Statistics Division http://unstats.un.org/unsd/methods/m49/m49regin.htm#europe

Table 1: Demographic characteristics of respondents and characteristics of SCT centres

8.4.2 Adherence assessment and intervention strategies

This study used an English-language instrument developed by Berben et al. 9, 10. The questionnaire's content validity was established based on experts' opinion, evidence from state-of-the-art adherence literature and pilot-testing.

The frequencies with which *adherence assessment strategies and screening for risk factors* were utilized was measured through responses to the following three items looking at

1. Questioning patients about nonadherence during follow-up
2. Screening for nonadherence risk factors during follow-up
3. Using electronic monitoring devices to assess nonadherence.

The regularity with which participants utilized 26 different adherences-enhancing interventions within the categories of educational/cognitive (6 items), counselling/behavioural (11 items), and psychological/affective (9 items) interventions was explored using items presented in table 2. For each assessment/screening method and intervention, nurses were asked to indicate their frequency of utilizing it, using a Likert scale scored from 0 ('*never'*) to 5 ('*all the time*'). In addition, nurses were asked to rate the perceived effectiveness of their reported assessment/screening methods and interventions using a scale scored from 0-3 (0 = *Don't know';* 1 = '*Not at all';* 2 = '*Somewhat'*; 3 = '*Extremely'*).

8.5 Data collection

All nurses who attended the opening session of the EBMT meeting were invited by the President of the EBMT Nurses Group to participate in the survey. When delegates entered the conference hall to attend the opening session, five members of the EBMT Nurses Group research subcommittee distributed the questionnaires and printed information about the survey. Completed questionnaires were either collected after the session or were returned to a designated collection box at the EBMT stand during the conference.

8.6 Data analyses

Descriptive statistics were used as appropriate (i.e., frequencies, percentages, means/standard deviations and medians/interquartile ranges). To describe assessment/screening methods and adherence-enhancing interventions, we calculated the prevalence of each strategy at the item level, using frequencies and percentages. Because most items yielded skewed answer patterns, the Likert scale responses for the frequencies of screening/assessment methods and interventions were regrouped into 3 values: *never* = 0 (originally 'never'); *seldom* = 1 (originally 'occasionally' and 'sometimes'); and *frequently and all the time* = 2 (originally 'frequently' and 'all the time'). For each of the three intervention categories

(*education/cognitive, counselling/behavioural,* and *psychological/affective*), we calculated the mean percentage of interventions that nurses reported using it '*frequently*', '*seldom*' and '*never'*. In order to show how many interventions are used frequently by nurses, the median and IQR for the total number of interventions nurses reported using 'frequently', as well as the number used within each of the three intervention categories was calculated. To estimate how many nurses used a variety of different intervention types, we calculated the number and proportion of participants who reported using one or more interventions from each of two or more intervention categories '*frequently*'. To assess the average perceived effectiveness of each of the three intervention categories, we calculated mean and standard deviations based on the effectiveness ratings (0-3) of all items reported used in that category. Prior to examining the relationship between the respondents' reported frequencies of using assessment/screening methods and adherenceenhancing interventions, along with their perceived effectiveness, we calculated frequency and effectiveness scores for each of the four domains: assessment/screening methods and three intervention categories. Analyses were performed using IBM SPSS Statistics (version 19.0.1; IBM Inc., Armonk, NY, USA) and Microsoft Office Excel 2008®.

8.7 Results

A total of 481 questionnaires were distributed, of which 173 (35.6%) were returned. Seventeen respondents reported providing no direct patient care; 13 had not filled-out large parts of the questionnaire. These 30 were therefore excluded from further analysis, leaving a final sample of 143 (29.7%) nurses with a mean age of 39.4 years (SD 8.3); 87.3% were female. The majority (71.3%) cared for adult patients; 81.6% cared for both autologous and allogeneic SCT recipients. Nurses had a mean working experience of 11 years (SD 6.6) in the SCT field. The characteristics of the sample and the SCT centres are presented in Table 1.

8.7.1 Practice patterns in view of strategies for the assessment of nonadherence and risk factors in daily practice

Just over two-thirds (67.8%) of participants reported 'frequently' asking patients about nonadherence during follow-up. Fewer than half (44.8%) reported the same level of screening for nonadherence risk factors during follow-up; and only 11.2% reported frequent use of electronic monitoring devices for nonadherence assessment.

8.7.2 Practice patterns in view of adherence enhancing interventions

Educational/cognitive adherence-enhancing interventions were most commonly used: 36.4% of nurses reported using them '*frequently*', followed by counselling/behavioural interventions (26.6%) and psychological/affective interventions (23.1%). Nurses reported using a median of 7 (IQR 6) ad-her-

ence-enhancing interventions '*frequently*' in the daily care of SCT-patients. Regarding individual intervention types, they used a median of 2 (IQR 2) educational/cognitive, 2 (IQR 3) counselling/behavioural and 2 (IQR 3) psychological/affective interventions. Most nurses (n=121, 84.4%) reported using a variety of interventions from all three categories (educational/cognitive, counselling/behavioural, and psychological/affective).

Examining the data at the item level revealed that providing reading materials (79%) and printed medication instructions (58.7%) were the most frequently used educational interventions. Less used educational interventions included showing video tapes (11.2%), offering educational classes (9.1%) and using computer assisted educational programs (3.5%). Of the counselling/behavioural interventions, 66.4% of respondents reported '*frequently*' training patients during their inpatient stay regarding correct medication intake; and 39.9% reported '*frequently*' providing adherence reminders during clinic visits. The most regularly used psychological/affective measures focused on involving family or support persons in adherence enhancing interventions (51.1%) and establishing partnerships with patients (49%). Few nurses indicated '*frequently*' utilizing support groups such as peer mentor programs (4.9%) or those focused solely on adherence (2.1%).

8.7.3 Perceived effectiveness of assessment strategies and interventions

The assessment strategy perceived as being most effective was questioning patients about medication adherence during follow-up visits; 44.7% of participants who used this intervention rated this as 'extremely effective'. Involving family members in the teaching process and providing reading materials were perceived as the most effective of the used adherence-building educational/cognitive interventions (Table 2). Of the respondents who reported their use, 57.4% rated them as 'extremely effective'. Among behavioural/counselling interventions, training patients how to take their medications correctly during inpatient stays was rated as the most effective, with 53.2% of users considering it as 'extremely effective'. For psychological/affective approaches, both involving family or support persons in education and behavioural interventions (52.9%) and establishing a partnership with patients and significant others (51.9%) were rated by their users as 'extremely helpful'. Comparing the interventions' perceived effectiveness indicated no significant differences between the three categories. Whereas educational/ cognitive interventions (2.60; SD 0.36) were rated slightly higher than the psychological/affective group (2.47; SD 0.37), the counselling/behavioural group (2.43; SD 0.32) fell very slightly below.

	Frequency of method/intervention (N=143)				Total number of nurses having utilized the method/ intervention[1]	Perceived effectiveness of interventions used[2]			
	Frequently n (%)	Seldom n (%)	Never n (%)	Not applicable/ missing n (%)	n	Extremely n (%)	Somewhat n (%)	Not at all n (%)	Don't know/ missing n (%)
Adherence assessment/screening methods									
Questioning patient about medication adherence during follow-up visits	97 (67.8)	17 (11.9)	10 (7)	18 (13.3)	**114**	51 (44.7)	47 (41.2)	0	16 (14.1)
Screening patients for risk factors for NA during follow-up	64 (44.8)	44 (30.8)	16 (11.2)	19 (13.3)	**108**	43 (39.8)	40 (37)	1 (0.9)	24 (22.3)
Using an electronic monitoring device	16 (11.2)	8 (5.6)	103 (72)	16 (11.2)	24	6 (25)	11 (45.8)	0	7 (29.2)
Educational/ cognitive interventions									
Providing reading materials	113 (79)	16 (11.2)	5 (3.9)	7 (4.9)	129	74 (57.4)	38 (29.5)	2 (1.6)	15 (11.7)
Providing printed medication instructions	84 (58.7)	39 (27.3)	14 (9.8)	6 (4.2)	123	60 (48.8)	44 (35.8)	1 (0.8)	18 (14.6)
Providing individual patient/family teaching	81 (56.6)	41 (28.7)	16 (11.2)	5 (3.5)	122	70 (57.4)	34 (27.9)	0	18 (14.7)
Showing video tapes	16 (11.2)	22 (15.4)	93 (65)	12 (8.4)	38	15 (39.5)	15 (39.5)	0	8 (21.0)
Offering educational classes	13 (9.1)	23 (16.1)	91 (63.6)	16 (11.2)	36	13 (36.1)	13 (36.1)	1 (2.8)	9 (25.0)
Using computer-assisted educational programs	5 (3.5)	22 (15.4)	104 (72.7)	12 (8.4)	27	7 (26)	9 (33.3)	0	11 (40.7)
Counselling/ behavioural interventions									
Training patients during inpatient recovery how to take medications	95 (66.4)	31 (21.7)	8 (5.6)	9 (6.3)	126	67 (53.2)	40 (34.7)	0	19 (15.1)
Teaching patients to use cueing	49 (34.3)	57 (39.7)	28 (19.6)	10 (6.4)	106	36 (34)	51 (48.1)	0	19 (17.9)
Reducing the complexity of the medication regimen	33 (23.1)	72 (50.3)	27 (18.9)	11 (7.1)	105	31 (21.7)	55 (38.5)	1 (1.0)	18 (17.1)
Tailoring medication regimen to patient's lifestyle	44 (30.8)	60 (42)	26 (18.2)	13 (9.1)	104	44 (42.3)	40 (38.5)	1 (1.0)	19 (18.2)
Providing adherence reminders during clinic visits	57 (39.9)	39 (27.3)	24 (16.8)	23 (16.1)	96	35 (36.4)	40 (41.7)	2 (2.1)	19 (19.8)
Providing dispensers for organizing medications	28 (19.6)	61 (42.7)	43 (30.1)	10 (7.7)	91	32 (35.6)	38 (42.2)	2 (2.2)	19 (20.0)
Behavioural counselling intervention	37 (25.9)	47 (32.9)	33 (23.1)	26 (18.2)	84	26 (31)	38 (45.2)	0	20 (23.8)
Recommend reminder systems	21 (14.7)	57 (39.9)	54 (37.8)	11 (7.7)	78	17 (21.8)	41 (52.6)	1 (1.3)	19 (24.3)

Medical counselling by a clinical pharmacist	28 (19.6)	31 (21.7)	72 (50.3)	12 (8.4)	59	25 (42.4)	22 (37.3)	0	12 (20.3)
Establishing adherence contracts with patients	17 (11.9)	36 (25.2)	76 (53.1)	14 (9.8)	53	17 (32.1)	25 (47.2)	0	11 (20.7)
Using reports from electronic monitoring devices as a feedback system	9 (6.3)	7 (4.9)	111 (77.6)	16 (11.2)	16	4 (25.0)	5 (31.3)	0	7 (43.7)
Psychological/ affective interventions									
Involving family or support persons in education and behavioural interventions	73 (51.0)	46 (32.2)	12 (8.4)	12 (8.4)	119	63 (52.9)	40 (33.6)	1 (0.8)	15 (12.6)
Providing telephone assistance if needed	63 (44.1)	48 (33.6)	24 (16.8)	8 (5.6)	111	51 (45.9)	41 (36.9)	0	19 (17.2)
Establishing a partnership with patient and significant other	70 (49.0)	36 (25.2)	13 (9)	24 (16.8)	106	55 (51.9)	34 (32.1)	2 (1.9)	15 (14.1)
Scheduling more frequent clinic visits in case of problems with NA	31 (21.7)	65 (45.5)	30 (21)	17 (11.9)	96	31 (32.5)	49 (51.1)	1 (1)	15 (15.6)
Scheduling calls to patients' homes in case of problems with NA	15 (10.5)	55 (38.5)	52 (36.4)	21 (14.7)	70	28 (40)	29 (41.4)	1 (1.4)	12 (17.2)
Establishing case management services for high-risk patients	22 (15.4)	43 (30.1)	59 (41.3)	19 (13.2)	65	24 (36.9)	23 (35.4)	3 (4.6)	15 (23.0)
Using motivational interviewing	13 (9.1)	33 (23.1)	79 (55.2)	18 (12.6)	46	8 (26.1)	26 (56.5)	0	12 (26.1)
Establishing peer-mentor programs	7 (4.9)	20 (14)	94 (65.7)	22 (15.4)	27	5 (18.5)	14 (48.2)	1 (3.7)	8 (29.6)
Establishing support groups directed at adherence	3 (2.1)	17 (11.9)	102 (71.3)	21 (14.7)	20	3 (2.1)	9 (45.0)	0	8 (40.0)

[1] Cell colours indicate the proportion of nurses who applied the method/intervention in clinical practice

≥75% ≥ 50% ≥ 25% < 25%

[2] Perceived effectiveness was only rated if the nurse used the intervention to enhance medication adherence

NA = Nonadherence

Table 2: Utilization of assessment/screening methods and interventions for nonadherence and their perceived effectiveness

8.8 Discussion

This is the first study to assess nurses' patterns of practice in the field of SCT regarding medication adherence assessment/screening methods and interventions. The results show that in this sample educational interventions are used most frequently and considered most effective by SCT nurses. The two interventions given the highest rankings with regard to usage, were providing reading materials and training patients during their inpatient stay. Providing individual patient/family teaching and providing reading materials were however considered most effective. In clinical practice, nurses used an average of seven adherence-enhancing interventions and each used at least two different intervention types.

8.8.1 Frequency of adherence enhancing interventions used

Overall, the educational interventions most commonly used in this study sample were providing reading materials (79%), providing printed medication instructions (58.7%), and initiating individual patient/family teaching (56.6%). Interestingly, these results echo those of a similar study on solid organ transplantation and cardiovascular care [9, 10]. With an average of 36% of educational/cognitive interventions used by nurses in our sample, this intervention type was most frequently employed. Once again, this intervention type was also most often used by nurses in solid organ transplantation (47%) and cardiovascular care (36%) [9, 10]. However, education alone does not guarantee that a patient will consistently engage in correct medication taking behaviour. Rather, it has been shown that complex programs which utilize multiple interventions delivered over a longer period of time are more likely to achieve better outcomes [14]. It seems possible that these more complex interventions are effective because they address a greater number of the potential barriers impacting a patient's ability to adhere to a therapy and provide reinforcement over time. Therefore, current expert opinions suggest employing individually tailored multi-faceted interventions focusing on a personal system change, i.e., 'a process of systematically improving individual systems through collaboratively shaping routines, involving supportive others in the care, and using medication self-monitoring to change and maintain behaviour' [19]. To give an example, an elderly patient might be at risk of forgetting to take the medication because of memory problems. An effective multi-faceted intervention could be to instruct family caregivers in the administration of the drugs and to use pill-boxes with a reminding system. Further, an adolescent SCT survivor could be at risk for forgetting a dose because of a busy (social) life, here it might be helpful to tailor the medication regimen to the patient's lifestyle (e.g. reschedule taking times) and use SMS reminders. Although most nurses in our sample reported using a variety of actions, we are unfortunately not aware if they also combined the different interventions in individual patient situations.

Consistent with the findings of Berben et al. [9, 10], this study's nurses frequently involved family or support persons in their interventions (51.1%). Our sample's second and third most commonly used psychological/affective interventions were 'establishing partnerships with patients and significant others'

(49%) and 'providing telephone assistance if needed' (44.1%). This is in accordance with Di Matteo's meta analyis (2004) suggesting social support and family cohesiveness considerably improve adherence in several chronically ill patient populations[20]. The applicability of these interventions' to the SCT setting however, warrants further testing since a recent systematic review of 62 trials testing 18 interventions only validated their efficacy in certain chronic conditions (e.g. depression, diabetes mellitus). Interventions that improved adherence across multiple clinical conditions included policy interventions to reduce patients' medication copayments or, systems interventions to offer case management, and patient-level educational interventions with behavioural support [21]. The ecological model of medication adherence explains this perspective. It says that medication adherence can be influenced by three distinct levels of the healthcare system. The micro-level involves patient-healthcare provider interactions (i.e. interventions directly focused at patients), the meso-level concerns the treatment centre or hospital, and the macrolevel encompasses the patient's healthcare system or the society [22].

8.8.2 Perceived effectiveness of used adherence enhancing interventions

Nurses in this survey reported using the strategies they personally considered most effective most regularly. These were 'providing reading materials', 'patient and family care' and 'Involving family or support persons in education and behavioural interventions'. Evidence clearly indicates that interventions with behavioural components are very effective [12, 14, 16-18]. However, many of them were perceived by nurses in this sample as less effective. For example, two thirds of our nurses seldom or never informed patients about reminder systems (e.g. SMS, mobile phone applications) yet results from a recent systematic review revealed evidence for the effectiveness of electronic reminders from eight randomized controlled trials [18]. The intervention used least by our cohort was the application of reports from electronic monitoring as a feedback system. It is likely that electronic monitoring devices were not known and/or not available for many nurses. However, a recent systematic review involving 79 randomized controlled trials showed an average increase of 20 % in medication adherence when electronic monitoring feedback was used as intervention [17]. To conclude, in order to improve medication adherence in SCT, it may be necessary to challenge healthcare professionals' current beliefs and practices and to develop multilevel intervention models which emphasize a patient centred approach and integrate greater behavioural support.

8.8.3 Study limitations

One major limitation of this study was the low response rate, which may have resulted from language barriers, as the questionnaire was only available in English and the conference was also attended by non-native English speaking colleagues potentially lacking the confidence to participate. Additionally, as this was a convenience sample of conference attendees, it might not accurately represent the majority of nurses working in SCT care. Further, only nurses were included in the survey, the perspectives of physicians and other healthcare workers would have added important information.

Regarding our data, certain gaps might have resulted from our respondents' work characteristics. For example, certain interventions would not be feasible for nurses working in paediatric or inpatient care, and as a consequence were marked ‘not applicable’ in our analyses. For future surveys the questionnaire should be refined to consider these aspects and also include questions about the implementation of multilevel interventions.

8.8.4 Implications for practice and future research

As nurses play a key role in assessing, monitoring and supporting patients in their pharmaceutical treatment including adherence to the prescribed medications, it is strongly recommended that the topic of adherence receives greater emphasis in their basic training and continuous education. With the increased use of new treatment protocols, maintenance therapy and oral anti cancer agents in the care of patients with haematological malignancies, nurses' training in medication management support is becoming increasingly important [23]. Early steps in tackling this issue have been taken by the EBMT Nurses Group, who organized several interactive workshops and have recently developed a multilingual nurse tailored information booklet on medication adherence in oral chemotherapy [24] The evidence on adherence enhancing interventions in cancer care and stem cell transplantation is limited [25]. Therefore, future studies should examine the prevalence of medication nonadherence during the stem cell transplant trajectory, identifying the points at which patients' needs are greatest concerning supportive interventions. Multisite interventional studies are needed to investigate the effectiveness of single and combined adherence enhancing interventions in SCT care. Such research is necessary to understand which interventions are consistently effective at facilitating patients' successful medication self-management.

8.9 Conclusions

Medication adherence is a critical factor in the efficacy of any treatment protocol. This study showed that nurses reported using various types of interventions, of which, despite previous studies' findings suggesting limited efficacy, educational approaches were most frequently used. It is therefore proposed that nurses be provided training to facilitate integration of more effective strategies into daily practice, e.g., multi-level behavioural interventions. Finally, as different techniques may be more effective within different patient groups (e.g. adults or children), it is strongly suggested that evaluation of initiated practice be treated as crucial to any initiated interventions.

8.10 References

1. Majhail NS, Rizzo JD. Surviving the cure: long term follow-up of hematopoietic cell transplant recipients. Bone Marrow Transplant 2013; 48: 1145-51.
2. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care 2004; 42: 200-9.
3. Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Evans R et al. Nonadherence consensus conference summary report. Am J Transplant 2009; 9: 35-41.
4. Banning M. A review of interventions used to improve adherence to medication in older people. Int J Nurs Stud 2009; 46: 1505-15.
5. Bishop MM, Rodrigue JR, Wingard JR. Mismanaging the gift of life: noncompliance in the context of adult stem cell transplantation. Bone Marrow Transplant 2002; 29: 875-80.
6. Partridge AH, Avorn J, Wang PS, Winer EP. Adherence to Therapy With Oral Antineoplastic Agents. Journal of the National Cancer Institute 2002; 94: 652-661.
7. Noens L, van Lierde MA, De Bock R, Verhoef G, Zachee P, Berneman Z et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. Blood 2009; 113: 5401-11.
8. Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. CA Cancer J Clin 2009; 59: 56-66.
9. Berben L, Bogert L, Leventhal M, Fridlund F, Jaarsma T, Norekvål T et al. Which interventions are used to enhance medication adherence in cardiovascular patients? A survey of current practice. Eur J Cardiovasc Nurs 2011; 10: 14-21.
10. Berben L, Dobbels F, Kugler C, Russell CL, De Geest S. Interventions used by health care professionals to enhance medication adherence in transplant patients: a survey of current clinical practice. Prog Transplant 2011; 21: 322-31.
11. De Bleser L, Matteson M, Dobbels F, Russell C, De Geest S. Interventions to improve medication-adherence after transplantation: a systematic review. Transplant International 2009; 22: 780-797.
12. Conn VS, Hafdahl AR, Cooper PS, Ruppar TM, Mehr DR, Russell CL. Interventions to improve medication adherence among older adults: meta-analysis of adherence outcomes among randomized controlled trials. Gerontologist 2009; 49: 447-62.
13. Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. Cochrane database of systematic reviews 2002: CD000011.
14. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. Cochrane database of systematic reviews 2008: CD000011.
15. Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. Interventions to enhance medication adherence. Cochrane database of systematic reviews 2005: CD000011.

16. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. Jama 2002; 288: 2868-79.
17. Demonceau J, Ruppar T, Kristanto P, Hughes DA, Fargher E, Kardas P et al. Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. Drugs 2013; 73: 545-62.
18. Vervloet M, Linn AJ, van Weert JC, de Bakker DH, Bouvy ML, van Dijk L. The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature. J Am Med Inform Assoc 2012; 19: 696-704.
19. Russell CL, Ruppar TM, Matteson M. Improving medication adherence: moving from intention and motivation to a personal systems approach. The Nursing clinics of North America 2011; 46: 271-81.
20. Di Matteo MR. Social Support and Patient Adherence to Medical Treatment: A Meta-Analysis. Health Psychology 2004; 23: 207-218.
21. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. Ann Intern Med 2012; 157: 785-95.
22. Berben L, Dobbels F, Engberg S, Hill MN, De Geest S. An ecological perspective on medication adherence. West J Nurs Res 2012; 34: 635-53.
23. Wood L. A review on adherence management in patients on oral cancer therapies. Eur J Oncol Nurs 2011; 16: 432-438.
24. European Group for Blood and Marrow Transplantation. Nursing education. In: Retrieved October 6th, 2012, from http://www.ebmt.org, 2011.
25. Mathes T, Antoine SL, Pieper D, Eikermann M. Adherence enhancing interventions for oral anticancer agents: A systematic review. *Cancer treatment reviews* 2014; **40:** 102-8.

CHAPTER 9:

DISCUSSION

9.1 Synthesis, discussion and perspectives

Even years after allogeneic stem cell transplantation, recipients face a continuing risk of developing serious late effects [1-3]. These effects, which often cause considerable discomfort, contribute to mortality rates 4 to 9 fold higher than observed in the age adjusted general population, and life expectancies 30% lower than average [4, 5].

To improve these figures, previous studies have focused on the pathophysiological understanding of late effects, as well as on treatment and disease related prediction of long-term complications. Their findings have helped clinicians and researchers to improve stem cell transplantation techniques and develop enhanced supportive care strategies [6]. Accompanying these developments, patients have been recognized as an invaluable source of information on the evolution of their conditions. Particularly over the past decade, patient-reported outcomes (PROs) have been increasingly incorporated into clinical care and research [7, 8]. To date, however, few studies have used PRO data to focus on patients' perspectives of late effects, symptom experiences or self-management strategies. Indeed, at the time of our preliminary research, no PRO instrument yet existed to measure late effect symptom experiences, and no investigations had yet focussed on components of patient self-management, i.e., their day-to-day management of chronic conditions to maintain daily life activities and improve health behaviours [9, 10]. However, to optimize patients' self-management, PRO instruments offer unique insights into both their experiences of long-term post-transplant symptoms and their health behaviours [11].

SCT survivorship begins with an intensive acute care episode, which then shifts to a life-long follow-up process. To prevent deterioration, to prevent, delay or minimize late effects, and ultimately to reduce morbidity and mortality, patients must engage actively and continuously in self-management tasks[12, 13]. To these ends, PRO instruments can be used to monitor adherence to preventive measures, enhance early detection techniques, and determine treatment options for symptomatic late effects and other chronic conditions. Because worsening of chronic health conditions (≈ late effects) could be related to patient's lifestyle choices, self-management is a topic, which demands in-depth exploration [11, 14, 15].

The research program of this doctoral thesis contributes in various ways to the evidence base regarding SCT patients' self-management in view of symptom experience and lifestyle. More specifically, this thesis consists of six research papers, each addressing a specific aspect of these topics.

The first paper **(Chapter 3)** illustrated the value of using PROs to gather patient perspectives on the experience of a haematological disease-exemplified in immune thrombocytopenia and summarized the steps necessary to develop an effective PRO instrument. It also discussed challenges to the integration of PROs into research and clinical practice.

The second **(Chapter 4)** described the development of the PROVIVO instrument – a new PRO instrument developed to measure late-effect symptom experience. Based on the PRO-CTCAE item library, the PROVIVO instrument was designed, refined, and prepared for use in its target regions according to Food and Drug Agency (FDA) guidance for PRO instrument development[16] and state-of-the-art recommendations for translation[17]**.** Using the PRO-CTCAE item library allowed the efficient compilation of a SCTspecific item bundle broadly applicable for late effect symptom screening and resulting in immediately actionable data. Throughout the development process, we involved patients as well as expert clinicians. To test the clarity and acceptance of item terms in the user population, we applied cognitive debriefings, the results of which demonstrated that items were fully understandable and relevant to the SCT survivor experience [18, 19].

In our third paper **(Chapter 5)** we reported on the refinement and preliminary validity testing of the newly developed PROVIVO instrument. Focussing on construct validity and relations to other variables, preliminary validity was explored in accordance with the "Standards for Educational and Psychological Testing" [20]. An exploratory factor analysis revealed an eight-factor model explaining 57.05% of variance. Cronbach's alphas indicated that internal consistency reliability was good for the entire scale (0.90), but only acceptable for the eight factor scores (0.53-0.82). Additional evidence supports relations between variables, e.g., between the number of symptoms and cGVHD occurrence, and between the number of late effects and performance status.

The PROVIVO instrument is a PRO instrument efficient and versatile enough to assess late effect symptom experiences in diverse clinical and research contexts, and which can easily be integrated into clinical information systems. Further research is recommended to test its value for at least five additional uses: (1) assessing symptom experience throughout the survivorship trajectory and identifying treatable problems; (2) improving communication and shared decision making between patients and healthcare professionals; (3) distinguishing between symptom patterns based on late effect types; (4) informing decisions about proposed changes to treatment plans; and (5) monitoring intervention responses.

Our fourth article **(Chapter 6)** identified and described considerable differences between SCT patients' health behaviours and those of the general Swiss population, including several specific issues in medication taking behaviour. To our knowledge this was the first study to provide population-based data on the prevalence of health behaviours among SCT survivors in Switzerland. One particular strength was its case-match control design, i.e., via propensity scoring, each survivor was matched with a control from a representative sample of the Swiss population [21]. The results were mixed: survivors were most likely to adopt beneficial health behaviours regarding not smoking and low alcohol consumption; however, relative to the general population, a considerable group engaged in unfavourable behaviours, particularly regarding physical activity and diet. These findings indicate a need for targeted interventions to promote a healthy lifestyle after SCT.

Among health behaviours, medication adherence to immunosuppressants (IS) is crucial: correct intake is essential to prevent and treat cGVHD. As no previous study had investigated the prevalence and consequences of post-SCT medication nonadherence (MNA), our fifth paper **(Chapter 7)** focussed on medication nonadherence and its associations to cGVHD. For the first time, we showed a relation between medication nonadherence and cGVHD grade, thereby highlighting a need for targeted interventions. In particular, patients prone to taking nonadherence and dose reduction were more likely to have moderate or severe cGVHD. We also found that those taking higher numbers of IS medications were more likely to be non-adherent. The converse was also true: IS nonadherence was less prevalent among those taking fewer co-medications.

As reducing MNA prevalence demands a clear understanding of healthcare providers' medication self-management support practice patterns, these were the focus of our sixth and final paper **(Chapter 8).** Concerning nurses' assessment and support of medication adherence, our evaluation of their current practice patterns showed that they most often applied educational strategies. However, state-of-the-art evidence suggests that educational interventions alone have limited efficacy, favouring instead a combination of educational, behavioural and psychological interventions [22, 23]. Therefore, resources devoted to optimizing healthcare providers' adherence support competencies would be a worthwhile investment.

Overall, rather than continuing to treat SCT survivorship according to the traditional acute-care paradigm, our findings support the integration of a chronic care model. Based on our findings, with a strong focus on practice implications, the remainder of this chapter proposes such a model. The final sections will deal with the model's policy implications and present suggestions for further research.

9.2 Proposing a new chronic care framework for survivorship

Regarding symptom management and health promotion, survivorship care should build on the chronic care paradigm, particularly self-management support, enabling patients to increase their control over and improve their health.

SCT's impact and lingering late effects have life-long consequences concerning survivors' daily lives [24-27]. With on-going survivorship, then, patients must assume increased responsibility for managing their follow-up care. Recognizing the magnitude of this job, the Institute of Medicine (IOM) report `From Cancer Patient to Cancer Survivor: Lost in Transition` outlines a survivorship care continuum based on four pillars [28]:

1. Prevention of new (primary) and recurrent cancers and late effects
2. Surveillance for recurrence or new cancers
3. Interventions for consequences of the cancer and its treatment (including physical consequences of symptoms such as pain and fatigue, psychological distress experienced by cancer survivors and their caregivers, and concerns related to employment, insurance, and disability)
4. Co-ordination between healthcare providers to ensure that survivors' health needs are all met.

The report recommends using systematically developed evidence-based clinical practice guidelines, assessment tools, and screening instruments to identify and manage late effects of cancer and its treatment. Further, it includes several specific recommendations on such topics as implementing quality measures for survivorship, supporting and developing new models of care coordination, educating healthcare providers, ensuring access to affordable care and integrating treatment summaries and survivorship care plans into survivorship care [28].

Equally importantly, it clearly describes the problem of shifting cancer care from a predominantly acute treatment system to one that embraces both effective/curative treatment of the disease ***and*** the care/management of long-term secondary effects. Still, in many cases, SCT follow-up care remains largely organized around acute episodes of illness and might not meet survivors' ongoing medical and psychosocial care needs [29]. Challenges to optimal care for SCT survivors include inadequate communication and coordination between SCT centres and community healthcare providers, lack of awareness of screening and prevention guidelines, insufficient financial and personal resources for survivorship care and the absence of tools to facilitate survivor care [30, 31]. It is assumed that delivery of optimal quality healthcare results in superior clinical outcomes [30-33], i.e., that patient outcomes will vary depending on how effectively centres manage their follow-up care. For example, in an observational multicentre study, Loberiza et al. have shown that the presence of physicians answering after-hours calls and a higher physician-per-patient ratio were associated with decreased 100-day post-SCT mortality among US transplant centres [34]. It can be hypothesized that other elements such as the integration of a patient self-management support approach will also positively influence outcomes.

In fact, most SCT centres still organize survivorship care reactively, i.e., becoming involved mainly when a patient becomes ill. Considering the high cost of acute treatment in comparison to those of on-going preventive measures, there is a clear need for a new model of SCT survivorship care – a proactive chronic care system based on lasting clinician-patient partnerships and focused on keeping patients as healthy as possible [35].

As one excellent example of such a system, providing guidance for healthcare organizations to improve chronically ill patient care, is Wagner et al.'s Chronic Care Model. Based on the principle that patients and healthcare providers share responsibility for problemsolving and outcomes during the care process [36, 37], this model consists of six building blocks (*1) healthcare system; 2) community;*

3) delivery system design; 4) clinical information systems; 5) decision support; and *6) self-management support*), and can be applied to a wide range of chronically ill populations. Increasing evidence from different patient populations supports implementing the model's components [38-45]. Related interventions can focus on three dimensions: the general community and its healthcare system (macro level), the healthcare institution (meso level) and the patient-health care provider interaction (micro level). Upon closer examination of Wagner et al.'s six building blocks, assuming that the healthcare system supports the improvement of chronic illness care, it must also be prepared to accept a system-wide reorganization. One important element of the updated system, partnerships with community organizations to support and develop interventions, will fill gaps in needed services.

Clinical information systems ensure timely access to key data both to individual patients and to patient populations. The datasets can be used for multiple purposes, including benchmarking, quality improvement and research. For example, by providing timely automated reminders for needed services, along with summaries of core data to plan and track care, a comprehensive clinical information system can greatly enhance individual patient care [9, 46, 47].

Decision support is provided through evidence-based guidelines that incorporate patients' perspectives and are integrated via reminders into efficient clinical information systems. As those involved in treatment decisions need ongoing training, the guidelines also suggest methods of staying up-to-date with the latest evidence [9, 46, 47].

Self-management support has evolved beyond the practice of merely providing information and increasing patient knowledge to include support for patients' health behaviour improvement, activities of daily life and day-to-day management of their conditions. Self-management support includes the use of proven programs that provide essential information, emotional support, and strategies for living with chronic illness conditions [9, 46, 47].

The delivery system design assures the delivery of effective, efficient clinical care and self-management support. This requires not only determining what care is needed, but clearly defining roles and tasks to ensure patient care via structured, planned interactions at regular intervals. To optimize both clinical care and self-management, patients whose needs are more complex may require periods of more intensive attention [9, 46, 47].

Based on the above reflections on the IOM [28] report, the Chronic Care Model [46,47] and its multi-level applications [48], we created the SCT Survivorship Care model. This care model is designed to facilitate productive interactions between informed patients and supportive healthcare providers, particularly concerning the key elements of cancer survivorship follow-up, i.e., prevention, surveillance, interventions, and coordination [28]. As a practical basis for these actions, it also incorporates four of the Chronic Care Model's six building blocks: 1) clinical information systems; 2) decision support 3) self-management support; and 4) delivery system design.

The third inner layer includes important tools for enhancing the quality of survivorship care as recommended by the IOM and leading associations [28, 30-33, 49, 50]. The model's implications regarding the micro, meso and macro levels of the healthcare system are also depicted.[48] At the micro-level, interventions can focus either on individual patients or on the relationships between patients, care-givers and healthcare professionals. Meso-level interventions deal with healthcare settings; and those at the macro level are aimed at public policy makers and society in general. Each level influences each of the others.

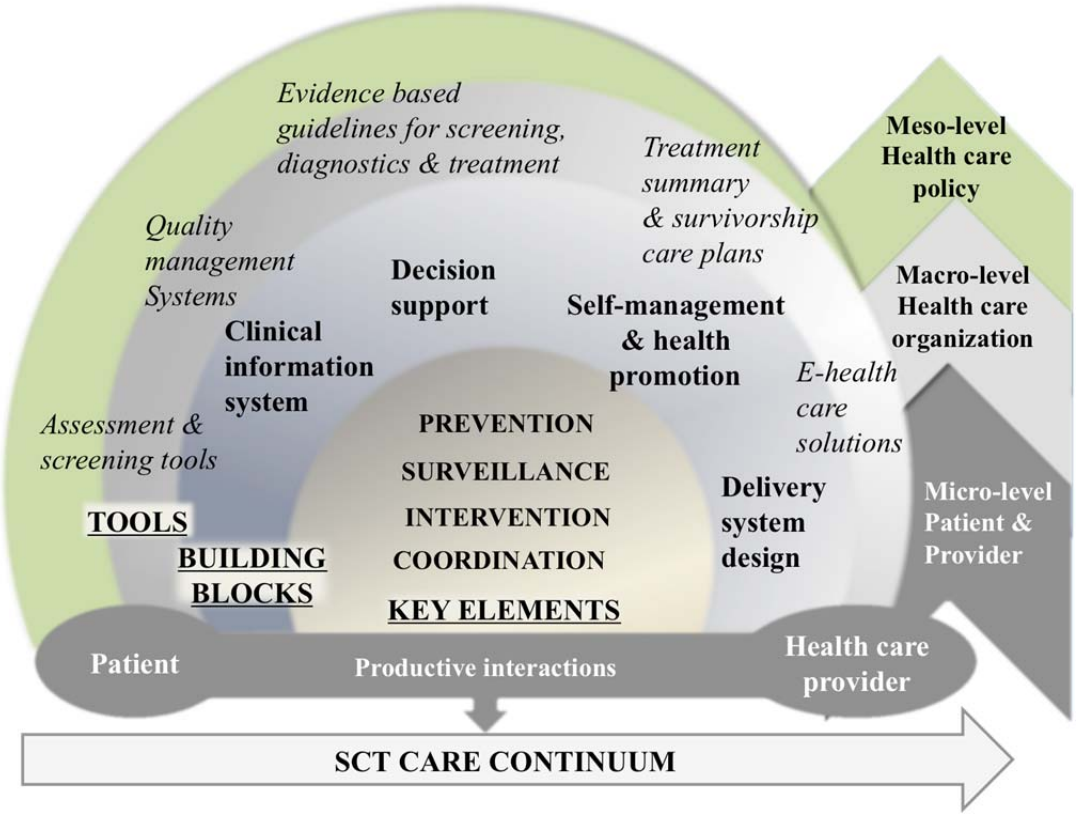
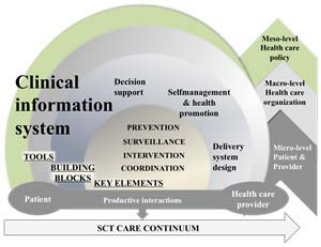


Figure 1: The SCT Survivorship Care Model

The findings of the PROVIVO research program support a systemic change to a chronic care SCT survivorship approach. Therefore, the following four sections provide a detailed discussion of the program's findings in light of the SCT Survivorship Care Model.

9.3 Clinical information systems



Clinical information systems assure ready access to key data on individual patients as well as populations of patients [9,10].

Integrating patient perspectives of late effect symptom experience and self-management into the clinical information system can be highly informative for understanding the consequences, safety and effectiveness of treatment.

Based on our adapted SCT survivorship care model, effective clinical information systems offer quick access to key data on individual patients and populations, include reminder systems, and facilitate performance and quality improvement monitoring [9, 46, 47]. Therefore, the integration of PRO data – both on symptom experience and selected health behaviours – to these systems will reveal valuable information.

Traditionally, for most clinical trials, data collection begins with investigators recording adverse events in medical charts, after which data managers transfer it into databases. Similarly, during clinical care, healthcare providers elicit and document information about side effects in patient charts. These include symptoms such as nausea, pain, fatigue, or sleep disturbances, most of which the patient could provide directly via a PRO questionnaire [51]. In addition to information on symptoms and reactions, questionnaires can include direct questions on health behaviours, thereby allowing important inferences concerning treatment effectiveness. For instance, in a case of non-response to immunosuppressants, a single item or scale might reveal that the underlying issue is nonadherence.

As clinicians and researchers, our work with SCT patients has to be set in relation to current developments in PRO instruments used in research and in cancer care. Recently, interest has emerged in the use of PRO measures directly integrated in clinical information systems – a concept which could provide novel opportunities for clinical practice *and* research [52]. In particular, innovative PRO applications within the broader context of patient-centeredness have recently emerged, reflecting a growing focus on the patient experience in clinical research and care delivery [53, 54]. According to the FDA [16] and the Patient-Centered Outcomes Research Institute [55], PROs should be increasingly used for (1) assessment of adverse events and side effects, (2) comparative effectiveness research, and (3) care quality assessment [56].

Each of these areas has become a focus of innovations in the logistics and science of PRO data collection, e.g., electronic interfaces (websites, tablet computers, or automated telephone systems). New information technology can also facilitate care sharing among healthcare providers, are available at low cost and can hugely accelerate information processing. PRO assessments can be tailored to specific

groups, and information and/or problem-solving strategies that focus on priorities can be delivered directly by healthcare providers, via websites or text messaging [52]. Also, via repeated PRO assessments, interventions can be evaluated and modified [50]. Additionally, a single PRO data source can be used for multiple purposes. For example, information based on PRO data collected through electronic patient records can be used to manage individual patient needs, or aggregated for safety surveillance systems, effectiveness research, and care quality assessments. More broadly, the emerging interest in PROs across healthcare contexts reflects a growing awareness that the patient perspective can be highly informative concerning the effectiveness, safety, and value of treatments [57].

In the PROVIVO instrument we have developed an important PRO instrument for measuring late effect symptom experiences. While it can easily be integrated into an SCT centre's clinical information system, the version currently exists only as a paper-pencil questionnaire. Converting it to an electronic format will require additional development and testing for validity and equivalence to the original paper-and-pencil version [58, 59]. When available, in addition to enhancing care delivery, an electronic PROVIVO version should be usable for multiple analytic purposes.

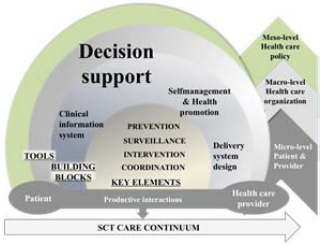
In this respect, Wood et al. (2013) provided important evidence regarding the feasibility of weekly-collected electronic PRO-CTCAE patient reports. The authors tested the feasibility of the clinical information system by using 34 symptom severity PRO-CTCAE items in 32 SCT patients during the first 100 days following transplantation. Offered a choice between paper-and-pencil and electronic reporting, the vast majority (94%) of patients chose the electronic system. Although patients were in the intensive acute SCT treatment phase, the median weekly response rate remained at 100% until discharge. Patients were satisfied with the questionnaire's readability, comfort, and content [60].

Further research supported the feasibility and credibility of integrated PRO symptom or quality of life assessments in clinical information systems in cancer care. In particular, positive effects were shown regarding patient-provider communication, patient satisfaction with care, and detection of unrecognised problems. Additionally, real-time PRO symptom assessment systems with integrated alarms and reminder systems improved treatment response monitoring.[61, 62] In terms of health behaviours, PRO information allows the care team to deliver proactive follow-up care and self-management support via effective reminder systems, performance measures providing feedback, and initiation of targeted interventions. However, if health behaviour assessment – an integral part of clinical information systems – is intended to improve patient outcomes, it must be connected with effective behavioural change/enhancing interventions [63].

To conclude, innovative clinical information systems should integrate PRO measurement in routine survivorship care. PRO datasets are increasingly used for multiple purposes: with growing benefits for quality of care and research on comparative effectiveness, they already contribute strongly to symptom experience and health behaviour assessments. However, while the current evidence is

promising, future research will be necessary to verify the effectiveness of interventions using PRO data collection in SCT or other survivorship programs.

9.4 Decision support



Following evidence-based guidelines, decision support hinges on patient perspectives and is integrated into daily clinical practice through reminders. [9,10]

Obtaining information on symptom experience and self-management problems via self-reporting is fundamental to decision making in SCT care.

Evidence-based practice guidelines provide standards for optimal chronic care and should be integrated into daily clinical practice through automated reminders [9]. However, while SCT-specific guidelines exist [64], no tools are yet available to improve their usage, such as reminder systems, feedback loops, and printed information materials for healthcare providers and patients [46, 47]. Also the current research program's PRO information on symptom experience and relevant health behaviours can offer important information which could be included in the development of such tools.

Clinical decisions regarding triaging for self-management interventions (e.g., smoking cessation), monitoring for problems in treatment efficacy (e.g., medication adherence), therapy changes (e.g., reduction of IS doses to reduce tremors), or supportive therapy (e.g., analgesic medication), all depend on information available via PROs. Also, patient-reported changes in symptom occurrence and distress can indicate whether an intervention is working.

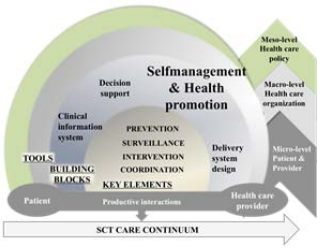
With the development of the PROVIVO instrument we offer a promising tool with the potential to guide clinical decision-making. Its two-dimensional reporting of symptom occurrence (frequency, severity) and distress are a particular strength [65]. For example, after completion of treatment, patients might feel unprepared for the occurrence of new symptoms and limitations, and might have difficulty interpreting their significance. For these patients, it is often unclear whether symptoms are due to a new illness, disease recurrence, or simply lingering effects, the uncertainty of which might cause symptom distress [66, 67]. Even survivors in complete remission or maintenance are frequently concerned about possible signs of relapse [68].

For example, responding to the PROVIVO questionnaire, a patient treated for a mantle cell lymphoma reported itching which, though *mild,* was severely distressing for him. Based on his self-report, topical treatment and further blood tests were initiated. Asking about his symptom distress, the nurse administering the instrument learned that he had experienced itching in the past, with the first diagnosis of his lymphoma. Therefore, additional emotional support by a psychologist could be arranged. This case illustrates how the PROVIVO can help a healthcare team make meaningful clinical decisions.

To effectively guide the decision-making process in survivorship care, PRO data should be embedded in a clinical information system, which triggers automatic reminders for healthcare providers to initiate appropriate interventions. Used alongside electronic symptom monitoring, such alerts have proven effective in several cancer follow-up studies [69, 70], and can also be used in behavioural interventions.

For the future, there is abundant room for further progress regarding electronic PRO reporting for decision support. Ideally, features should include simple interfaces, reminders to patients to self-report, and alerts to clinicians concerning interventions. Clear illustrations of longitudinal symptom and health behaviour trajectories, notifications to staff when patients miss scheduled self-reporting appointments, and triggers for patient self-management interventions would also be important elements of such a system. The easier it is for healthcare providers to work with PRO information, the more likely it is that they will adopt it as a tool for clinical decision making in SCT survivorship care.

9.5 Self-management support and health promotion



Self-management aims at supporting patients in their day-to-day management of chronic conditions, to maintain daily life activities and to improve health behaviours. It acknowledges the patients' central role in their care and includes the use of proven intervention. [9,10]

Our study's findings indicate the need for self-management interventions as an integral part of SCT survivorship care.

Considering the increasing longevity of the SCT survivor population–and the consequent growth of that population – [71], the work described here emphasizes self-management's central role concerning our SCT Survivorship Care Model. In particular, by supporting symptom management and healthy

lifestyle patterns, self-management has a high potential to delay or prevent new, secondary and tertiary morbidities [11]. Our findings revealed high numbers of symptoms in a significant number of patients, indicating the need to integrate symptom management into self-management support. Furthermore, regarding lifestyle choices, several contraindicated behaviours were detected, including low physical activity, a diet low in fruits and vegetables, and medication nonadherence. However, only smaller subgroups of patients persisted in unfavourable behaviours regarding smoking, elevated alcohol consumption and unprotected sun exposure.

In addition to reducing proven risk factors, primary disease prevention includes developing healthy behaviours, such as improving nutrition and increasing physical activity. Secondary prevention strategies include reporting for scheduled follow-up tests, participating in suggested interventions, receiving recommended vaccinations, responding to reminders to address follow-up care plans and actively supporting medication management. Finally, in addition to medical management of late effects, tertiary prevention relies heavily on patient involvement, especially via self-management activities, e.g., symptom reporting and management or adherence to medical and dietary recommendations. Strategies for these three levels of prevention certainly overlap. For example, supporting medication adherence has implications in both secondary (e.g., preventing cGVHD) and tertiary prevention (e.g., reducing the risk of disease elevation) [11, 72].

Of the full range of recommended preventive self-management activities, four have been proven to contribute outstandingly to a longer and healthier life: adequate physical activity, healthy diet, non-smoking, and moderate alcohol consumption. Evidence from the general population clearly indicates that their benefits include slowed progression of existing chronic conditions and decreasing mortality.[73] Compared to people who engage in none of these behaviours, a large-scale prospective study (N= 23.125) demonstrated that participants who engaged in all four were 66% less likely to die early from cancer, 65% less likely to die early from cardiovascular disease, and 57% less likely to die early from other causes [74].

Apart from observational descriptions of long-term post-SCT health status [2, 6, 75-77], little research has examined health behaviours' impacts on morbidity and mortality in this patient group. It has been acknowledged, however, that regular physical activity results in reduced fatigue and an attenuated risk of developing diabetes or cardiovascular conditions, while lower fruit/vegetable intake is associated with greater risk of dyslipidaemia and diabetes [78], and non-smoking correlates with fewer days of hospitalization and better overall survival [79]. Among CML patients who received SCT, the 5-year survival rate was highest among non-smokers (68%), compared to low-dose smokers (1-9 pack-years: 62%) and high-dose smokers (>10 pack years, 50% survival) [80].

To date, no intervention study has examined self-management and health promotion in long-term post-SCT patients. However, systematic reviews and meta-analyses of self-management and health promotion interventions in solid tumour cancer survivor populations indicate promising results

[14]. Physical activity interventions have shown beneficial effects on diverse aspects of health-related quality of life including emotional well-being and social functioning, and also against diverse symptoms such as sleep problems, fatigue, and pain [81]. Further results suggest that physical activity interventions are safe for cancer survivors, producing improvements in fitness, strength, physical functions, and, alongside dietary interventions, nutrition-related biomarkers and body weight. Preliminary evidence also suggests that combining interventions to target diet and exercise concurrently may positively influence biomarkers associated with progressive disease and overall survival (e.g., insulin levels, oxidative DNA damage, tumor proliferation rates) [82-84]. However, in both short-term and long-term follow-up groups, findings on smoking cessation interventions remain inconclusive, as a meta-analysis could not show a consistent decrease in the prevalence of smokers [85].

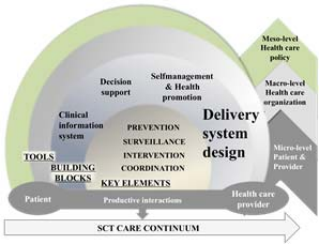
Regarding adherence enhancing interventions aimed at cancer survivor populations, the few available results are conflicting. Of the six published studies on the topic, only one employing education, pill shaping and restructuring of the physical environment showed a significant benefit [86]. And while results on symptom management and survivorship concerns are similarly rare, positive results have been shown for provider-patient-communication enhancement, lowering symptom distress and improving emotional well-being [61, 87, 88].

Overall, research has demonstrated that, after cancer diagnosis, individuals who improve their self-management and health behaviours feel better, experience less fatigue, and may even decrease their risk of cancer recurrence [84, 89, 90]. Still, the effectiveness of interventions may be affected by multiple mediating or moderating factors, e.g., patient age (current and at diagnosis/treatment), genetic risk profile, and concurrent symptom experience. Clearly, more intervention research is needed to identify effective means of supporting SCT survivors to enact and maintain meaningful improvements in their self-management behaviours.

However, what is the optimal time to initiate self-management support? And which components should be included in an inventory of self-management interventions? Certainly, self-management support is a continuous process. Although the period immediately following cancer diagnosis has been called a "teachable moment," as it is a period when patients are thought to be particularly receptive to enhancing health behaviours [91, 92], the literature indicates that, after initial signs of progress, many survivors relapse into unhealthy behaviour patterns, with only a subgroup proving capable of significant long-term behavioural changes [93]. Intervention timing (i.e., *which intervention in which follow-up phase?*) and intensity (i.e., *how much intervention is needed to improve a specific behaviour?*), as well as channels of delivery (e.g., *what member of the care team is responsible for what? which media will be most effective?*) must be carefully considered in developing programs to meet the needs of this vulnerable population [94].

Finally, all self-management support in survivorship care programs should emphasize the patient's central role, i.e., the net value of any such program depends directly on the extent to which patients' needs are met. Therefore, on one hand, SCT patient support should reflect topics that impact survivors' health; on the other, it should consider the patient's concerns and restraints, e.g., a high symptom burden. The long-term effects of SCT involve stress not only for patients but also for their families. Therefore, self-management interventions should also recognize the concerns of family or partner caregivers, who have to deal with uncertainty, adapt to changing roles, and balance patient needs against their own [95].

9.6 Delivery system design



The delivery system design assures the delivery of effective, efficient clinical care and self-management support. That requires determining tasks and roles for ensuring the patient gets optimal care using structured, planned interactions between providers. [9,10]

The findings of this study indicate a need to change from the current care delivery system to one that considers the shifting balance between acute and chronic healthcare needs in SCT patients.

The integration of a chronic care approach to SCT survivorship requires a new care delivery model – one which redefines both service arrangements and coordination of the involved multidisciplinary healthcare providers. To assure that each SCT survivor receives appropriate and comprehensive care, the necessary actions (including assessments, treatments, and supportive interventions) should be planned, coordinated, and delivered by a multidisciplinary team [35]. The new care delivery system must provide survivors with access to appropriate evidence-based treatment, while organizing all necessary services in a timely and technically competent manner, with clear communication and shared decision-making between patients and healthcare providers across the entire survivorship continuum [30, 32, 96]. Care should follow survivorship care plans, which also guide disease and late-effect surveillance and specify appropriate self-management actions [33].

Increasing evidence in chronically ill patient populations supports the effectiveness and implementability of a delivery system change towards a collaborative chronic care approach [38-45]. As an example, Bissonnette's (2013) prospective quasi-experimental study illustrated how a successful system change can improve kidney transplant recipients' self-management support. The study's results were promising: participating patients were more likely to attain targeted clinical outcomes (e.g.,

improved blood pressure, favourable renal function) and participate in discussions about treatment options, and required fewer emergency room visits and rehospitalisations [40].

Replacing the current SCT care system with a collaborative chronic care approach will require interventions at all levels of the healthcare system: public officials will need to redraft policies (macro level), healthcare institutions (meso level) will need to reallocate resources, and the direct clinical practitioners (micro level) will need to refocus on long-range care objectives. This section will focus on the micro and meso levels, providing an example of a possible self-management intervention for SCT patients; the next section will illustrate the implications at the policy level.

At the patient care level, an advanced practice nurse would coordinate the care program and the collaboration of the multidisciplinary team. Tools and interventions would be implemented based on the SCT Survivorship Chronic Care Model. In addition to the currently-used physical examinations and laboratory tests, patients would be asked to complete PRO self-management assessments at defined intervals. These would cover symptom experience (via the PROVIVO instrument), a comprehensive set of health behaviour tasks (e.g., regarding medication taking, smoking, weight control, physical activity and diet) and additional supportive care needs. Each patient would also receive a survivorship care plan [33], which would be discussed with an advanced practice nurse in a regularly scheduled counselling session.

Based on the survivorship care plan, the self-management assessments, and any issues that might arise, subsequent individually-tailored interventions would be initiated [94]. Symptom management strategies would follow state-of-the-art practice guidelines.[64] Behavioural interventions should be chosen in accordance with Michie et al.'s taxonomy, combining cognitive/behavioural and psychological interventions to draw upon skill development and consolidation of favourable behaviours [23, 97-99]. Motivational interviews, combining brief written (one page) instructions with oral instructions to shape the patient's knowledge, support goal-setting, and provide advice on behavior self-monitoring [100] would be the most often applied interventions.

As medication management support should be a major component of the intervention program, multiple support strategies, e.g., reminders to take medications regularly, dose modifications and special packaging, should focus on this topic [23, 97-99]. Additional use of an electronic Medication Event Monitoring System (an electronic pill box that records the date and time of each removal of the cap) could provide feedback data for patients to track their medication taking progress [101-103].

The intervention would reflect an institutional (meso-level) policy outlining the specific roles and tasks of the team members. The healthcare providers would meet weekly for interprofessional patient rounds. During these conferences, additional measures would be implemented and ongoing educational training offered.

In summary, we see a definite need for a change in the current system of survivorship care delivery to reflect the chronic nature of SCT survivorship. In our opinion, a nurse-led collaborative care approach would have the most potential to improve SCT patients' clinical outcomes. However, this conclusion should be further tested in a randomized controlled trial.

9.7 Policy implications

Our findings imply that self-management support, focussing on both symptom management and health behaviour promotion, should be implemented as an integral part of SCT survivorship care.

This doctoral thesis has far-reaching implications for clinical practice and for health policy. This section follows on previous illustrations of a possible advanced practice nurse-led multicomponent self-management program for SCT survivors. To implement such a system change will require action across all healthcare levels. As implications on the micro and meso level have been described above, this section will focus on the actions necessary on the macro level of the Swiss healthcare system. Three main issues should be addressed by policy initiatives: (1) promotion of policy changes to support the implementation of a comprehensive survivorship care program: (2) legislation and promotion of education and training programs for healthcare professionals working in survivorship care; (3) educational public health initiatives promoting health behaviours proven to lower the risks or ameliorate the effects of various chronic diseases.

9.7.1 Promotion of policy changes that support the implementation of comprehensive survivorship care programs

One major barrier to the widespread implementation of comprehensive SCT survivor care programs is the lack of cost-coding and reimbursement for self-management interventions. Switzerland has a mandatory health insurance system which covers costs for follow-up consultations and medication [104]. However, as the current policy favours paying for acute physician-led care, nurses are not reimbursed for executing self-management interventions in the outpatient setting. This increases the risk of costly and avoidable patient transitions to and from acute care facilities. To adequately recognize and compensate nurse-led services – including self-management interventions – in outpatient settings, and to support the development and evaluation of an efficient and effective chronic care paradigm, changes to the current reimbursement legislations are essential. This would support the development of continuous survivorship care programs focussed on care planning, self-management enhancement, prevention, and late-effect management.

9.7.2 Education programs for healthcare professionals working in survivorship care

Our fifth study revealed that the most commonly used strategies to support patient medication-taking self-management were educational/cognitive. However, knowledge alone may not be sufficient to change deeply impressed habits. Instead, drawing upon skill development and consolidation of favourable behaviours, combinations of cognitive, psychological and behavioural interventions more effectively engage patients in their own medication management [22, 23, 97, 105, 106].

Cancer follow-up provides an opportune time for clinicians to counsel patients on health promotion; however, self-management support is not yet regularly implemented in most survivorship clinics [15]. One possible explanation is that, since few graduate health science curricula include modules on innovative behavioural interventions, proportionally few clinicians have the knowledge and training to provide them [107]. If this is true, it highlights a serious gap in the competencies of the healthcare professionals who deal with cancer survivors' emerging and evolving needs for on-going chronic care [108, 109].

Developing and running state-of-the-art survivorship care programs will demand a clinical work force appropriately skilled to provide services based on a chronic care approach [32]. To date, most healthcare professionals working in survivorship care have developed their skills and competences on an ad-hoc basis, and few institutions offer associated online courses [110] or post-graduate training programs [111]. Still, pioneer examples of curriculum based survivorship training programs for healthcare professionals are currently running [112-115].

Clearly, political, educational and institutional efforts are urgently needed to develop post-graduate and continuous education programs for survivorship care. The first step is to define the required skills. As introduced in the current study, the SCT Survivorship Care Model provides guidance on the key components of cancer survivorship chronic care. These include the use of appropriate assessment instruments, development of individualized treatment summaries and care plans, promotion of health behaviour self-management skills, provision of information and behavioural change techniques, cooperation within the multidisciplinary team to optimize comprehensive care, and provision of care guided by evidence-based practice guidelines [112-115]. Since nurses will play a major role in future survivorship care, it is especially important that educational and organizational leaders support their preparation by providing on-going education and training [35, 116].

9.7.3 Public health initiatives dealing with health behaviours and chronic diseases

While the two issues addressed above dealt with the implications of a chronic care approach to SCT care delivery, the third addresses primary and secondary prevention of chronic diseases in the general society, and would therefore contribute indirectly to SCT survivors' health function. Observing health behaviour trends in the general population, western healthcare systems face several problems in terms of smoking, alcohol consumption, and diet-related imbalances [117].

In particular, sedentary behaviours and high density diets are major factors of population-wide weight gain [118, 119]. Obesity has nearly doubled in Europe over the past 20 years, regardless of previous levels in most countries [117]. The consequences include growing prevalences of diabetes, hypertension, and elevated cancer risk [120].

These trends are even more alarming for SCT survivors, who already have an elevated risk for developing various chronic diseases at an early age.[78, 121] For a survivor who has received a high-toxicity treatment such as total-body irradiation, many such diseases can be fatal. However to effectively address healthy lifestyle as a primary – and potentially, for cancer survivors, a secondary-preventive measure, this topic requires top-level priority as a public health issue. In recent years, several national health-related initiatives (e.g., on passive smoking and on fruit and vegetable consumption in schools and workplaces) have achieved surprising success [122]; however, continuous, concerted action is urgently needed to promote the elements of a healthy lifestyle as preventive measures against chronic disease.

9.8 Perspectives for future research

Future research should aim at (1) further psychometric testing of the PROVIVO instrument; (2) prospective studies examining the relations between the trajectory of symptom experience, and self-management behaviours after SCT; and (3) testing of the efficacy of a multi-component intervention program to manage symptoms and support self-management.

Based on this thesis' findings, we recognize manifold directions for future research: (1) further psychometric testing of the PROVIVO instrument; (2) prospective studies examining the relations between symptom experience trajectories and self-management behaviours after SCT; and (3) tests of the effectiveness and outcomes of multi-component self-management interventions integrated in a collaborative chronic care approach to SCT survivorship.

For validity testing, we used the AERA Standards for Educational and Psychological Testing, which acknowledge that confidence in a questionnaire develops based on the long-term accumulation of psychometric data provided by a variety of testing procedures. To date, we have only been able to test the preliminary validity of the PROVIVO instrument using a cross-sectional design. As a result, we could neither capture changes in symptoms over time nor assess re-test reliability or predictive validity. It should also be stressed that the AERA guidelines will soon be updated to include enhanced coverage of test fairness, educational accountability, workplace testing, and technology [123]. Therefore, we recognize that our preliminary validity results represent only an initial step in validation. Subsequent steps should include examining the instrument's responsiveness to change over time and developing interpretation guidelines, e.g., concerning minimally clinically important differences [124].

Further, there is a clear need for prospective research investigating the relations between the trajectory of symptom experience and behavioral patterns after SCT. The survivorship literature includes little information on long-term symptom trajectories after SCT, i.e., it is unclear how long symptoms persist, or of which patient, disease, or treatment characteristics correlate with which levels of severity or distress. Optimally, future studies exploring symptom trajectories should use graphic techniques such as heat intensity mapping [125] or innovative statistical approaches such as latent profiling [126], which identifies underlying characteristics that contribute to the likelihood/risk of membership in a particular latent profile [126]. Such knowledge can allow clinicians to proactively modify strategies to mitigate or prevent future symptoms and late effects. For instance, patients identified as specifically at risk for developing higher levels of pain, anxiety, and depression might benefit from consultations with a mental health nurse or psychologist before these symptoms occur. Such research would acknowledge different symptom patterns which call for tailored assessment and management approaches.

To advance current knowledge on the interplay of biophysiological, behavioural and psychosocial factors for outcomes after SCT, larger cohort studies are needed. The nationwide Swiss Transplant Cohort Study (STCS), an open prospective cohort study, offers an excellent research framework to describe characteristics of transplant populations, to report clinical and psychosocial outcomes and to explore specific risk factors that influence these outcomes. The STCS includes all solid organ and stem cell recipients in Switzerland [127]. Based on Dew et al.'s adapted biopsychosocial framework [128], the STCS measures five psychosocial domains: (1) physical/functional (e.g., perceived health status, sleep quality, daytime sleepiness); (2) psychological (e.g., depression, stress); (3) behavioural (e.g., medication adherence, smoking, drug use, physical activity, sun protection); (4) social (e.g., work capacity/return to work); and (5) global quality of life. Factors relating to the healthcare system (e.g., trust in the transplant team) are also considered [129]. The resulting data are best suited to analysis in view of post-SCT clinical outcomes, e.g., to identify socioeconomic, psychosocial and behavioural factors that distinguish between survivors with better or poorer clinical outcomes.

To improve long-term outcomes after SCT, alongside the integration of a collaborative chronic care approach for SCT survivorship, a multi-component self-management intervention is strongly recommended. As such an intervention program is complex, its development and testing are challenging and require extensive preparative work. The overall process will include considerations of ways to maximize trial efficacy and implementation via fidelity monitoring and measurement, as well as the selection of an appropriate design, target population and control group. Attention should also be paid to identifying barriers to behaviour change among SCT survivors, and to delivery channels and methods of overcoming those barriers. Ideally, a clustered randomized trial would test the efficiency of such a program. Also, the role of technology in intervention delivery and measurement will require careful consideration. Integral to this study, analyses will weigh the costs of delivery against potential savings from decreased morbidity and mortality and increased function and quality of life [130].

9.9 Conclusion

The research program presented here was innovative, presenting, for the first time, a PRO instrument measuring late-effect symptom experience after SCT. Its findings add significantly to the scarce available knowledge both of symptom experiences in SCT survivorship and of long-term survivors' health behaviours. They also support the association between medication nonadherence and the occurrence of cGVHD. Moreover, this research program provides insight into current practice patterns of healthcare professionals relative to the assessment and support of medication adherence. Finally, it has enabled us to outline specific issues and additional topics of interest for further research on SCT patient self-management, particularly regarding symptom experience and health behaviours.

9.10 References

1. Rovo A, Daikeler T, Halter J, Heim D, Tsakiris DA, Stern M *et al.* Late altered organ function in very long-term survivors after allogeneic hematopoietic stem cell transplantation: a paired comparison with their HLA-identical sibling donor. *Haematologica* 2011; **96:** 150-5.
2. Rovo A, Tichelli A. Cardiovascular complications in long-term survivors after allogeneic hematopoietic stem cell transplantation. *Semin Hematol* 2012; **49:** 25-34.
3. Tichelli A, Rovo A, Passweg J, Schwarze CP, Van Lint MT, Arat M *et al.* Late complications after hematopoietic stem cell transplantation. *Expert Rev Hematol* 2009; **2:** 583-601.
4. Martin PJ, Counts GW, Jr., Appelbaum FR, Lee SJ, Sanders JE, Deeg HJ *et al.* Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. *J Clin Oncol* 2010; **28:** 1011-6.
5. Bhatia S, Francisco L, Carter A, Sun CL, Baker KS, Gurney JG *et al.* Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study. *Blood* 2007; **110:** 3784-92.
6. Bhatia S. Long-term health impacts of hematopoietic stem cell transplantation inform recommendations for follow-up. *Expert Rev Hematol* 2011; **4:** 437-52.
7. Ganz PA, Goodwin PJ. Health-related quality of life measurement in symptom management trials. *J Natl Cancer Inst Monogr* 2007; **37:** 47-52.
8. Williams LA, Yucel E, Cortes JE, Cleeland CS. Measuring symptoms as a critical component of drug development and evaluation in hematological diseases. *Clin Investig* 2013; **3:** 1127-1138.
9. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. *Jama* 2002; **288:** 1775-9.
10. Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. *Jama* 2002; **288:** 2469-75.
11. Grady PA, Gough LL. Self-Management: A Comprehensive Approach to Management of Chronic Conditions. *Am J Public Health* 2014**:** e1-e7.
12. Savani BN, Griffith ML, Jagasia S, Lee SJ. How I treat late effects in adults after allogeneic stem cell transplantation. *Blood* 2011; **117:** 3002-9.
13. Syrjala KL, Martin PJ, Lee SJ. Delivering care to long-term adult survivors of hematopoietic cell transplantation. *J Clin Oncol* 2012; **30:** 3746-51
14. Ligibel J. Lifestyle factors in cancer survivorship. *J Clin Oncol* 2012; **30:** 3697-704.
15. McCorkle R, Ercolano E, Lazenby M, Schulman-Green D, Schilling LS, Lorig K *et al.* Self-management: Enabling and empowering patients living with cancer as a chronic illness. *CA Cancer J Clin* 2011; **61:** 50-62.
16. Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims Federal Register, 2009.

17. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A *et al.* Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health* 2005; **8:** 94-104.
18. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E *et al.* Content validity establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force report: part 2 assessing respondent understanding. *Value Health* 2011; **14:** 978-88.
19. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E *et al.* Content validity establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1 eliciting concepts for a new PRO instrument. *Value Health* 2011; **14:** 967-77.
20. American Educational Research Association. Standards for educational and psychological testings. Washington; DC: AERA, 1999.
21. Blackstone EH. Comparing apples and oranges. *J Thorac Cardiovasc Surg* 2002; **123:** 8-15.
22. Conn VS, Hafdahl AR, Cooper PS, Ruppar TM, Mehr DR, Russell CL. Interventions to improve medication adherence among older adults: meta-analysis of adherence outcomes among randomized controlled trials. *Gerontologist* 2009; **49:** 447-62.
23. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *The Cochrane database of systematic reviews* 2008**:** CD000011.
24. Jim HS, Syrjala KL, Rizzo D. Supportive care of hematopoietic cell transplant patients. *Biol Blood Marrow Transplant* 2012; **18:** S12-6.
25. Mosher CE, Duhamel KN, Rini C, Corner G, Lam J, Redd WH. Quality of life concerns and depression among hematopoietic stem cell transplant survivors. *Support Care Cancer* 2011; **19**:1357-65.
26. Mosher CE, Redd WH, Rini CM, Burkhalter JE, DuHamel KN. Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: a review of the literature. *Psychooncology* 2009; **18:** 113-27.
27. Norkin M, Hsu JW, Wingard JR. Quality of Life, Social Challenges, and Psychosocial Support for Long-Term Survivors After Allogeneic Hematopoietic Stem-Cell Transplantation. *Semin Hematol* 2012; **49:** 104-109.
28. Institute of Medicine and National Research Council of the National Academies. *From Cancer Patient to Cancer Survivor: Lost in Transition*, National Academies Press, 2006.
29. Sun CL, Francisco L, Baker KS, Weisdorf DJ, Forman SJ, Bhatia S. Adverse psychological outcomes in long-term survivors of hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study (BMTSS). *Blood* 2011; **118:** 4723-4731.

30. McCabe MS, Bhatia S, Oeffinger KC, Reaman GH, Tyne C, Wollins DS *et al.* American Society of Clinical Oncology statement: achieving high-quality cancer survivorship care. *J Clin Oncol* 2013; **31:** 631-40.
31. Majhail NS, Rizzo JD. Surviving the cure: long term follow-up of hematopoietic cell transplant recipients. *Bone Marrow Transplant* 2013; **48:** 1145-51.
32. Howell D, Hack TF, Oliver TK, Chulak T, Mayo S, Aubin M *et al.* Models of care for post-treatment follow-up of adult cancer survivors: a systematic review and quality appraisal of the evidence. *J Cancer Surviv* 2012; **6:** 359-71.
33. Ganz PA, Casillas J, Hahn EE. Ensuring quality care for cancer survivors: implementing the survivorship care plan. *Semin Oncol Nurs* 2008; **24:** 208-17.
34. Loberiza FR, Jr., Zhang MJ, Lee SJ, Klein JP, LeMaistre CF, Serna DS *et al.* Association of transplant center and physician factors on mortality after hematopoietic stem cell transplantation in the United States. *Blood* 2005; **105:** 2979-87.
35. Beavers J, Lester J. Survivorship care for adult recipients of hematopoietic cell transplantations. *Clin J Oncol Nurs* 2010; **14:** 136-9.
36. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness: the chronic care model, Part 2. *Jama* 2002; **288:** 1775-9.
37. Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A. Improving chronic illness care: translating evidence into action. *Health Aff (Millwood)* 2001; **20:** 64-78.
38. Renders CM, Valk GD, Griffin SJ, Wagner EH, Eijk Van JT, Assendelft WJ. Interventions to improve the management of diabetes in primary care, outpatient, and community settings: a systematic review. *Diabetes care* 2001; **24:** 1821-33.
39. Renders CM, Valk GD, Griffin S, Wagner EH, Eijk JT, Assendelft WJ. Interventions to improve the management of diabetes mellitus in primary care, outpatient and community settings. *The Cochrane database of systematic reviews* 2001**:** CD001481.
40. Bissonnette J, Woodend K, Davies B, Stacey D, Knoll GA. Evaluation of a collaborative chronic care approach to improve outcomes in kidney transplant recipients. *Clin Transplant* 2013; **27:** 232-8.
41. Zwerink M, Brusse-Keizer M, van der Valk PD, Zielhuis GA, Monninkhof EM, van der Palen J *et al.* Self management for patients with chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews* 2014; **3:** CD002990.
42. Kroon Féline PB, van der Burg Lennart RA, Buchbinder R, Osborne Richard H, Johnston Renea V, Pitt V. Self-management education programmes for osteoarthritis. *Cochrane Database of Systematic Reviews* 2014**:** CD008963.
43. Martin F, Caramlau Isabela O, Sutcliffe P, Martin S, Bayley J, Choudhry K. Self-management interventions for people living with HIV/AIDS. *Cochrane Database of Systematic Reviews* 2010**:** CD008731.

44. Pal K, Eastwood Sophie V, Michie S, Farmer Andrew J, Barnard Maria L, Peacock R *et al.* Computer-based diabetes self-management interventions for adults with type 2 diabetes mellitus. In: *Cochrane Database of Systematic Reviews* 2013: CD008776.pub2.
45. Savage E, Beirne Paul V, Ni Chroinin M, Duff A, Fitzgerald T, Farrell D. Self-management education for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2011**:** CD007641.pub2.
46. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. *The Milbank quarterly* 1996; **74:** 511-44.
47. Wagner EH, Austin BT, Von Korff M. Improving outcomes in chronic illness. *Managed care quarterly* 1996; **4:** 12-25.
48. McLeroy KR, Bibeau D, Steckler A, Glanz K. An ecological perspective on health promotion programs. *Health education quarterly* 1988; **15:** 351-77.
49. Borras JM, Albreht T, Audisio R, Briers E, Casali P, Esperou H *et al.* Policy statement on multidisciplinary cancer care. *Eur J Cancer* 2014; **50:** 475-80.
50. Clauser SB, Wagner EH, Aiello Bowles EJ, Tuzzio L, Greene SM. Improving modern cancer care through information technology. *American journal of preventive medicine* 2011; **40:** 198-207.
51. Cleeland CS. Symptom burden: multiple symptoms and their impact as patientreported outcomes. *J Natl Cancer Inst Monogr* 2007; **37:** 16-21.
52. Basch E. New Frontiers in Patient-Reported Outcomes: Adverse Event Reporting, Comparative Effectiveness, and Quality Assessment. *Annual Review of Medicine* 2014; **65:** 307-317.
53. Wu AW, Bradford AN, Velanovich V, Sprangers MA, Brundage M, Snyder C. Clinician's checklist for reading and using an article about patient-reported outcomes. *Mayo Clin Proc* 2014; **89:** 653-61.
54. Haggstrom DA, Doebbeling BN. Quality measurement and system change of cancer care delivery. *Medical care* 2011; **49:** 21-27.
55. Methodology Committee of the Patient-Centered Outcomes Research Institute (PCORI). Methodological standards and patient-centeredness in comparative effectiveness research: the PCORI perspective. *Jama* 2012; **307:** 1636-40.
56. Selby JV, Beal AC, Frank L. The Patient-Centered Outcomes Research Institute (PCORI) national priorities for research and initial research agenda. *Jama* 2012; **307:** 1583-4.
57. Basch EM, Reeve BB, Mitchell SA, Clauser SB, Minasian L, Sit L *et al.* Electronic toxicity monitoring and patient-reported outcomes. *Cancer J* 2011; **17:** 231-4.
58. Zbrozek A, Hebert J, Gogates G, Thorell R, Dell C, Molsen E *et al.* Validation of electronic systems to collect patient-reported outcome (PRO) datarecommendations for clinical trial teams: report of the ISPOR ePRO systems validation good research practices task force. *Value Health* 2013; **16:** 480-9.

59. Coons SJ, Gwaltney CJ, Hays RD, Lundy JJ, Sloan JA, Revicki DA *et al.* Recommendations on evidence needed to support measurement equivalence between electronic and paperbased patientreported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force report. *Value Health* 2009; **12:** 419-29.

60. Wood WA, Deal AM, Abernethy A, Basch E, Battaglini C, Kim YH *et al.* Feasibility of frequent patient-reported outcome surveillance in patients undergoing hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2013; **19:** 450-9.

61. Berry DL, Hong F, Halpenny B, Partridge AH, Fann JR, Wolpin S *et al.* Electronic selfreport assessment for cancer and self-care support: results of a multicenter randomized trial. *J Clin Oncol* 2014; **32:** 199-205.

62. Chen J, Ou L, Hollis SJ. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. *BMC Health Serv Res* 2013; **13:** 1472-6963.

63. Dusseldorp E, van Genugten L, van Buuren S, Verheijden MW, van Empelen P. Combinations of Techniques That Effectively Change Health Behavior: Evidence From Meta-CART Analysis. *Health Psychol* 2013; **25:** 25.

64. Majhail NS, Rizzo JD, Lee SJ, Aljurf M, Atsuta Y, Bonfim C *et al.* Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2012; **18:** 348-71.

65. Leventhal H, Brissette I, Leventhal EA. The common-sense model of self-regulation of health and illness. In: Florence K, Cameron LD, Leventhal H (eds). *The Self-regulation of Health and Illness Behaviour*. Routledge, 2003, pp 43-65.

66. Potrata B, Cavet J, Blair S, Howe T, Molassiotis A. Understanding distress and distressing experiences in patients living with multiple myeloma: an exploratory study. *Psychooncology* 2011; **20:** 127-34.

67. Bennion AE, Molassiotis A. Qualitative research into the symptom experiences of adult cancer patients after treatments: a systematic review and meta-synthesis. *Support Care Cancer* 2013; **21:** 9-25.

68. Sheldon LK, Kazmi M, Klein C, Berry DL. Concerns of stem cell transplant patients during routine ambulatory assessment. *Patient preference and adherence* 2013; **7:** 15-20.

69. Cleeland CS, Wang XS, Shi Q, Mendoza TR, Wright SL, Berry MD *et al.* Automated symptom alerts reduce postoperative symptom severity after cancer surgery: a randomized controlled clinical trial. *J Clin Oncol* 2011; **29:** 994-1000.

70. Bennett AV, Jensen RE, Basch E. Electronic patient-reported outcome systems in oncology clinical practice. *CA Cancer J Clin* 2012; **62:** 337-47.

71. Gratwohl A, Baldomero H, Passweg J. Hematopoietic stem cell transplantation activity in Europe. *Curr Opin Hematol* 2013; **20:** 485-93.

72. Demark-Wahnefried W, Pinto BM, Gritz ER. Promoting health and physical function among cancer survivors: potential for prevention and questions that remain. *J Clin Oncol* 2006; **24:** 5125-31.

73. Ford ES, Bergmann MM, Kroger J, Schienkiewitz A, Weikert C, Boeing H. Healthy living is the best revenge: findings from the European Prospective Investigation Into Cancer and Nutrition-Potsdam study. *Arch Intern Med* 2009; **169:** 1355-1562.

74. Ford ES, Zhao G, Tsai J, Li C. Low-Risk Lifestyle Behaviors and AllCause Mortality: Findings From the National Health and Nutrition Examination Survey III Mortality Study. *American Journal of Public Health* 2011; **101:** 1922-1929.

75. Sun CL, Francisco L, Kawashima T, Leisenring W, Robison LL, Baker KS *et al.* Prevalence and predictors of chronic health conditions after hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. *Blood* 2010; **116:** 3129-3139.

76. Tichelli A, Rovo A, Socie G. Late effects after hematopoietic stem cell transplantation critical issues. *Curr Probl Dermatol* 2012; **43:** 132-49.

77. Socié G, Rizzo JD. Second Solid Tumors: Screening and Management Guidelines in Long-Term Survivors After Allogeneic Stem Cell Transplantation. *Semin Hematol* 2012; **49:** 4-9.

78. Chow EJ, Baker KS, Lee SJ, Flowers ME, Cushing-Haugen KL, Inamoto Y *et al.* Influence of conventional cardiovascular risk factors and lifestyle characteristics on cardiovascular disease after hematopoietic cell transplantation. *J Clin Oncol* 2014; **32:** 191-8.

79. Ehlers SL, Gastineau DA, Patten CA, Decker PA, Rausch SM, Cerhan JR *et al.* The impact of smoking on outcomes among patients undergoing hematopoietic SCT for the treatment of acute leukemia. *Bone Marrow Transplant* 2011; **46:** 285-90.

80. Marks DI, Ballen K, Logan BR, Wang Z, Sobocinski KA, Bacigalupo A *et al.* The effect of smoking on allogeneic transplant outcomes. *Biol Blood Marrow Transplant* 2009; **15:** 1277-87.

81. Mishra SI, Scherer RW, Geigle PM, Berlanstein DR, Topaloglu O, Gotay CC *et al.* Exercise interventions on health-related quality of life for cancer survivors. *The Cochrane database of systematic reviews* 2012; **15**: CD007566.pub2.

82. Irwin ML, Mayne ST. Impact of nutrition and exercise on cancer survival. *Cancer J* 2008; **14:** 435-41.

83. Pekmezi DW, Demark-Wahnefried W. Updated evidence in support of diet and exercise interventions in cancer survivors. *Acta Oncol* 2011; **50:** 167-78.

84. Spark LC, Reeves MM, Fjeldsoe BS, Eakin EG. Physical activity and/or dietary interventions in breast cancer survivors: a systematic review of the maintenance of outcomes. *J Cancer Surviv* 2013; **7:** 74-82.

85. Nayan S, Gupta MK, Strychowsky JE, Sommer DD. Smoking cessation interventions and cessation rates in the oncology population: an updated systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 2013; **149:** 200-11.

86. Mathes T, Antoine SL, Pieper D, Eikermann M. Adherence enhancing interventions for oral anticancer agents: a systematic review. *Cancer Treat Rev* 2014; **40:** 102-8.
87. Cimprich B, Janz NK, Northouse L, Wren PA, Given B, Given CW. Taking CHARGE: A self-management program for women following breast cancer treatment. *Psychooncology* 2005; **14:** 704-17.
88. Berry DL, Blumenstein BA, Halpenny B, Wolpin S, Fann JR, Austin-Seymour M *et al.* Enhancing Patient-Provider Communication With the Electronic Self-Report Assessment for Cancer: A Randomized Trial. *Journal of Clinical Oncology* 2011; **29:** 1029-1035.
89. Christy SM, Mosher CE, Sloane R, Snyder DC, Lobach DF, Demark-Wahnefried W. Long-term dietary outcomes of the FRESH START intervention for breast and prostate cancer survivors. *Journal of the American Dietetic Association* 2011; **111:** 1844-51.
90. Alfano CM, Molfino A, Muscaritoli M. Interventions to promote energy balance and cancer survivorship: priorities for research and care. *Cancer* 2013; **119:** 2143-50.
91. McBride CM, Puleo E, Pollak KI, Clipp EC, Woolford S, Emmons KM. Understanding the role of cancer worry in creating a "teachable moment" for multiple risk factor reduction. *Soc Sci Med* 2008; **66:** 790-800.
92. Demark-Wahnefried W, Aziz NM, Rowland JH, Pinto BM. Riding the crest of the teachable moment: promoting long-term health after the diagnosis of cancer. *J Clin Oncol* 2005; **23:** 5814-30.
93. Gritz ER, Fingeret MC, Vidrine DJ, Lazev AB, Mehta NV, Reece GP. Successes and failures of the teachable moment: smoking cessation in cancer patients. *Cancer* 2006; **106:** 17-27.
94. Stull VB, Snyder DC, Demark-Wahnefried W. Lifestyle interventions in cancer survivors: designing programs that meet the needs of this vulnerable and growing population. *J Nutr* 2007; **137:** 243-248.
95. Beattie S, Lebel S. The experience of caregivers of hematological cancer patients undergoing a hematopoietic stem cell transplant: a comprehensive literature review. *Psychooncology* 2011; **20:** 1137-50.
96. Chubak J, Aiello Bowles EJ, Tuzzio L, Ludman E, Rutter CM, Reid RJ *et al.* Perspectives of cancer survivors on the role of different healthcare providers in an integrated delivery system. *J Cancer Surviv* 2014; **8:** 229-38.
97. De Bleser L, Matteson M, Dobbels F, Russell C, De Geest S. Interventions to improve medicationadherence after transplantation: a systematic review. *Transpl Int* 2009; **22:** 780-97.
98. De Geest S. Immunosuppressive drugs and nonadherence in transplantation. *Journal of Renal Nursing* 2010; **2:** 58-63.
99. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC *et al.* Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Ann Intern Med* 2012; **157:** 785-95.

100. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W *et al.* The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 2013; **46:** 81-95.

101. Demonceau J, Ruppar T, Kristanto P, Hughes DA, Fargher E, Kardas P *et al.* Identification and assessment of adherenceenhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. *Drugs* 2013; **73:** 545-62.

102. Vervloet M, Linn AJ, van Weert JC, de Bakker DH, Bouvy ML, van Dijk L. The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature. *J Am Med Inform Assoc* 2012; **19:** 696-704.

103. De Bleser L, De Geest S., Vincke B, Ruppar T, Vanhaecke J, Dobbels F. How to test electronic adherence monitoring devices for use in daily life: a conceptual framework. *Comput Inform Nurs* 2011; **29:** 489-95.

104. Reinhardt UE. The Swiss health system: regulated competition without managed care. *Jama* 2004; **292:** 1227-31.

105. Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. Interventions to enhance medication adherence. *Cochrane database of systematic reviews* 2005; **4:** CD000011.

106. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *Jama* 2002; **288:** 2868-79.

107. Hauer KE, Carney PA, Chang A, Satterfield J. Behavior change counseling curricula for medical trainees: a systematic review. *Acad Med* 2012; **87:** 956-68.

108. Gilbert SM, Miller DC, Hollenbeck BK, Montie JE, Wei JT. Cancer survivorship: challenges and changing paradigms. *The Journal of urology* 2008; **179:** 431-8.

109. Uijtdehaage S, Hauer KE, Stuber M, Go VL, Rajagopalan S, Wilkerson L. Preparedness for caring of cancer survivors: a multi-institutional study of medical students and oncology fellows. *J Cancer Educ* 2009; **24:** 28-32.

110. Macmillan Cancer Support. *Survivorship*. [retrieved 23 June 2014]. Available from: http://learnzone.org.uk/courses/.

111. University of Sheffield. *The context of cancer care*. [retrieved 23 June 2014]. Available from: http://www.shef.ac.uk/hsccpd/courses-az/cancer/mlevel_context_cancer_care.

112. Uijtdehaage S, Hauer KE, Stuber M, Rajagopalan S, Go VL, Wilkerson L. A framework for developing, implementing, and evaluating a cancer survivorship curriculum for medical students. *Journal of general internal medicine* 2009; **24:** 1009-1024.

113. Grant M, Economou D, Ferrell B, Bhatia S. Preparing professional staff to care for cancer survivors. *J Cancer Surviv* 2007; **1:** 98-106.

114. Grant M, Economou D, Ferrell B, Uman G. Educating health care professionals to provide institutional changes in cancer survivorship care. *J Cancer Educ* 2012; **27:** 226-32.

115. Campbell MK, Tessaro I, Gellin M, Valle CG, Golden S, Kaye L *et al.* Adult cancer survivorship care: experiences from the LIVESTRONG centers of excellence network. *J Cancer Surviv* 2011; **5:** 271-82.

116. Warnock C, Siddall J, Freeman J, Greenfield D. Emerging nursing roles for late effects care for children and young adults with cancer. *European journal of oncology nursing* 2013; **17:** 242-9.

117. OECD. Health at a Glance: OECD Indicators [PDF on Internet] OECD Publishing: [2013; retrieved 19 February 2014]. Available from: http://dx.doi.org/10.1787/health_glance-2013-e

118. Ludwig DS, Friedman MI. Increasing adiposity: Consequence or cause of overeating? *Jama* 2014; **311:** 2167-2168.

119. Powell LM, Han E, Chaloupka FJ. Economic contextual factors, food consumption, and obesity among U.S. adolescents. *J Nutr* 2010; **140:** 1175-80.

120. Bastien M, Poirier P, Lemieux I, Despres JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. *Prog Cardiovasc Dis* 2014; **56:** 369-81.

121. Armenian SH, Chow EJ. Cardiovascular disease in survivors of hematopoietic cell transplantation. *Cancer* 2014; **120:** 469-79.

122. Federal Statistical Office. *Die Schweizerische Gesundheitsbefragung in Kürze: Konzept, Methode, Durchführung*. [PDF on Internet] [updated November 2011; cited 19 February 2014]. Available from: http://compass-data.unil.ch/SGB-Documentation/ESS_SGB_2007%-20Konzept%20in%20Kuerze.pdf

123. American Pschological Association. *Revised Standards for Educational and Psychological Testing to be published in spring* 2014 [retrieved 19 February 2014]. Available from: *http://www.apa.org/science/about/psa/2013/10/revised-standards.aspx*.

124. Brozek JL, Guyatt GH, Schunemann HJ. How a well-grounded minimal important difference can enhance transparency of labelling claims and improve interpretation of a patient reported outcome measure, *Health Qual Life Outcomes*. 2006; **4**: 69.

125. Lanuza DM, Lefaiver CA, Brown R, Muehrer R, Murray M, Yelle M *et al.* A longitudinal study of patients' symptoms before and during the first year after lung transplantation. *Clin Transplant* 2012; **26:** E576-89.

126. Kim HJ, Abraham I, Malone PS. Analytical methods and issues for symptom cluster research in oncology. *Curr Opin Support Palliat Care* 2013; **7:** 45-53.

127. Koller MT, van Delden C, Muller NJ, Baumann P, Lovis C, Marti HP *et al.* Design and methodology of the Swiss Transplant Cohort Study (STCS): a comprehensive prospective nationwide long-term follow-up cohort. *European journal of epidemiology* 2013; **28:** 347-55.

128. Dew MA, Switzer GE, DiMartini AF, Matukaitis J, Fitzgerald MG, Kormos RL. Psychosocial assessments and outcomes in organ transplantation. *Prog Transplant* 2000; **10:** 239-59.

129. De Geest S, Burkhalter H, Berben L, Bogert LJ, Denhaerynck K, Glass TR *et al.* The Swiss Transplant Cohort Study's framework for assessing life-long psychosocial factors in solid-organ transplants. *Prog Transplant* 2013; **23:** 235-46.

130. Katz M. *Evaluating Clinical and Public Health Interventions: A Practical Guide to Study Design and Statistics*, Cambridge University Press: Cambridge, 2010.

CURRICULUM VITAE

PERSONAL DATA

NAME: Monika Kirsch

DATE OF BIRTH: August 29th, 1980

NATIONALITY: German

ADDRESSES

BUSINESSES: **INSTITUTE OF NURSING SCIENCE, FACULTY OF MEDICINE**
University of Basel, Bernoullistrasse 28, 4056 Basel, Switzerland
T: +41 (0)61 267 09 53
Email: monika.kirsch@unibas.ch

UNIVERSITY HOSPITAL BASEL
Department of Haematology, Petersgraben 4, 4001 Basel, Switzerland
T: +41 (0)61 328 50 85
Email: monika.kirsch@usb.ch

EDUCATION

GRADUATE

2010 – present **PHD (DR. SC. MED.) IN NURSING SCIENCE**
Institute of Nursing Science, Faculty of Medicine, University of Basel, Switzerland

2007 – 2009 **MASTER OF NURSING SCIENCE**
Institute of Nursing Science, Faculty of Medicine, University of Basel, Switzerland

UNDERGRADUATE

2006 – 2007 **BACHELOR OF SCIENCE IN NURSING**
Institute of Nursing Science, University of Basel, Switzerland

2000 – 2003 **REGISTERED NURSE IN GENERAL NURSING**
School of Nursing, Krankenpflegeschule Kreiskrankenhaus Dormagen, Germany

1997 – 2000 **ABITUR (GENERAL QUALIFICATION OF UNIVERSITY ENTRANCE)**
Bettina von Arnim Gymnasium, Dormagen, Germany

APPOINTMENTS AND POSITIONS

ACADEMIC

01/2010 – 07/2014	**RESEARCH ASSISTANT** Institute of Nursing Science, Faculty of Medicine University of Basel, Switzerland

NON-ACADEMIC / CLINICAL APPOINTMENTS

01/2010 – present	**ADVANCED PRACTICE NURSE** Outpatient clinic of the Department of Haematology University Hospital Basel, Switzerland
10/2007 – 01/2010	**STAFF NURSE** Stem cell transplant unit, Department of Haematology, University Hospital Basel, Switzerland
01/2005 – 09/2007	**STAFF NURSE** Internal Medicine and Oncology, University Hospital Basel, Switzerland
08/2003 – 01/2005	**STAFF NURSE** Chrischona Klinik, Bürgerspital Basel, Switzerland

LICENSURE AND CERTIFICATION

2003	Nursing License Switzerland, Swiss Red Cross Registration - (AKP20047759)
2003	Nursing License Germany

MEMBERSHIP IN PROFESSIONAL AND SCIENTIFIC SOCIETIES

2010 – present	**SWISS TRANSPLANT COHORT STUDY** Psychological Interest Group (STCS-PSIG)
2010 – present	**BASEL LEUVEN ADHERENCE RESEARCH GROUP (LBARG)**
2010 – present	**SWISS ONCOLOGY NURSING ASSOCIATION** (ONKOLOGIEPFLEGE SCHWEIZ) Member of the Professional Association for Oncology Nurses
2009 – present	**SWISS NURSING ASSOCIATION (SBK-ASI)**
2007 – present	**Nurses Group of the EUROPEAN GROUP FOR BLOOD AND MARROW TRANSPLANTATION (EBMT)** 2008-2012 Position in the EBMT Nurses Group Research Committee

RESEARCH GRANTS

Kirsch M, Halter J, Stüssi G, Dobbels F, De Geest S. PROVIVO-Patient reported outcomes in view of symptom experience and self-management of adult long-term survivors after haematopoietic stem cell transplantation - A mixed methods study. 2011-2014, Swiss Cancer League & Foundation Cancer Research Switzerland KFS: Direct costs: 112.900 CHF. Role: co-investigator.

Kirsch M, Halter J, Stüssi G, Dobbels F, De Geest S. PROVIVO-Patient reported outcomes in view of symptom experience and self-management of adult long-term survivors after haematopoietic stem cell transplantation – A mixed methods study. 2011-2014, Stiftung zur Krebsbekämpfung Nr. 280 Direct costs: 15.000 CHF. Role: co-investigator.

RESEARCH AWARDS

EBMT BEST NURSING POSTER 2009

Kirsch M, Dietz E, Erhard C, Arber C, Hasemann W. Development of an evidencebased information brochure for nurses about early detection and prevention of delirium in HSCT patients – A practice development project. Annual Meeting of the European Group for Blood and Marrow Transplantation. 2009, March 29-April 1, Gotenborg, Sweden.

EBMT BEST ORAL PRESENTATION 2014

Gresch B, **Kirsch M,** Fierz K, Halter J, Nair G, De Geest S. Medication nonadherence to taking immunosuppressants after allogeneic hematopoietic stem cell transplantation is associated with cGVHD: PROVIVOmed – A multicentre cross-sectional study. Annual Meeting of the European Group for Blood and Marrow Transplantation. 2014, March 30- April 2, Milan, Italy.

PUBLICATIONS

PEER REVIEWED JOURNALS

Gresch B, **Kirsch M**, Fierz K, Halter J, Nair G, De Geest S. Medication nonadherence to immunosuppressants after allogeneic stem cell transplantation is associated with cGVHD: PROVIVOmed – A multicentre cross-sectional study; will be submitted to Bone Marrow Transplantation.

Kirsch M, Halter JP, Stussi G, Nair G, Dobbels F, De Geest S. Symptom experience of late effects after allogeneic haematopoietic stem cell transplantation: Refinement and preliminary validity testing for construct validity and relation to other variables of the PROVIVO instrument, will be submitted to Supportive Care in Cancer.

Kirsch M, Mitchell SA, Halter JP, Stussi G, Dobbels F, Basch E, De Geest S. Development of a Patient Reported Outcome instrument for assessing symptoms of late effects in survivors after allogeneic stem cell transplantation: PROVIVO – a mixed methods study; European Journal of Oncology Nursing, in press.

Kirsch M., Götz A, Halter JP, Schanz U, Stüssi G, Dobbels F, De Geest S. Differences in health behaviours between recipients of allogeneic haematopoietic stem cell transplantation and the general population: A matched control study. Bone Marrow Transplantation, in press.

Kirsch M, Berben L, Johansson E, Calza S, Eeltink C, Stringer J, Lipptrot S, De Geest S. Adherence enhancing interventions used by nurses in stem cell transplant care: A survey from the Nurses Group of the European Group for Blood and Marrow Transplantation; European Journal of Cancer Care 2014; 7(10): 12172

De Geest S, Burkhalter H, Berben L, Bogert L, Denhaerynck K, Glass T R, Goetzmann L, **Kirsch M**, Kiss A, Koller M T, Piot-Ziegler C, Schmidt-Trucksass A. For The Psychosocial Interest Group Swiss Transplant Cohort. The Swiss Transplant Cohort Study's framework for assessing life-long psychosocial factors in solid-organ transplants. Progress in Transplantation 2013; 23: 235-246.

Kirsch M, Klaassen R, De Geest S, Ionova T, Matzdorff A, Dobbels F. Understanding the importance of using Patient Reported Outcome Measures in patients with Immune Thrombocytopenia. Seminars in Hematology 2013; 50: 39–42.

Kirsch M, Halter J, De Geest S. Self-reported symptoms and concerns in long-term survivors attending follow-up visits after Haematopoietic Stem Cell Transplantation: A cross-sectional single centre evaluation. Journal of Nursing Care 2012; 116

Kirsch M, Crombez P, Calza S, Eeltink C, Johansson E. Health care professionals' perspective on patient information in stem cell transplantation: A study from the Nurses Group of the European Group for Blood and Marrow Transplantation. Bone and Marrow Transplantation 2011; 47: 1131–1133.

Senn B, **Kirsch M**, Sanz C C, Karlou C, Tulus K, De Leeuw J et al. How cancer research could benefit from the Complex Intervention Framework: students' experiences of the European Academy of Nursing Science summer school. European Journal of Cancer Care 2011; 20: 1–4.

OTHER JOURNALS

Kirsch M, De Geest S. Krebsnachsorge ist eine Teamaufgabe. Krankenpflege 2012; 3: 31-32

Senn B, Koller A, **Kirsch M**, Spichiger E, De Geest S. Pflegeforschung in der Onkologie., Krebsforschung Schweiz (Ed.), Bern, Jahresbericht 2010. 2012;16-17.

Kirsch M, Leppla L. Welche Informationen brauchen Patienten mit einer hämatoonkologischen Erkrankung? Onkologiepflege Schweiz 2011; 1: 6-9.

Kirsch M, De Geest S. Wie weiter nach einer Stammzelltransplantation. Krebsforschung Schweiz (Ed.), Bern, Jahresbericht 2010. 2011; 16-17.

BOOKS / CHAPTERS IN BOOKS

Dobbels F, Ganiats T, De Geest S, Ionnova T, Kalyadina S, **Kirsch M**, Salek S. Patient reported outcomes in patients with hematological disorders. In European Hematology Association Scientific Working Group Quality of Life and symptoms (Ed.), Guidelines: Patient-Reported Outcomes in Hematology, Genoa: Forum service editore, 2012; 25-50.

Dobbels F, Grainger J, Imbach P, Ionnova T, **Kirsch M**, Newland A. Immune thrombocytopenia. European Hematology Association Scientific Working Group Quality of Life and symptoms (Ed.), Guidelines: Patient-Reported Outcomes in Hematology, Genoa: Forum service editore, 2012; 108-117.

THESIS

MASTER THESIS

Institute of Nursing Science, University of Basel, Switzerland, 2009

Self reported symptoms and concerns in long-term survivors after haematopoietic stem cell transplantation.

SUPERVISED MASTER THESIS

Naegele, M., Kirsch, M., Engelhardt, M., Fierz, K., De Geest, S., Descriptive Longitudinal Study of Symptom Experience of Multiple Myeloma Patients Treated with Autologous Stem Cell Transplantation Following High Dose Chemotherapy, 2013, unpublished thesis

Gresch, B., Kirsch, M., Fierz, K., Halter, J., Nair, G., De Geest, S., Medication nonadherence in long-term survivors taking immunosuppressants after allogeneic stem cell transplantation (PROVIVOmed): a multicenter cross-sectional study, 2013, unpublished thesis

Götz, A., Kirsch, M., De Geest, S., Self-management behaviours of adult long-term survivors after allogeneic stem cell transplantation: A secondary data analysis of the PROVIVO project, 2012, unpublished thesis

PRESENTATIONS

INTERNATIONAL

Kirsch M, Götz A, Halter J, Nair G, Stussi G, Dobbels F, De Geest S. Differences in health behaviours between survivors after allogeneic haematopoietic stem cell transplantation and the general population: the PROVIVO study. Annual Meeting of the European group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplantation 49 (suppl. 1) 393; 2014, March 30 –April 2, Milan, Italy.

Gresch B., **Kirsch, M**., Fierz, K., Halter, J., Nair, G., De Geest, S., Medication nonadherence in long-term survivors taking immunosuppressants after allogeneic stem cell transplantation (PROVIVOmed): a multicenter cross-sectional study, Annual Meeting of the European Group

for Blood and Marrow Transplantation (EBMT) 2014, Bone Marrow Transplantation 49 (suppl. 1) 394; 2014, March 30 –April 2, Milan, Italy.

Gresch B., **Kirsch, M**., Fierz, K., Halter, J., Nair, G., De Geest, S., Medication nonadherence in long-term survivors taking immunosuppressants after allogeneic stem cell transplantation (PROVIVOmed): a multicenter cross-sectional study, Annual Meeting of the European Society for Patient Adherence, COmpliance and Persistence (ESPACOMP) 2013, November 15-16, Budapest.

Kirsch M, Preliminary study results of the PROVIVO study: Self-management behaviours after allogeneic stem cell transplantation. Annual Meeting of German-Austrian-Swiss GvHD Symposium. 2012, November 9, Basel, Switzerland.

Calza S, Eeltink, C, Crombez P, **Kirsch M**, Johansson E. Planned research activities 2012-2013, Annual Meeting of the European group for Blood and Marrow Transplantation (EBMT). Bone and Marrow Transplant 47: 470 (suppl. 1), 2012, April 1-4, Geneva, Switzerland.

Kirsch M, Berben L, Johansson E, Crombez P, Calza S, Eeltink C, De Geest S. Adherence enhancing interventions used by nurses in stem cell transplant care. Annual Meeting of the European group for Blood and Marrow Transplantation EBMT. 2012, April 1-4, Geneva, Switzerland.

Kirsch M, Mitchell, S.A, Halter J, Stussi G, Dobbels F, Basch E, De Geest S. Development of a Patient Reported Outcome instrument for assessing symptoms of late effects in survivors after allogeneic stem cell transplantation: PROVIVO – A mixed methods study. Annual Meeting of the European group for Blood and Marrow Transplantation EBMT. Bone Marrow Transplantation 47: 462 (suppl. 1), 2012, April 1-4, Geneva, Switzerland.

Johansson E, **Kirsch M**, Calza S, Eltrienk C, Crombez P. Health care professionals' perspective on patients' received information throughout the first year of stem cell transplantation. Annual Meeting of the European group for Blood and Marrow Transplantation EBMT. 2011, April 3-6, Paris, France.

Kirsch M. The shadowing experience: Valuing the link between nursing research and the development of innovative nursing roles in the care for patients with haematopoietic stem cell transplantation – A field report. Annual Meeting of the European group for Blood and Marrow Transplantation EBMT. 2010, March 21-24, Vienna, Austria.

Calza S, Johansson E, Eltrienk C, Crombez P, **Kirsch M**. Patient information needs. Annual Meeting of the European group for Blood and Marrow Transplantation EBMT. 2010, March 21-24, Vienna, Austria.

Kirsch M. Late effects of the therapy – the lymphoma patient. 1st Study Day of the Lymphoma Working Party & Nurses Group of the European Group of Blood and Marrow Transplantation EBMT. 2010, February 19, Barcelona, Spain.

NATIONAL

Kirsch M., Beckmann S., Mauthner O. Selbstmanagement & Transplantation. Neues aus Forschung & Praxis, Congress of the Swiss Nursing Association (SBK). 2014, June 4-6, Basel, Switzerland.

Kirsch M. PROVIVO: Für eine gute pflegerische Nachsorge bei Patienten nach Stammzelltransplantation, CareArt. 2014, June 2-3, Basel, Switzerland.

Kirsch M. Zu sich Sorge tragen: Nachsorge nach einer Lymphomerkrankung, JubiläumsTagung der Schweizerischen Patientenorganisation für Lymphombetroffene und ihre Angehörige zum 10. Welt-Lymphom-Tag. World Lymphoma Awareness Day (WLAD). 2013, September 14, Basel, Switzerland.

Kirsch M. Leben nach Stammzelltransplantation: Informationstag für Patienten/Innen & deren Angehörige – Sich etwas Gutes tun. Patient Education day. 2013, June 22, Basel, Switzerland.

Kirsch M on behalf of the PROVIVO research team, Self-management behaviours of adult long-term survivors after allogeneic stem cell transplantation. Annual Meeting of Swiss Blood Stem Cell Transplantation. 2013, January 18, Berne, Switzerland.

Kirsch M. Entwicklungen in der HämatoOnkologie-Pflege – Wo stehen wir und wo könnte es hingehen? Onkologiepflege Schweiz Kongress. 2011, March 27, Berne, Switzerland.

Kirsch M. Auswertung des Fragebogens zur Jahreskontrolle: Symptome und Probleme von Patienten nach einer hämatopoietischen Stammzelltransplantation. Patient Education Day. 2010, November 12, University Hospital Basel, Switzerland.

Kirsch M. Komplikationen und Genesungsverlauf in den ersten 3 bis 6 Monaten nach einer Hämatopoietischen Stammzelltransplantation. Education Day Swiss National Nurses Group, Group for Blood and Marrow Transplantation EBMT. 2010, November 2, Berne, Switzerland.

Kirsch M. Welche Beschwerden beschreiben andere Betroffene nach einer autologen Stammzelltransplantation? Resultate einer Masterarbeit, Patient Education Day. University Hospital Basel. 2010, August 27, Basel, Switzerland.

Kirsch M. Self-reported symptoms and concerns in long-term survivors after haematopoietic stem cell transplantation. Presentation Master thesis. 2010, June 14, University Basel, Switzerland.

POSTER PRESENTATION

Gerwig N, **Kirsch M**, Berger C, Erhardt C., Stern M, Medinger M, Hasemann W. Delirium management in stem cell transplant recipients: A practice development project. Annual Meeting of the European group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplantation 49 (suppl. 1) 403; 2014, March 30 – April 2, Milan, Italy.

Kirsch M, Götz A, Halter J, Nair G, Stussi G, Dobbels F, De Geest S. Self-management in long-term survivors after allogeneic Haematopoietic stem cell transplantation – A cross-sectional multicentre study. Annual Meeting of the European group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplantation 48 (suppl. 1) 462; 2013, April 1-4, London, United Kingdom.

Höhener C, Degen-Kellerhals S, **Kirsch M**. Longitudinal assessment of viral infections in haematopoietic stem cell transplant recipients and development of a standard operation procedure for the prevention of viral infections at an outpatient clinic. Annual Meeting of the

European Group for Blood and Marrow Transplantation. Bone Marrow Transplantation 47 (suppl. 1) 425; 2011, April 3-6, Paris, France.

Kirsch M, Halter J, De Geest S. Symptome und Probleme von Patienten im Langzeitverlauf nach einer hämatopoieitschen Stammzelltransplantation. Congress of the Swiss Nursing Association (SBK). 2010, May 26-28, Lucerne, Switzerland.

Kirsch M, Halter J, De Geest S. Self-reported symptoms and concerns in long-term survivors after haematopoietic stem cell transplantation. Annual Meeting of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplantation 46 (suppl. 1) 379; 2010, March 22-23, Vienna, Austria.

Kirsch M, Dietz E, Erhard C, Arber C, Hasemann W. Development of an evidence based information brochure for nurses about early detection and prevention of delirium in HSCT patients – A practice development project. Annual Meeting of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplantation 45 (suppl. 1) 353; 2009 March 29-April 1, Gotenborg, Sweden.

INTERNET PUBLICATIONS

Kirsch M. The shadowing experience: Valuing the link between nursing research and the development of innovative nursing roles in the care for patients with haematopoietic stem cell transplantation – A field report, Retrieved November 9, 2010 from www.ebmt.org/6Nurses-Group/june10/ebmt-ng-educationalscholarship.html

Kirsch M. European Group for Bone Marrow Transplant Educational Scholarship Report: The shadowing experience: Valuing the link between nursing research and the development of innovative nursing roles in the care for patients with haematopoietic stem cell transplantation – A field report, Retrieved December 8, 2010 from http://onsopcontent.ons.org/Publications/SIGNewsletters/bmsct/bmsct21.3.html

TEACHING EXPERIENCE

BACHELOR OF NURSING SCIENCE, UNIVERSITY OF BASEL, COURSES TAUGHT

2010 – 2014	Living with Chronic Illness Teaching assistant, lecture, seminar Bachelor´s Degree of Nursing Science Curriculum, Institute of Nursing Science, University Basel
2010 – 2014	Advanced Nursing Practice Coordinator and teacher action learning, lecture, seminar Bachelor´s Degree of Nursing Science curriculum Institute of Nursing Science, University of Basel, Switzerland

2010 – 2014	Student Advisor and Student Mentor Advice of students, support of students in research practicum University Basel, Institute of Nursing Science

OTHER EDUCATIONAL ACTIVITIES

2010 – present	Lecturer for nursing care, late effects and self-management after stem cell transplantation at the course for specialised nursing in stem cell transplantation University Hospital Basel
2014 – present	Lecturer for late effects after stem cell transplantation at the course for specialized nursing in stem cell transplantation University Hospital Zurich
2014 – present	Lecturer for nursing care for stem cell transplant recipients at the Oncology Nursing Association Switzerland