



# **Development, Implementation and Testing of an Integrated Model of Care for Allogeneic Stem Cell Transplantation facilitated by eHealth Technology – The SMILE Study**

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### List of Abbreviations

alloSCT	Allogeneic Stem Cell Transplantation
APN	Advanced Practice Nurse
BANANA	Basel Approach for CoNtextual ANALysis
BCT	Behavior Change Technique
BCW	Behavior Change Wheel
CC	Care Coordinator
CCM	Chronic Care Model
CG	Control Group
CICI	The Context and Implementation of Complex Interventions framework
CIM	Chronic Illness Management
COM-B	Capability-Opportunity-Motivation-Behavior
DARE	New DAta New REsponsibilities
DRKS	Deutsches Register für Klinische Studien
EBMT	European Society of Blood and Marrow Transplantation
eCCM	eHealth Enhanced Chronic Care Model
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
ePRO	electronic Patient Reported Outcome
FiB	University Hospital Freiburg im Breisgau, Germany
GvHD	Graft-versus-Host Disease
ICM	Integrated Care Models
IG	Intervention Group
NIH	National Institute of Health
RCT	Randomized controlled trial
SELFIE	<b>S</b> ustainable int <b>E</b> grated chronic care mode <b>L</b> s for multi-morbidity: delivery, <b>F</b> inancing, and performanc <b>E</b>
SMILeApp	SMILe Smartphone Application for the patient
SMILeCare	SMILe Web Browser Application for the care-cordinator SMILe-ICM allogeneic SteM cell transplantatlon faciLitated by eHealth-Integrated Care Model
TDF	Theoretical Domains Framework
UCD	User-Centered Design
WHO	World Health Organization

### Summary

Allogeneic stem cell transplantation (alloSCT) is the last chance of cure for patients with a variety of malignant and non-malignant hematological diseases.<sup>1, 2</sup> Over the last two decades, improvements in treatment and supportive care have led to rising numbers of transplants and long-term alloSCT survivors.<sup>3</sup> However, alloSCT survivors have a 70-90% risk of early complications and a 30–50% risk of late effects such as graft-versus-host disease (GvHD), as well as psychosocial symptoms such as fatigue (9-70%), depression (8-20%) or emotional distress (22-43%).<sup>4</sup>

This makes them chronically ill persons with complex care needs.<sup>5</sup> Due to their weakened physical condition and persistent symptoms in the first year post-alloSCT, many patients find it difficult to follow self-management or health behavior recommendations.<sup>6, 7</sup> This can lead to non-adherence towards immunosuppressive medication (64.6-65.7%), physical activity (26,8%) or infection prevention (41.6%).<sup>6-10</sup> In addition to contributing to high first year post-alloSCT re-admission rates, such non-adherence might also negatively impact long-term outcomes.<sup>6, 9</sup>

Consequently, patients and caregivers need better preparation to self-manage and coordinate care after hospital-to-home transfers.<sup>11, 12</sup> However, the growing numbers of alloSCT-patients who have complex long-term care needs and require long-term follow-up, particularly regarding self-management support, care coordination and continuity of care, are straining transplant centers' resources considerably.<sup>12</sup>

To ease that strain, innovative integrated care models (ICMs) following the principles of chronic illness management to address not only biomedical but also behavioral and psychosocial dimensions to make patients active partners in their own care.<sup>13</sup> For example, the Chronic-Care Model (CCM) both combines four critical dimensions of chronic illness care—patient self-management support, decision support, clinical information systems and delivery system design—gives guidance on how to reengineer and reorient traditional acute care models to follow the principles of chronic care.<sup>14</sup> The more dimensions are combined, the more effective the results.<sup>15</sup>

In 2015, with the addition of eHealth, the CCM became the eHealth-Enhanced Chronic Care Model (eCCM).<sup>16</sup> The eCCM indicates how eHealth can contribute to long-term care delivery, including what is needed regarding eHealth education for both patients and healthcare professionals. Evidence from systematic reviews and meta-analyses in chronically ill, cancer and organ transplant populations found that providing eCCM-based care resulted in improved biomedical, behavioral, psychosocial and economic outcomes.<sup>17-19</sup>

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Within SCT, however, only two randomized controlled trials—both integrating just single eCCM components—have been published to date.<sup>20,21</sup> Both studies focused on very specific treatment phases (in-patient; >3 years post-alloSCT), and were neither conceptually embedded nor reflective of a comprehensive approach addressing all eCCM dimensions. To the best of our knowledge, no eHealth-facilitated integrated care model has yet been developed for the alloSCT setting.

Although alloSCT centers could benefit from well-designed integrated care models, designing and implementing such models supported by eHealth in routine care is not straightforward. As examples, previous eHealth studies in chronically ill and cancer patients showed adoption problems regarding the technology: 44%–67% of the patients discontinued use of the eHealth components.<sup>22-24</sup> Asked for their reasons, many described technology barriers such as limited usefulness or unclear instructions.<sup>25-27</sup> Further, currently available eHealth applications often lack evidence-base or theoretical underpinnings and/or end-user-oriented development.<sup>28</sup> Together, both are vital regarding successful uptake and sustained use. To solve this challenge, we chose a combination of implementation science, behavioral science and computer science methods.

The overall aim of this dissertation was to develop and implement an eHealth-facilitated integrated care model for allogeneic **Stem** cell transplantation facilitated by **e**Health (SMILe-ICM). The SMILe project is an international, multi-phase, multi-site implementation science project aiming at developing (phase A), implementing and testing (phase B) the SMILe-ICM within various clinical settings. Embedded within it, focusing on the project's description and theoretical underpinnings, this dissertation's central aim is to develop and prepare the SMILe-ICM's implementation and testing for the first participating center, University Hospital Freiburg im Breisgau, Germany.

**Chapter 1** provides a general introduction to the field of alloSCT, including the current state of science regarding eHealth-facilitated ICMs in chronically ill, cancer, solid organ transplantation and alloSCT populations. This chapter also includes a short introduction to the three methodologies used—those of implementation science, behavioral science and computer science—as well as a description of the SMILe project and the first setting. All of this will lead to the rationale behind this dissertation. **Chapter 2** provides a detailed description of the dissertation's specific aims.

The article presented in **Chapter 3** describes the methodology and findings of the contextual analysis conducted in Freiburg im Breisgau as the first step of the SMILe project's phase A. To facilitate the contextual analysis, we used a sequential explanatory mixed-methods design, including surveys of five clinicians and 60 adult alloSCT patients, three focus-group interviews with clinicians and 10 individual interviews with alloSCT

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patients. The contextual analysis had three major aims: 1) to identify the organization's structural characteristics and practice patterns in view of chronic illness management; 2) to assess how self-management and behavioral support was supported; and 3) to assess the target clinicians' and alloSCT patients' technology openness regarding eHealth use along the eCCM dimensions. Our findings showed that the prevailing care model was predominantly acute care-oriented, lacking any interdisciplinary or chronic care focus. Most gaps were found within the dimensions of self-management support and delivery system design. The three health behaviors that would profit most from transplant team support were medication adherence, physical activity and infection prevention. Also, patients' high self-reported levels of insecurity in recognizing, judging and acting upon symptoms underscored the further need symptom management support. Both clinicians and patients were open towards eHealth, but rather as complementing human contact than replacing it. Our synthesis of the contextual findings indicated a choice of eight implementation strategies, including creating new clinical teams or revising professional roles.

**Chapter 4** describes the development of the SMILe-ICM, as informed by external evidence, stakeholder input, and especially the contextual analysis findings described in **chapter 1**. With implementation science methods to guide our progress, the development process consisted of four steps: 1) construction of a model based on a theoretical foundation; 2) theory-guided intervention development using behavioral science methods; 3) the choice and development of the delivery mode (human and/or technology) using behavioral and computer science methods; and finally 4) description of the intervention's characteristics and use in daily clinical practice.

More specifically, the SMILe-ICM fits within the eHealth Enhanced Chronic Care Model's four self-management intervention modules: recognizing and acting on symptoms; adhering to infection prevention measures; adhering to the prescribed medication regimen; and maintaining the prescribed amount of physical activity. Interventions are delivered in two ways—partly face-to face, by an Advanced Practice Nurse/care coordinator, who is embedded within the transplant team, and partly via the SMILe technology, i.e., the SMILeApp application. As the main technological interface between the care coordinator and the patients, the SMILeApp is installed on each patient's smartphone or tablet PC. This prompts the patient to enter a daily set of medical and symptom-related parameters and transfers them to the transplant center, where they can be monitored by the care coordinator over the first year post-alloSCT. For the transplant center to receive, process and respond to patient-entered information, the transplant team members use the SMILeCare web browser application.

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**Chapter 5** describes the process of creating the SMILe-ICM's eHealth components via methods originally used in agile software development and user-centered design. The article deals with how, driven by the principles of implementation science, behavioral theory-guided content development was transferred into software features, resulting in the SMILe-ICM's smooth-running embedded eHealth components. The interdisciplinary team's collaboration at specified interaction points led to clear, timely communication and efficient interactions between the various specialists. To facilitate content development, user stories were formulated to define the key software features, which were then prioritized and developed iteratively via agile software development principles. After two rounds of usability testing, the one prototype intervention module developed thus far has received high ratings on the system-usability scale.

**Chapter 6** lays out the study protocol of phase B of the SMILe project, i.e., the implementation and testing of our new care model within the first clinical setting, the University Hospital Freiburg im Breisgau, Germany (FiB). To highlight potential associations between the intervention components, the implementation strategies, contextual factors, the assumed mechanisms of change and the expected outcomes (short-term and long-term), as well as its intended patient-, organizational-, and societal level impacts, it also provides a logic model.

The SMILe-ICM and its first-year post-alloSCT implementation pathway will be tested within a single-center non-blinded hybrid 1 effectiveness-implementation RCT regarding effectiveness (i.e., total healthcare utilization costs (primary outcome); re-hospitalizations, lengths of stay, medication non-adherence, treatment burden, health-related quality of life, graft-versus-host disease, re-hospitalization-free survival, and survival) and implementation (i.e., feasibility, acceptability, appropriateness, fidelity) outcomes.

Based on a sample size calculation, 70 patients will be randomly allocated 1:1 to either the intervention or the usual care group. Standardized unit costs will be applied to calculate total healthcare utilization costs. Quantitative data will be collected using blinded standardized methodology using established measures. Implementation will be evaluated using mixed methods. Intention-to-treat and per-protocol analyses will be conducted using generalized linear models, the Kaplan-Meier method and the log-rank test, respectively. Qualitative data will be analyzed using mind-mapping techniques and thematic analysis.

**Chapter 7** synthesizes and discusses the key findings in light of available evidence, likely future perspectives, limitations and implications for clinical practice, research or policy. This chapter's content is guided by the Sustainable integrated chronic

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care modeLs for multi-morbidity: delivery, **F**inancing, and performanc**E** (SELFIE) framework.<sup>29</sup>

This dissertation's scientific contribution is both clinical and methodological. That is, the SMILe-ICM is expected to improve alloSCT patients' biopsychosocial outcomes while providing guidance on the used methodologies. Implementation science methods—in this case, the use of a contextual analysis to inform the co-development of behavioral theory-based content, combined with the use of computer science methods—can be used as blueprints for other projects to develop, scale up or scale out eHealth-facilitated-ICMs.

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# Chapter 1

## Introduction



### Undergoing allogeneic hematopoietic stem cell transplantation

Allogeneic stem cell transplantation (alloSCT) is a well-established curative treatment for a variety of malignant and non-malignant hematological diseases, including acute leukemia or aplastic anemia.<sup>1</sup> Before alloSCT, the patient receives intensive radio- and/or chemotherapy as a conditioning therapy to suppress their immune system before the transfusion of healthy matched (related or unrelated) donor stem-cells that will restore the blood production system.<sup>2</sup> During the acute treatment phase, patients are typically hospitalized for 5-7 weeks while their bone marrow recovers. Once blood counts are acceptable and any acute complications resolved, patients are discharged and followed up as outpatients.

In the last decades, treatment and supportive care advances such as reduced conditioning and improved matching have reduced mortality and improved outcomes, resulting in increasing numbers of alloSCT survivors.<sup>3, 4</sup> Consequently, the most recent survey of the European Society of Blood and Marrow Transplantation (EBMT) showed transplant rates increasing unabated, with a record of 19,630 alloSCTs reported in 2018 in Europe.<sup>4</sup> Switzerland's three transplant centers perform a combined total of roughly 260 alloSCT annually. With 40 transplant centers, Germany reports more than 3500 alloSCTs per year.<sup>5, 6</sup>

AlloSCT patients' survival rate steadily increases from 50-60% after the first year to 80-90% survival chance beyond the second year post-alloSCT.<sup>7, 8</sup> By 2030, an estimated half-million alloSCT long-term survivors are expected solely in the United States, with another one million living in other countries.<sup>9</sup> In the early post-alloSCT phase, most deaths are tied to disease relapse, infections and the complication of newly transplanted donor cells attacking the patient's organs, i.e., graft-versus-host-disease (GvHD).<sup>10</sup>

Between 30% and 70% of alloSCT patients experience at least one episode of GvHD, which is the second most common cause of death in alloSCT recipients after relapse.<sup>10, 11</sup> While mild forms of GvHD are tolerated because of the required alloreactivity to clear any remaining malignant cells, moderate to severe forms are potentially lethal. The most common preventive strategy is suppressing the new immune system with immunosuppressive medication for the first 6–12 months. As this leaves patients immunocompromised, they need to adhere strictly to their care teams' behavioral recommendations (e.g., medication taking, infection prevention measures).<sup>12</sup>

Additionally, recent SCT recipients often also suffer from biopsychosocial symptoms such as pain (21-25%), sleep disturbance (14-51%), sexual dysfunction (6-80%), emotional distress (22-43%) or cognitive impairment (10-60%).<sup>13</sup> While these may have few direct long-term consequences, they can contribute to non-adherence to

important health behaviors such as immunosuppressant medication intake (64.6-65.7%), physical activity (26.8%), infection prevention (41.6%), and diet (7.5-88.8%)<sup>14</sup>,<sup>15</sup>, any of which can negatively impact long-term outcomes.<sup>16</sup>

For example, evidence indicates that immunosuppressant non-adherence is a major risk factor for poor outcomes in solid organ transplantation.<sup>17</sup> Likewise, early studies in alloSCT patients showed a relationship between non-adherence to immunosuppressants and chronic graft-versus-host disease (cGvHD)<sup>14, 18</sup>, which can reduce quality of life, increase morbidity and mortality, and increase overall healthcare needs.<sup>19, 20</sup>

Also, even beyond the first months, alloSCT patients not only have a 70-90% risk of developing late effects, e.g., chronic graft-versus-host disease (30-70%), endocrine (9-99%), cardiovascular (5-22%), or neurocognitive diseases (20-42%), skeletal problems (4-50%), fatigue (9-70%) or depression (8-20%)<sup>3, 11, 21, 22</sup> but also bear a life-long risk of developing secondary malignancies.<sup>23</sup> AlloSCT patients high prevalence of these and other complications places them among the rapidly growing population of chronically ill persons with complex care needs.<sup>8, 20</sup> Lifestyle factors and patient self-management limitations may further contribute to the occurrence and progression of late effects and co-morbidities.<sup>16</sup>

### 1.1.1 The case for re-engineering alloSCT care

Although life-long follow-up, patient and family engagement in self-management, and continuity of care span the alloSCT care continuum, the first months post-alloSCT are typically the most complex phase regarding care coordination and self-management support.<sup>24, 25</sup> When alloSCT recipients move from full inpatient support to less frequent and less intense out-patient follow-up, both they and their caregivers are often inadequately prepared to effectively self-manage new symptoms or complications and can feel overburdened.<sup>25-28</sup> Several publications have highlighted their high readmission rates (24.4-51%) compared to cancer or other chronically ill populations.<sup>29-31</sup>

The most common reasons for readmission include neutropenic fever due to infections in the first 30 days post-SCT; acute or chronic GvHD; and liver, lung, renal, musculoskeletal or neurological complications.<sup>29, 32</sup> The first year post-alloSCT is generally the most critical; however, when readmissions occur in the subsequent months and years, uncontrolled symptoms are often the underlying reason.<sup>29, 32</sup>

Unfortunately, transplant centers' resources are strained in view both of the growing numbers of alloSCT-patients in follow-up and of their complex long-term needs, particularly regarding self-management support, care coordination and continuity of care.<sup>24, 25, 27</sup> A re-engineering of alloSCT care processes towards an interdisciplinary chronic care-oriented approach is urgently needed.<sup>33</sup>

### 1.1.2 Moving from acute care to integrated care models

As acute care models tend to focus on stabilizing or curing patients with acute conditions, they tend to lack an integrated, interdisciplinary care approach that addresses not only biomedical but also behavioral and psychosocial dimensions across the care continuum.<sup>24, 34</sup> Persons with chronic conditions need integrated models of care that are based on accepted principles of chronic illness management (CIM). The most effective of these models strengthen patient-centered care systems by promoting the comprehensive provision of quality services across every possible aspect of each patient's life.<sup>35</sup> Designed according to the multidimensional needs of the target population and the individual and based on empirical evidence, integrated care models offer effective methods of balancing resource costs against outcome values by targeting their triple aim of i.e. improving population health, improving patient experience, reducing costs/ preventing increased costs.<sup>35-37</sup>

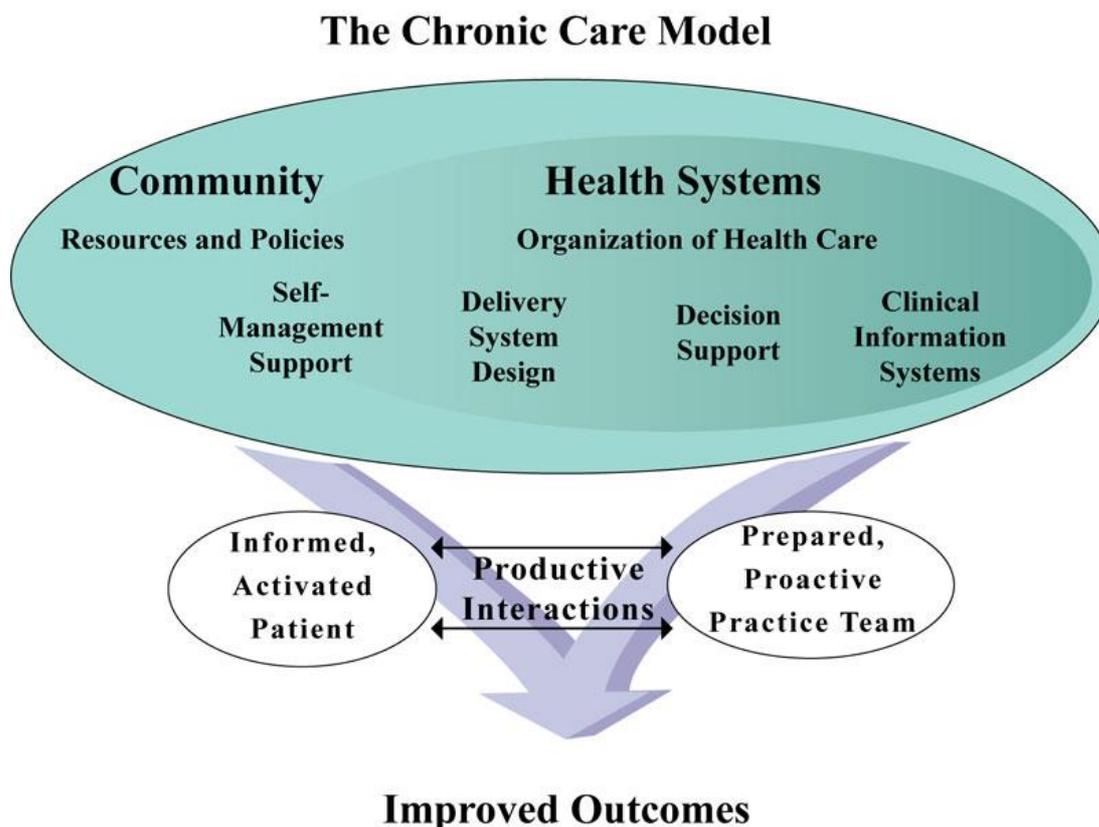
To promote and manage these new integrated care models (ICMs), nurses are taking leading roles.<sup>38</sup> Indeed, those in advanced roles, such as Advanced Practice Nurses (APNs), occupy central positions in ICMs.<sup>39, 40</sup> By fulfilling essential aspects of chronic care management (e.g., self-management support, continuity of care, first point of access), APNs have gained expert knowledge, complex decision-making skills and clinical competencies for expanded practice.<sup>41, 42</sup> Crucially, they are also normally qualified to operate within the country- and context-specific regulations governing multidisciplinary teams.<sup>43, 44</sup> With their unique insight into patients' needs, as nurses tend to work at the junction of health and social care services. This allows them a vantage point from which they can often anticipate gaps between patients' needs and the health delivery system's offerings. On a day-to-day basis, it also places them in a key position to monitor and maintain the quality of patient care.

Recently, supported by a systematic review on optimal delivery of post-alloSCT follow-up care, the National Institute of Health's Healthcare Delivery Working Group advanced an integrated alloSCT care approach promoting a multidisciplinary approach between oncologists, hematologists, internists, various other specialists and nurses.<sup>33, 45</sup> Their proposed collaboration focusses on improved handling of patient needs and more efficient use of resources.<sup>46, 47</sup> To sustain this transformation of care processes and practice patterns towards a fully integrated care model, we recommend the use of proven existing frameworks. Guiding this transition from acute-care- towards chronic-care-oriented healthcare models, these will facilitate practice pattern transformations at the levels of individuals, units, organizations, and entire healthcare systems.<sup>35</sup>

### 1.1.3 The Chronic Care Model

For example, the Chronic Care Model (CCM) is a well-established organizational framework that includes guidance on how to improve care for chronically ill populations.<sup>48</sup> The CCM (Figure 1) combines six dimensions: the community, the health system, patient self-management support, decision support, clinical information systems and delivery system design.<sup>48</sup>

Figure 1: The Chronic Care Model<sup>49</sup>



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Evidence-based components under each dimension support productive interactions between informed patients who participate actively in their care and providers with the necessary resources and expertise (Table 1). Driven by effective and productive interactions between prepared, proactive practice teams and informed, activated patients, the CCM addresses complex care needs with a strong focus on enhancing patient outcomes.<sup>48, 50</sup> Evidence supports the CCM's efficacy in chronic illness (e.g., asthma, heart failure, diabetes, depression). These include reduced mortality risk, improved health behaviors, and increased quality of life<sup>50-52</sup>, alongside favorable economic outcomes (i.e., lower costs, fewer hospital readmissions).<sup>53-56</sup> As a general rule, the more CCM dimensions are implemented, the better the outcomes.<sup>57</sup>

**Table 1:** CCM inner dimensions and example components

Dimension	Components
Self-management Support	<ul style="list-style-type: none"> <li>• Underscore the patient's central role in managing health</li> <li>• Use effective self-management support strategies, e.g., assessment, goal-setting, action planning, problem-solving</li> <li>• Organize internal and community resources to provide ongoing self-management support to patient</li> </ul>
Delivery System Design	<ul style="list-style-type: none"> <li>• Define roles and distribute tasks among team members</li> <li>• Use planned interactions to support evidence-based care</li> <li>• Provide clinical case management for complex patients</li> <li>• Ensure regular follow-up by the care team</li> </ul>
Decision Support	<ul style="list-style-type: none"> <li>• Embed evidence-based guidelines into daily clinical practice</li> <li>• Share evidence-based guidelines and information with patients to encourage their participation</li> <li>• Use proven provider education methods</li> <li>• Integrate specialist expertise and primary care</li> </ul>
Clinical Information system	<ul style="list-style-type: none"> <li>• Provide timely reminders for providers and patients</li> <li>• Identify relevant subpopulations for proactive care</li> <li>• Facilitate individual patient care planning</li> <li>• Share information with patients/providers to coordinate care</li> <li>• Monitor performance of practice team and care system</li> </ul>

Note: Adapted from <sup>58</sup>

## 1.2 EHealth as enhancement of chronic care

The “use of information and communication technology for health”—eHealth—has already had a major influence on global healthcare possibilities.<sup>59</sup> eHealth is an umbrella term for diverse uses of electronic information technology and communication uses, e.g., telemedicine, telecare, interfaces, e.g., e-mail, text messages and hardware platforms, e.g., smart phones and other mobile health (mHealth) devices. Technologies can be either interactive or non-interactive. Some are embedded within care models; others are stand-alone solutions.<sup>60</sup> eHealth offers new ways to deliver interventions that facilitate self-management, behavior change or remote monitoring of patient-reported outcomes. One major advantage is that, in the event of deterioration, eHealth minimizes both reporting and reaction times. It may also enable clinicians to tailor their communication quickly and easily, to prepare more efficiently for consultations and to minimize health care system resource use while focusing on each patient’s specific needs.<sup>61, 62</sup>

Hence, the use and implementation of eHealth has the potential to fuel this needed innovation. This also drives the European eHealth Action Plan <sup>63</sup> aiming at addressing and removing challenges in the care for chronically ill, which is also in line with the objectives of the Digital Agenda for Europe. <sup>64</sup>

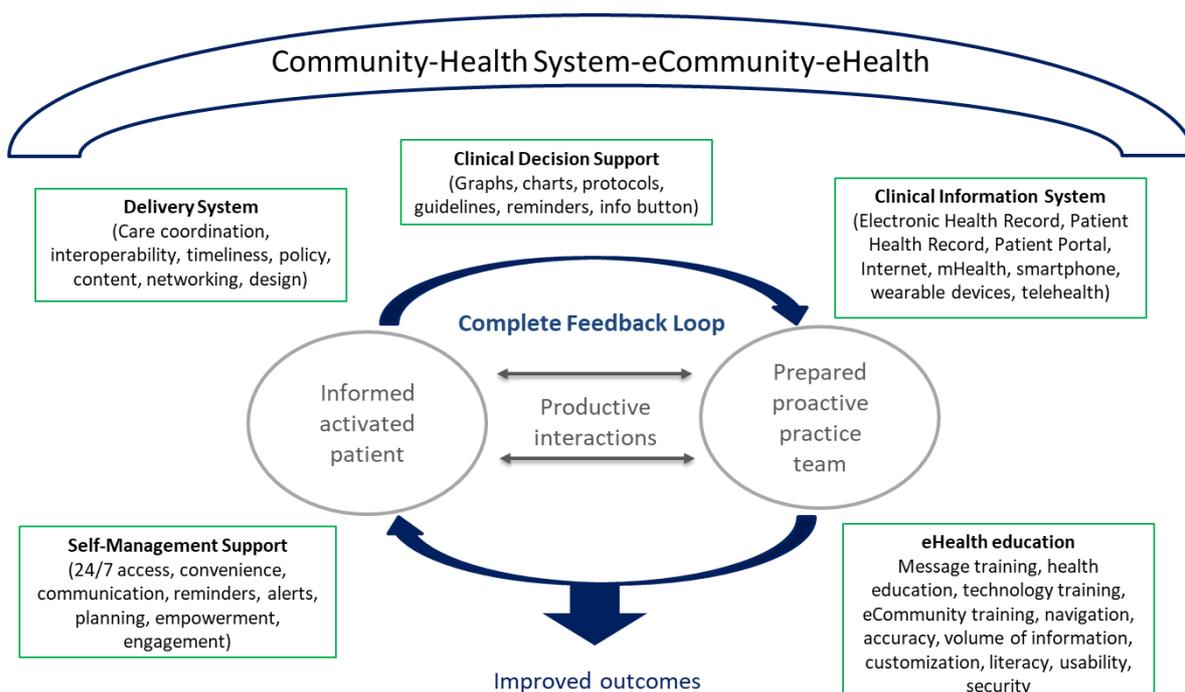
Within stem cell transplantation (SCT), the National Institute of Health (NIH) Hematopoietic Cell Transplantation Late Effects Initiative also encourages eHealth-based innovations in the care of alloSCT patients. <sup>65</sup> Two other NIH reports emphasized the urgent need for eHealth-facilitated ICMs, especially those supporting self-management and targeting medication nonadherence or other important health behaviors (e.g., physical inactivity, or healthy eating).<sup>13, 45</sup>

### 1.2.1 EHealth-facilitated ICMs in chronically ill

In 2015, Gee and colleagues used eHealth technology to enhance the CCM, while adding the dimension of eHealth education. This led to the eHealth Enhanced Chronic Care Model (eCCM).<sup>66</sup> Additionally, the eCCM provides guidance on how eHealth can be used to facilitate self-management support, re-engineer care delivery, systematize clinical decisions, integrate clinical information systems, or deliver educational components (Figure 2). Perhaps most importantly, though, at its very center, the eCCM encourages continuous feedback loops between patients and clinicians. By enabling direct intensive remote communication, these loops foster proactive patient/care team decisions.

**Figure 2:** The eHealth Enhanced Chronic Care Model developed by Gee et al. <sup>67</sup>

Figure printed with permission of the first author Perry M. Gee



In chronically ill populations, eHealth-supported self-management, e.g., via electronic monitoring of vital signs and symptoms—followed, in the event of alarming symptoms or health deterioration, by tailored nurse feedback—has already been shown to reduce hospital readmissions.<sup>68, 69</sup> Similarly, systematic reviews and meta-analyses on eCCM use in other chronic illness populations have produced compelling evidence of favorable biomedical, behavioral, psychosocial and economic outcomes.<sup>70-79</sup>

For example, several meta-analyses of randomized controlled trials (RCTs) found that eHealth-facilitated care models including at least two eCCM building blocks—e.g., self-management support and decision support—had beneficial effects on biomedical outcomes including systolic and diastolic blood pressure, LDL cholesterol<sup>70</sup> and HbA1c levels.<sup>77, 78, 80</sup> In patients with cardiovascular disease, eHealth interventions using web-based data monitoring, telemedicine and short message service support had positive effects on overall cardiovascular outcomes (e.g., myocardial infarction, stroke, hospitalizations, all-cause mortality).<sup>71</sup> In patients with congestive heart failure or chronic obstructive pulmonary disease, all-cause mortality dropped significantly when eHealth interventions included home tele-monitoring and structured telephone follow-up.<sup>70</sup>

Regarding behavioral outcomes, two systematic reviews reported significant improvements in medication adherence with an eHealth-facilitated ICM using web-based information as well as online and telephone-based care management to support collaboration and active patient engagement.<sup>74, 79</sup> Also, a recent meta-analysis concluded that eHealth interventions are effective to improve medication adherence in asthma patients, especially when combining electronic medication monitoring with audiovisual and text message reminders.<sup>79</sup> However, the overall evidence on behavioral change remains inconclusive. While one meta-analysis found consistent reductions in weight and body mass index in RCTs using eHealth interventions with web-based data monitoring and tele-medical support<sup>71</sup>, other studies reported mixed results regarding the impact of computer-based assessment, education and graphical feedback, as well as action planning and problem solving for self-management of physical activity and dietary behavior (i.e., reduced dietary fat/increased fruit and vegetable intake).<sup>72, 81-84</sup>

In view of psychosocial outcomes, two systematic reviews found that eHealth interventions featuring automated telephone communication systems embedded in complex multimodal packages (e.g., symptom monitoring by health professionals and interactive voice response), produced significant benefits for depressive symptoms in patients with chronic diseases.<sup>74, 84</sup> Other meta-analyses and systematic reviews have noted significant intervention effects of self-management support using web-based systems for self-monitoring, electronic reminders, visits and email-contact with the health care team, alongside connections to other patients (to promote patient empowerment).<sup>70,</sup>

<sup>82</sup> One systematic review also found that eHealth interventions such as tele-medicine-supported education and self-management programs improved quality of life in several chronic illness populations (e.g., asthma, COPD, congestive heart failure).<sup>70</sup>

While evidence regarding the eHealth-facilitated ICM's economic outcomes remains limited, several systematic reviews and meta-analyses have found significant reductions in all-cause hospitalizations <sup>70,71</sup>, all-cause emergency department visits (e.g., OR=0.27, CI 0.11 to 0.66 <sup>70</sup> – a 40% reduction) and hospitalization days (-30%).<sup>82</sup> Likewise, a recent systematic review evaluating telemedicine programs' effects on net expenditures in chronically ill populations concluded that they generally reduce costs. <sup>73</sup> However, while it is known that there are broad cost ranges between intervention components, disease types, eHealth equipment used and additional services provided, it is common that no information is available on overall program costs. This lack makes it difficult to make a solid economic case to policy makers, care providers or other stakeholders when considering what levels of reimbursement would be necessary to sustain these programs.<sup>73</sup> Moreover, most studies on eHealth-facilitated ICMs in chronically ill tested their interventions in highly controlled populations and settings with far fewer implementation challenges than in real-life settings. Although some systematic reviews conclude that researchers need to focus more on assessing and tackling barriers to the adoption of eHealth chronic care models, understanding facilitators and choosing appropriate implementation strategies, little evidence is available to support such conclusions.<sup>70, 72</sup>

### 1.2.2 EHealth-facilitated ICMs in organ transplantation and cancer care

The two groups of patients whose care needs are comparable with those of alloSCT patients are the cancer and solid organ transplant populations. Therefore, for guidance regarding the eHealth-facilitated ICMs, we considered evidence from one meta-analysis <sup>76</sup> and three studies in solid organ transplantation <sup>68, 69, 85-87</sup> as well as one meta-review <sup>88</sup>, three systematic reviews <sup>89-91</sup> and one landmark RCT <sup>92, 93</sup> in cancer patients.

#### *Organ transplant setting*

To compare the benefits and problems associated with eHealth interventions, Tang et al. <sup>76</sup> analyzed 21 transplantation trials—9 in kidney, 5 in multi-organ, 5 in lung, 1 in liver and 1 in heart transplantation. Finding little evidence either of improved short-term medication adherence (risk ratio, 1.34; CI, 1.12-2.56;  $I^2 = 75\%$ ) or of self-monitoring behavior (risk ratio, 2.58; CI, 1.56-4.27;  $I^2 = 0\%$ ), they suggested that individualized, multifunctional interventions combining more than one mode of delivery (human versus technology) might produce better outcomes.<sup>76</sup> However, several weaknesses may have

affected their results. For example, all of their included studies had small sample sizes; only 9% were based on behavioral theory; and only 5% of the tested interventions were designed with the participation of their end users (patients/clinicians).<sup>76</sup>

A recently conducted single-center, pre-post observational pilot study by Schenkel and colleagues examined 28 lung transplant patients exposed to a novel post-discharge home monitoring program.<sup>94</sup> The monitoring included data transfer between bluetooth-enabled devices measuring blood pressure, heart rate, weight, blood glucose, oxygen saturation, pulmonary function and physical activity levels. The technological component also allowed patients to self-report signs and symptoms, track appointments and medication adherence and receive educational materials. Compared to the usual care group (UCG) the intervention group (IG) had fewer readmissions (IRR: 0.56; 95% CI: 0.41 – 0.76;  $p < 0.001$ ), fewer days readmitted (IRR: 0.46; 95% CI: 0.42 – 0.51;  $p < 0.001$ ), and less time spend in hospital (IRR: 0.52; 95% CI: 0.51 – 0.54;  $p < 0.001$ ). Unfortunately, the authors did not report on their development process, or on any observed negative effects or barriers experienced by the patients.<sup>85</sup>

One RCT conducted by Schmid and colleagues evaluated eHealth-facilitated case management in the follow-up of 46 kidney transplant patients.<sup>69</sup> Based on patient-reported data collected via an interactive terminal at each patient's home, the care team provided risk-adjusted chronic care management. The system allowed remote tele-monitoring and prompt real-time video consultations with the care coordinator. It also prompted patients daily to report on their fluid balance, vital signs, immunosuppressive intake and symptoms. As the primary patient contact person, the care coordinator provided them feedback and support tailored to their values and issues. Intervention patients showed better medication adherence ( $r=0.62$ ), improved health-related quality of life ( $r=0.42$ ), reduced healthcare utilization ( $r=0.62$ ), and fewer ( $r=0.44$ ) and shorter ( $r=0.41$ ) unplanned re-hospitalizations. This resulted in a total cost saving of roughly 3000€ per patient per year in the first year post-transplant.<sup>68, 69</sup> Again, information on how the intervention's developed is absent. Also, the authors indicated that the current German healthcare reimbursement practices were an obstacle to the intervention's sustained implementation or scaling-up.<sup>69</sup>

Another RCT tested the efficacy of the Pocket PATH® eHealth intervention, which was developed using end user involvement to support self-management in the first year post-lung transplantation (e.g., recording daily measurements of relevant health indicators, tracking trends in measurements, recognizing critical values, and decision-making support regarding when/whether to contact clinicians).<sup>95</sup> That intervention also generated an automatic reminder for the patient to call the transplant coordinator whenever a critical value was recorded. At one year post-lung transplantation the

intervention group showed better self-monitoring (OR 5.11, 95% CI 2.95–8.87), adherence to medical treatment (OR 1.64, 95% CI 1.01–2.66), and reporting of abnormal health indicators (critical values of, e.g., spirometry, vital signs, symptoms) to clinicians (OR 8.9, 95% CI 3.60–21.99) compared to the usual care group.<sup>95</sup> In view of re-hospitalizations (OR 0.78, 95% CI 0.36–1.66,  $p=0.51$ ) and mortality, no differences were observed between the two groups (hazard ratio 1.71, 0.68–4.28,  $p = 0.25$ ) beyond one year post-transplantation.<sup>86</sup>

Regardless of the overall reported benefits of the above-cited studies, it must be noted that all had small sample sizes and most had short-follow-up periods. None reported adequately on negative effects and very few used content development processes that were theory-driven or involved their end users (patients and/or clinicians). Considering Tang et al's conclusion in their systematic review on eHealth interventions in organ transplant patients <sup>76</sup>, these deficits would likely hinder uptake in real-world contexts.

### *Cancer Setting*

In cancer research, one meta-review summarized evidence gathered by 10 systematic reviews regarding the effects of eHealth on patients and caregivers confronted with cancer.<sup>88</sup> The authors reported effects on perceived support, knowledge levels, and patients' information competence; however, their findings for psychological wellbeing, depression and anxiety, and quality of life were inconsistent. No effects were found regarding physical and functional wellbeing. However, few of the included reviews focused on any specific type of cancer, making it challenging to evaluate differences in patients' informational or support needs.<sup>88</sup>

Warrington and colleagues conducted a systematic review of studies published between 2000 and 2017 focusing on electronic systems for patients to report and manage side-effects.<sup>91</sup> Of the authors' 41 identified systems, 24 (58%) allowed clinicians to remotely monitor electronic patient-reported outcomes (ePROs), 17 (41%) provided alerts for clinicians in the event of alarming symptoms, 19 (46%) involved features to monitor ePROs over time with graphs presented to patients and 17 (41%) provided general information about side effects. Features providing tailored and automated feedback to patients were less frequent (12; 29%); and only 6 (15%) offered the option of communicating with clinicians.<sup>91</sup> Also, the broad heterogeneity of outcomes and measurements used and the limited information provided about the tested systems' content and features precluded evaluation of associations between either the eHealth systems or their outcomes.<sup>91</sup>

Aapro and colleagues recently performed a scoping review on eHealth tools aimed at supporting cancer patients.<sup>89</sup> Of the 66 publications identified, 38 (58%) used

eHealth solutions that combined ePROs with remote monitoring; 21 (32%) also provided self-management support and reported improvements in various symptoms (i.e., fatigue, pain, anxiety), quality of life and overall survival.<sup>89</sup> The authors also report on key factors facilitating the uptake and use of eHealth systems. The most important of these were ease of use, reassurance, high usability and usefulness, improved communication, correct alerts and short response times, patient empowerment and the convenience of real-time symptom reporting. The most substantial barriers were problems with the technology or connectivity, limited usefulness, lack of clarity regarding language and false alerts.<sup>89</sup>

Hernandez Silva and colleagues performed a systematic review of mHealth interventions focusing specifically on pain, psychological distress, fatigue, and sleep in cancer survivors.<sup>90</sup> From the seven studies they reviewed, four reported improvements in fatigue, three in pain and two in sleep outcomes, with mixed results for psychological distress. Once again, though, due to the limited number of studies available, the authors could not draw firm conclusions regarding factors influencing the use and uptake of mHealth interventions.<sup>90</sup>

One of the most important studies of the past decade was Basch and colleagues' RCT in a sample of 766 patients with advanced cancer.<sup>93</sup> Via a web-based ePRO questionnaire platform, intervention group patients provided self-report data on 12 common symptoms. If patients reported severe or worsened symptoms, an email alerted study nurses to telephone the patient with non-systematic symptom management feedback.<sup>93</sup> Regarding health-related quality of life, compared to the control group (who received usual care), a much greater percentage of the intervention group showed improvement (34% vs. 18%, respectively) and significantly fewer showed deterioration (38% vs. 53%;  $p < 0.001$ ). The intervention group also showed improved quality of life-adjusted survival (mean: 8.7 vs. 8.0 months,  $p = 0.004$ ), fewer emergency room visits (34% vs. 41%,  $p = 0.02$ ) and hospitalizations (45% vs. 49%,  $p = 0.08$ )<sup>93</sup>, as well as a significantly longer median overall survival (31.2 months vs. 26.0 months,  $p = 0.03$ ).<sup>92</sup> The publication of these results led to a substantial increase in the number of commercial apps targeting cancer patients' needs or monitoring ePROs.<sup>89</sup> However, despite these impressive results, the authors' scant reporting regarding the delivered interventions' exact content, mode of delivery, theoretical underpinnings or mode of behavior change mean these interventions mainly remain a black box.

### 1.2.3 EHealth-facilitated ICMs in alloSCT care

EHealth-facilitated ICMs are also promising as a means of strengthening alloSCT follow-up care. However, no previously-published model covers two or more of the eCCM dimensions.<sup>24</sup> Only two randomized controlled trials have integrated even single

eCCM components. Bryant et al. (2020) integrated a self-management support component by implementing ePROs into routine care during the first two weeks post-autologous (n=45) and alloSCT (n=31), followed by tailored nurse support.<sup>96</sup> As results, the authors reported reduced peak symptom burden ( $p=0.03$ ) in the intervention group (compared to the control group). Syrjala et al. (2018) tested an internet-based survivorship care program including self-management support and decision support components by offering an online educational website with and without online problem-solving support for long-term survivors (>3 years post-autologous (n=182) and alloSCT (n=566)). Their results showed reduced treatment distress for the intervention group ( $p=0.032$ ).<sup>97</sup> However, both studies were neither conceptually embedded nor reflective of all eCCM dimensions and focused only on very specific treatment phases.

While these RCTs in alloSCT produced promising results, overall feasibility and patient satisfaction remain uncertain. Another recently conducted pilot trial testing only telehealth visits pre- and post-SCT in mainly autologous SCT patients (80% autologous; 20% allogeneic) also reported barriers, including suboptimal communication or delays of physical examinations.<sup>98</sup> Patients stated they would prefer a mix of in-person and telehealth counseling to pure telehealth follow-up.

### 1.3 Marrying Implementation-, behavioral -and computer science methods

Despite compelling evidence on the beneficial effects of eHealth integration into care models in chronically ill populations successful implementation of eHealth applications for cancer and organ transplant patients in clinical practice is often problematic.<sup>70, 71, 99, 100</sup> Researchers often test their interventions within tightly controlled settings that allow them to focus on the interventions' internal validity. While this is certainly valuable, success in clinical trials is no guarantee of implementation. In fact, as many as two-thirds of findings that survive the clinical trial phase never cross the gap between clinical trials and the complexities of clinical practice.<sup>101</sup>

One major problem is that researchers tend to focus more on general patient populations than on target contexts with specific user needs. For example, researchers testing ready-made, commercially available eHealth applications, either as components to be added to established care models or within controlled trial settings, commonly reported adoption problems, with 44% to 67% of patients discontinuing the use of the offered eHealth applications.<sup>102-105</sup> This was mostly due to a poor fit between the tested applications and users' needs and/or preferences, the context of use or a lack of behavioral theory guiding content development.<sup>102-106</sup> Any of these reasons would be enough to mask the value of an otherwise excellent digitally delivered intervention.

The current evidence suggests that integrated care models using eHealth have

much stronger chances of successful, sustainable implementation if they are constructed using principles drawn from various disciplines. While the eCCM can provide guidance for developing the needed innovation in alloSCT care, rolling out an eHealth-facilitated ICM within a real-world context will benefit hugely from the application not only of implementation science<sup>107</sup>, but also of behavioral and computer science methodologies, i.e. use of behavioral theory, the application of a user-centered design (UCD), and agile software development processes.<sup>105, 108-110</sup> In addition to supporting the context-specific development of an eHealth-facilitated ICM, marrying these methodologies will provide the necessary behavioral underpinnings and end-user development process orientation that are necessary to impact outcomes. The following paragraphs describe these methodologies.

### 1.3.1 Implementation science methods

As the above evidence and examples suggest, it cannot be assumed that complex interventions such as eHealth-facilitated ICMs can easily be implemented into daily clinical practice.<sup>111</sup> Overall, as few as 14% of high-quality empirical findings are ever translated into routine clinical practice; and of those, only a fraction are implemented sustainably.<sup>112</sup> And even when successful implementation does occur, it takes a mean of 17 years.<sup>112</sup>

Implementation shortfalls are major contributors to research waste. Generally speaking, research waste occurs in two forms. Research waste I is avoidable methodological weaknesses within studies, e.g., an insufficient evidence base or incomplete reporting; research waste II refers to the common failure to translate and implement evidence-based innovations from the trial world to real-world contexts.<sup>101</sup> Although measures are available to reduce research waste I (e.g., obligatory registration of studies, the creation of clinical trial units, the publication of reporting guidelines), these usually focus on conducting studies and reporting results. The problem was, the authors of even the most methodologically sound studies had serious difficulty translating their findings into routine clinical practice.<sup>101</sup> I.e., sustainable implementation is by no means a natural outcome of scientific rigor or efficacy.

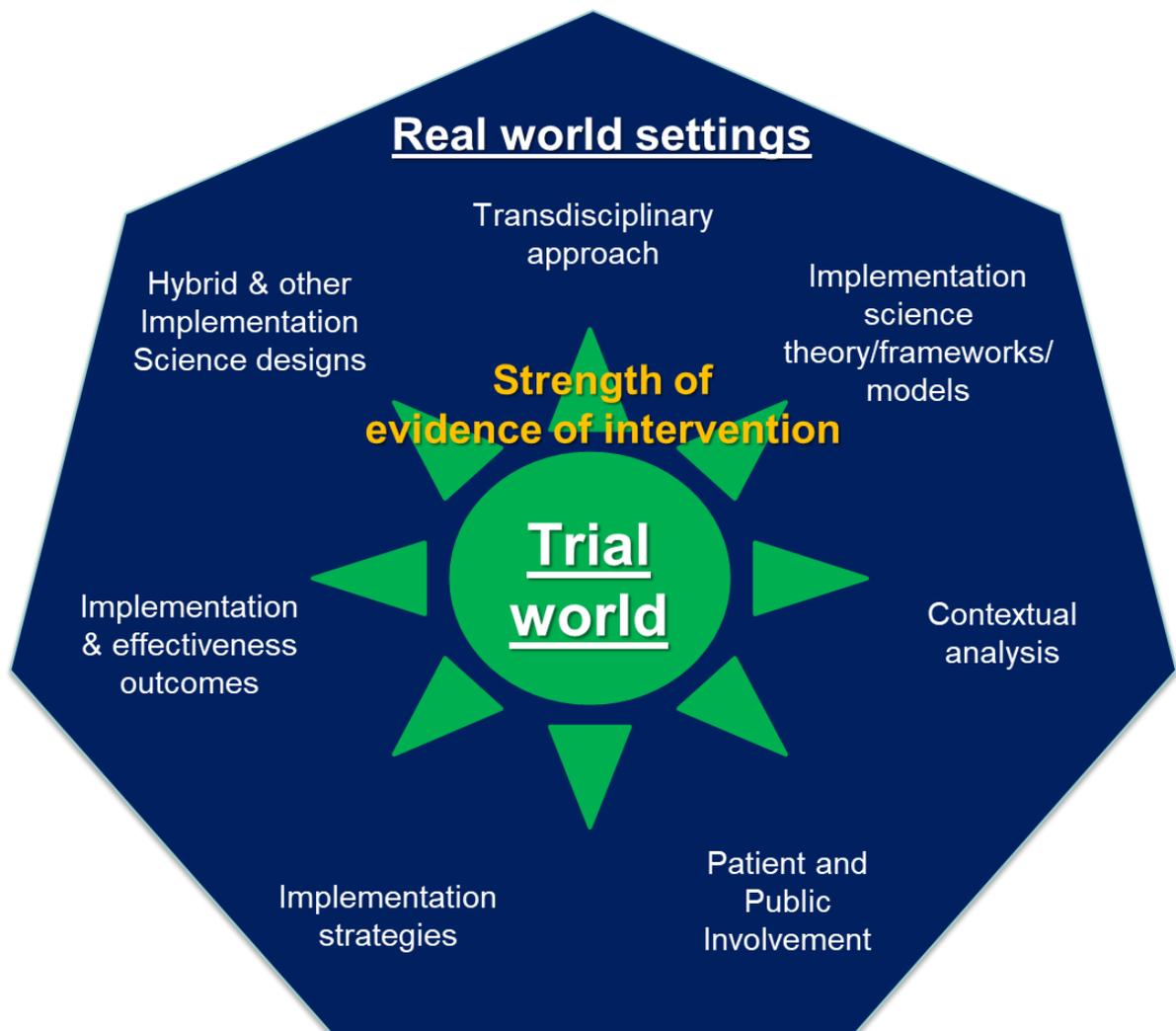
The recognition led to calls for a methodology focused on implementation. Implementation science answers those calls.<sup>113, 114</sup> Augmenting existing clinical research methods, implementation science methods apply a comprehensive view at the patient, provider, organization, and policy levels of healthcare to facilitate the translation of research findings into routine clinical use.<sup>111, 114</sup>

Implementation science is “the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine

practice, and, hence, to improve the quality and effectiveness of health services and care".<sup>115</sup> Its strength lies in its panoramic methodological considerations. From the earliest stages of research, these focus on charting a course from project planning, through clinical trials and dissemination of findings to sustainable implementation in real-world settings.<sup>101</sup>

For an intervention as complex as an eHealth-facilitated ICM, successful implementation requires the application of seven implementation science-specific methods. These are depicted in Figure 3 (below), followed by a brief summary of each.  
107, 116

**Figure 3:** The Basel Heptagon of Implementation Science<sup>101</sup>



### *1. Transdisciplinary research teams*

Implementation science projects are typically conducted by transdisciplinary teams, as the implementation scientist's knowledge and skills do not replace but complement those of other team members. EHealth-facilitated ICM teams might also include clinical experts, behavioral scientists, software engineers and usability/user experience specialists.

### *2. Implementation science-specific theoretical frameworks or models*

Either all or key parts of implementation science studies should be guided by implementation science-specific models. Nilsen and colleagues have divided the vast range of implementation science theories, models, and frameworks into five basic categories: 1) process models; 2) determinant frameworks; 3) classic theories; 4) implementation theories; and 5) evaluation frameworks. While process models (e.g., the Ottawa Model) help describe the translation of research into practice <sup>117</sup>, determinant frameworks, classic theories and implementation theories (e.g., CFIR, Theory of Diffusion, COM-B) <sup>118</sup> support the understanding of factors that influence implementation outcomes <sup>119, 120</sup>, while evaluation frameworks facilitate evaluation of implementation processes. (e.g., RE-AIM).<sup>121</sup>

### *3. The contextual analysis*

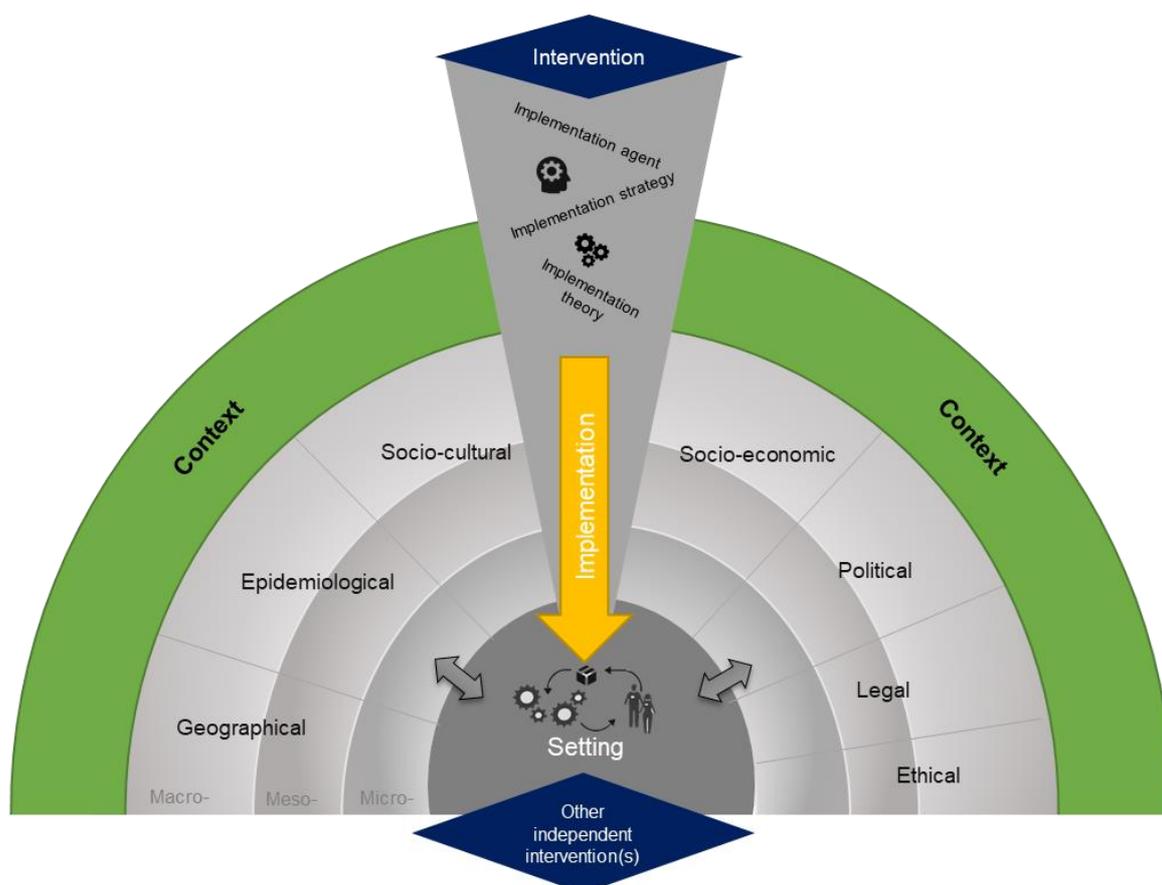
Conducting a contextual analysis allows researchers to understand which specific characteristics of their target settings require consideration within the intervention. These analyses also inform intervention design and the choice of contextually relevant strategies (also referred to as implementation strategies) that will later facilitate implementation. <sup>122</sup>

The relevance of context in implementation science is mirrored in the abundance of theories, frameworks or models available for its analysis. Unfortunately, existing frameworks use heterogeneous definitions both of context and its relevant dimensions. <sup>123</sup> To allow a reliable contextual analysis—one informed by multiple sources, including patients, caregivers and clinicians—the implementation team needs a solid theoretical framework upon which to assess and map relevant dimensions and factors that will later shape the project (in our case, the development and implementation of an eHealth-facilitated ICM). <sup>124</sup> Existing frameworks provide limited “how-to” support, since the factors they deal with are commonly too generic to provide sufficient detail to perform a meaningful contextual analysis.<sup>122</sup> Truly useful methodological guidance on how to conduct and use contextual analyses findings is scarce.

One theoretical structure that offers particularly meaningful guidance for contextual analysis is the Context and Implementation of Complex Interventions (CICI) framework.<sup>125</sup> Designed to guide researchers through both determinant and evaluative

territory, the CICI Framework does not simply describe the three dimensions of context, implementation and setting, but also describes their interactions with one another and with the intervention (Figure 4). Context comprises seven domains, implementation five; and setting refers to the physical location where an intervention is meant to be implemented.<sup>125</sup> As this model does not explain how to perform a detailed assessment of a prospective setting, complementary support from another model is needed. To fill this gap, the eCCM is particularly useful, as it has the capacity to operationalize all necessary CIM dimensions.<sup>66</sup> Embedded within the CICI framework, the five inner eCCM dimensions (self-management support, delivery system design, decision support, clinical information systems and eHealth education) guide the user through a thorough contextual analysis that covers setting-specific structural characteristics, practice patterns concerning CIM, and clinicians' and patients' openness towards eHealth.

**Figure 4:** Adapted from the Context and Implementation of Complex Interventions framework.<sup>125</sup> (Figure printed with permission of the first author, Lisa Pfadenhauer)



**Note:** The context and implementation of complex interventions (CICI) framework includes three dimensions: context, implementation and setting. There are seven contextual domains: geographical, epidemiological, socio-cultural, socio-economic, political, legal and ethical. Implementation consists of dedicated agents, strategies, theory, processes, and outcomes. Within the setting, the intervention and its implementation interact with the context. The grey layers represent the micro, meso and macro levels, on which implementation, context and setting can occur. Apart from the intervention of interest, the context and the way the intervention of interest is implemented may be advanced or compromised by other interventions working independently but targeting the same setting and population.

### *4. Patient and Public Involvement*

Implementation science projects depend heavily on the vigorous involvement of all relevant stakeholder groups. This extends from intervention co-design to User-Centered Design and the discussion of outcomes and strategies needed for implementation.<sup>101</sup> For our purposes, intervention co-design refers to a participatory development approach that brings together all relevant end users to help design solutions that fit the context. When designing eHealth components, a User-Centered Design approach is one method of involving end users early in the development process. At this and every other stage, the central aim is to produce highly usable products that fit the target context and end user needs.<sup>126</sup>

### *5. Implementation strategies*

Implementation strategies are “methods or techniques used to enhance the adoption, implementation, and sustainability of a clinical program or practice”.<sup>127</sup> To describe the active ingredients of an implementation process, Powell and colleagues defined a set of 73 discrete implementation strategies.<sup>128</sup> These strategies include activities such as conducting a local needs assessment, setting up new clinical teams, revising roles or developing educational materials.<sup>128</sup> The strategies appropriate to implement and sustain a new program or practice depend on the characteristics of the setting where it will be used, i.e., the choice and application of each implementation strategy is always setting/context-specific.<sup>129</sup>

### *6 & 7. Implementation and effectiveness outcomes & Hybrid and other implementation science designs*

An implementation’s success is reflected well beyond its effectiveness outcomes. Evaluation should also cover implementation pathways and outcomes. An intervention’s implementation outcomes include its acceptability, feasibility, fidelity or reach. All of these give insights into the success of a new program or practice’s implementation.<sup>130</sup>

Studies that focus both on effectiveness and on implementation outcomes can use hybrid effectiveness-implementation designs.<sup>116</sup> These serve two aims. First, by testing an intervention’s effectiveness alongside its implementation outcomes (e.g., acceptability, adaptability, fidelity, and reach), they address the problem in terms of adoption, uptake or sustainability of interventions in day-to-day clinical practice.<sup>131</sup> Second, both to describe the effects of interactions between an intervention and its implementation and to generate knowledge about the chosen implementation pathway, researchers can apply mixed-methods evaluations (i.e., a combination of quantitative and qualitative methodology). Mixed-methods evaluations also provide valuable insights on how to optimize implementation strategies while scaling out programs or practices to other settings.<sup>132</sup>

Based on the strength of evidence concerning the intervention under consideration and the balance of priorities between effectiveness and implementation outcomes, three types of hybrid design—hybrid 1,2, or 3—are possible.<sup>116</sup> For a hybrid 1 design, the primary focus is on testing an intervention’s effectiveness, while also gathering implementation information. A hybrid 2 design places equal weight on an intervention’s effectiveness data and its implementation processes/strategies; and a hybrid 3 design primarily tests the implementation strategies, while also gathering information on effectiveness outcomes.<sup>131</sup>

In **Chapter 3**, the article titled “Clinicians and Patients Perspectives on Follow-up Care and eHealth support after Allogeneic Hematopoietic Stem Cell Transplantation: A Mixed-Methods Contextual Analysis as part of the SMILe Study” presents how we developed a new methodological approach to conduct a contextual analysis by merging “The context and implementation of complex interventions framework” and the eHealth “Enhanced Chronic Care Model”, and by using mixed methods. The article also summarizes the findings and describes how they informed the choice of implementation strategies to facilitate the development and implementation of an eHealth-facilitated ICM for alloSCT patients in Freiburg im Breisgau, Germany.

### 1.3.2 Implementation and behavioral science driving the content development

For this project, our contextual analysis provided vital information on how to re-design alloSCT care from the current acute-care perspective towards an eHealth-facilitated ICM approach.<sup>133</sup> As alloSCT patients are at a high risk for chronic long-term complications, they require comprehensive, proactive follow-up care that integrates behavioral and psychosocial support to improve long-term outcomes. This is not yet covered by the current model of care; and while we are certain that, across countries, diseases and settings, the future of health care will include eHealth, we also understand that the chances of successfully implementing any care model into a clinical setting without first understanding the target context and the end-users’ needs and preferences are extremely small.

Indeed, despite the plethora of studies or commercial eHealth applications available, only a handful have been developed in collaboration with patients, clinicians and behavioral scientists.<sup>105, 134</sup> For example, several reviews of eHealth applications for patients with cancer found that a most lack a theoretical base: documentation on only six of 23 reviewed apps referred to a theory or model of behavior change.<sup>105</sup> Fewer than 20% refer to empirical studies or background source information; only 11.3% were found

to be evidence-based; and just 10.3-50% involved clinicians in their development processes.<sup>135-137</sup> Such omissions result not only in gaps separating the needs and preferences of end-users (whether patients or clinicians) from the eHealth solutions offered, but also in non-effective content in terms of behavior change.<sup>134</sup> For our eHealth-enhanced integrated care model, we intend to minimize such gaps and increase the chances of sustainable uptake by basing our content on implementation science principles and behavioral theory.<sup>105</sup>

While implementation science methods promote rigorous methods of involving all relevant stakeholders, inform choices of implementation strategies and facilitate development of context-adapted content, those same methods also drive theory-guided content development. This ensures the use of proven behavior change content, while anticipating clear sets of possible user actions.

### 1.3.3 Context and theory-guided development of the SMILe-ICM

Applying our newly-designed methodological approach allowed us to perform a contextual analysis in the first alloSCT treatment center.<sup>133</sup> This revealed important findings concerning structural characteristics, CIM-related practice patterns and technology openness from the perspectives of clinicians and patients.

The analysis revealed that the current care model focuses mainly on diagnosing and managing problems, i.e., it is acute-care driven. In- and outpatient care is mostly separate, with limited collaboration between the two clinician teams. Outpatient alloSCT follow-up is mainly physician-driven, focusing primarily on medical therapy options, with no nurse involvement in care delivery and limited attention to patient self-management or behavioral support. These results directly informed our development of the ICM in allogeneic **Stem**-cell-transplantation facilitated by **eHealth** (SMILe-ICM).

Based on our contextual analysis, we choose the eCCM as our guiding model for the construction of the SMILe-ICM. By facilitating a more interdisciplinary team approach, the eCCM allowed us to improve the connection between the in- and outpatient settings. And regarding continuity of care and self-management support, it uses eHealth to supplement human contact between patients and providers, not to replace it.

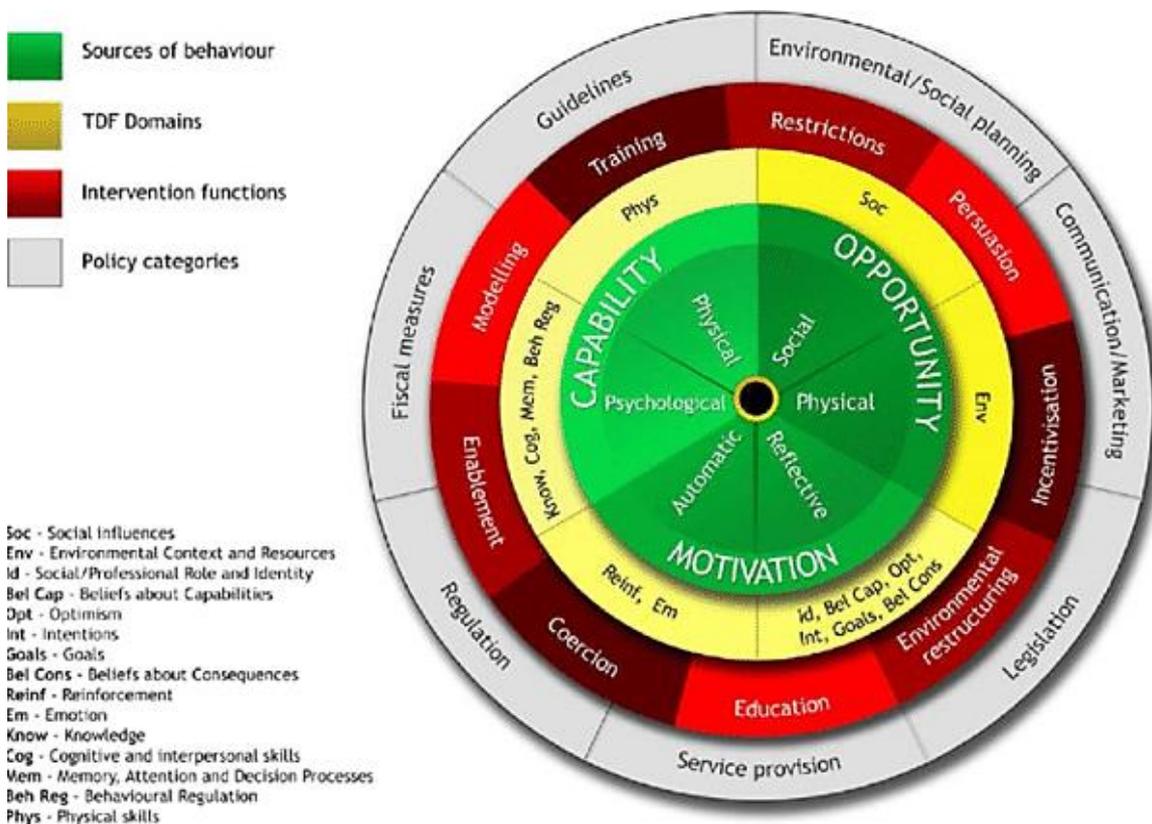
Based on the contextual and scientific evidence, four self-management intervention modules have been identified which need to embed within the SMILe-ICM: monitoring and follow-up of symptoms, infection prevention, medication adherence and physical activity. However, to be effective, interventions need to follow a causal behavioral pathway related to a health behavior important to the target group, i.e., they need to target specific behaviors linked to a desired outcome. The integration of behavior change techniques (BCTs)—commonly defined as the active ingredients of behavior

change interventions—allows the construction of reproducible interventions that trigger changes in these behaviors’ psychological determinants and consequently improve health outcomes.<sup>138</sup> One of the most respected behavioral frameworks currently available is Michie’s Behavior Change Wheel (the BCW).<sup>120</sup> As depicted in Figure 5 (below), the BCW provides solid methodological guidance for the development of systematic, content-adapted interventions that integrate effective BCTs.<sup>120, 139</sup>

The Behavior Change Wheel is a systematic three-stage, eight-step approach that combines 19 tested behavior change frameworks to help clinicians understand, explain and, most importantly, change patient behaviors.<sup>120</sup> With the Capability-Opportunity-Motivation-Behavior (COM-B) Model at its hub, it can also be combined with the Theoretical Domains Framework (TDF).<sup>120</sup>

Working with 14 domains representing theoretical constructs such as knowledge, skills, goals or beliefs belonging to COM-B components, the TDF synthesizes key theoretical constructs used in behavioral theories. Combined with the COM-B, it helps to identify the changeable behavioral problems that are most likely to impact the desired outcomes.<sup>139</sup>

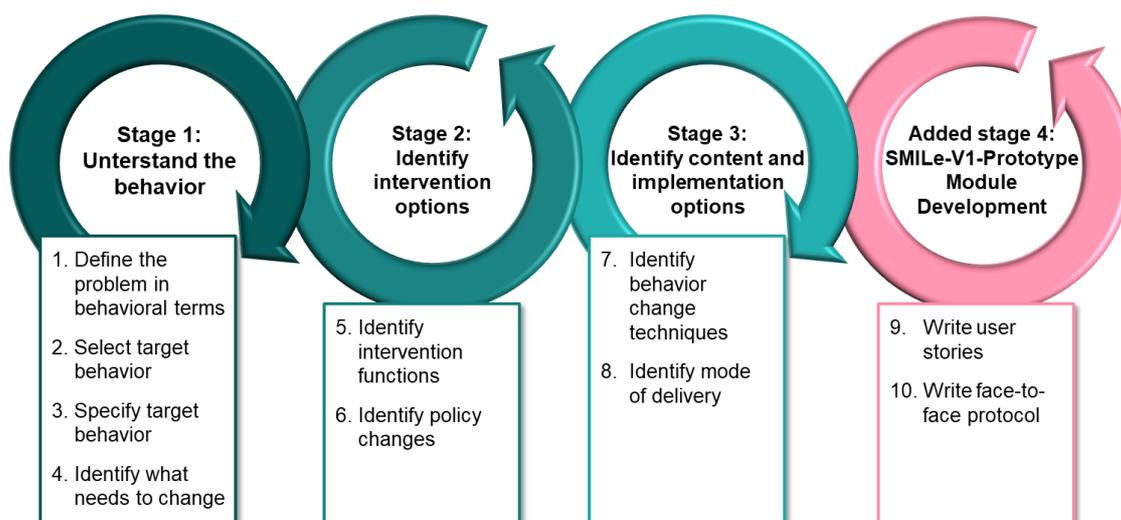
Figure 5: The Behavior-Change-Wheel <sup>120</sup>



Following the three-stage, eight-step Behavior Change Wheel, target behaviors can be defined by mapping both empirical evidence and contextual information to the COM-B taxonomy. After choosing intervention functions for all target behaviors, intervention developers can select appropriate TDF domains and BCTs. Application of the six APEASE criteria—affordability, practicability, effectiveness, acceptability, safety and equity—after each stage helps to prioritize intervention functions and BCTs.

The next step of our SMILe-ICM's development was to define the mode of delivery (human (face-to-face) and/or technology-based). As this is the final step of the BCW's final stage, we have added a fourth stage to accommodate two additional steps that support ongoing SMILe-ICM module development. This stage involves writing a face-to-face intervention protocol and a description of the functionalities to be digitized as *user stories* (Figure 6). The detailed process of intervention development for the medication adherence module, which is outside the scope of this dissertation, is very well described in an article by Ribaut et al. <sup>140</sup>

**Figure 6:** The stages and steps of the BCW, including our added stage 4.



In **Chapter 4**, the article, “Development of an Integrated Model of Care for allogeneic **Stem** cell transplantation facilitated by **e**Health—The SMILe Study” presents the SMILe-ICM's development process. This process consisted of four steps: 1) an account of the SMILe-ICM's set-up within a theoretical foundation; 2) a theory-guided intervention development phase using behavioral science methods; and 3) the choice and development of a delivery method (human/technology) that uses behavioral and computer science methods. These steps resulted in step 4—a description both of the intervention's characteristics and of its use in daily clinical practice.

### 1.3.4 Implementation-, behavioral-, and computer science methods driving the software development process

The combination of methodologies from three fields—implementation-, behavioral-, and computer science—helps balance context-specific requirements with end-user needs, while providing a stable theoretical underpinning for content. We are confident that this will increase the resulting intervention’s technology acceptance and overall sustainability.<sup>105, 108, 141</sup> However, such a combination is rare to date and mainly employed in the conception phase of eHealth-facilitated ICMs.<sup>105, 141, 142</sup>

The process of creating associated eHealth software components is less clear: the team responsible for defining content works often separately from the team creating the actual software. Handing a fully defined blueprint over to a software team and waiting until it is finished bears the obvious risk that the delivered components will not look or function as intended.<sup>143</sup> To avoid such problems, we employed agile software development processes.

Coined in 2001, “agile software development” signifies a family of development processes that value and focus on individuals and interactions, working software, customer collaboration and responses to change over processes and tools, comprehensive documentation, contract negotiation and the definition and adherence to a plan.<sup>110</sup> As the name implies, agile development promotes fast, iterative processes, in which working software increments are created, delivered and discussed regularly via collaboration between self-organizing, cross-functional teams.<sup>143</sup>

Ideally, agile software development can be combined with user-centered design (UCD),<sup>109</sup> an iterative design process with the goal of developing highly usable and accessible products.<sup>126</sup> Following UCD principles, intervention designers place end-users’ (e.g., patients/caregivers/clinicians) preferences, needs and feedback at the center of each design process phase. While helping researchers to focus closely on creating high-priority functionality, it acknowledges the value of stakeholder groups, encouraging regular presentations of current product increments to them. In addition to ensuring that products will be effective, UCD ensures that the intended users find them usable and manageable, thereby enhancing their acceptability.<sup>108, 144</sup>

#### *Legal requirements of eHealth components*

Both the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) have recognized software’s growing role as a medium for diagnostic or therapeutic devices. The FDA currently defines medical software (or eHealth components) either as applications intended to be used either as medical devices or as parts of hardware medical devices.<sup>145</sup>

Meanwhile, in Europe, several attempts have been made to provide software developers with guidance regarding which standards to use when developing software components. For example, the European Commission's eHealth Action Plan 2012-2020 defined a policy roadmap and digital agenda that also included Medical Device Regulation (MDR) EU2017/754, which was launched in 2017 and is set to become operational in May 2021.

However, boundaries between non-medical and medical device software components remain poorly defined. Any eHealth components that collect electronic patient-reported outcomes such as symptoms or vital signs can easily fall under the new regulations as soon as they go beyond displaying values.<sup>61</sup> These new regulations, which are meant to protect the end-users, may instead place major obstacles in the way of development: medical devices require tightly-controlled development and complex certification processes that include risk-analyses, extensive documentation and ongoing quality management—all of which can easily go beyond the limited resources of academic project teams.

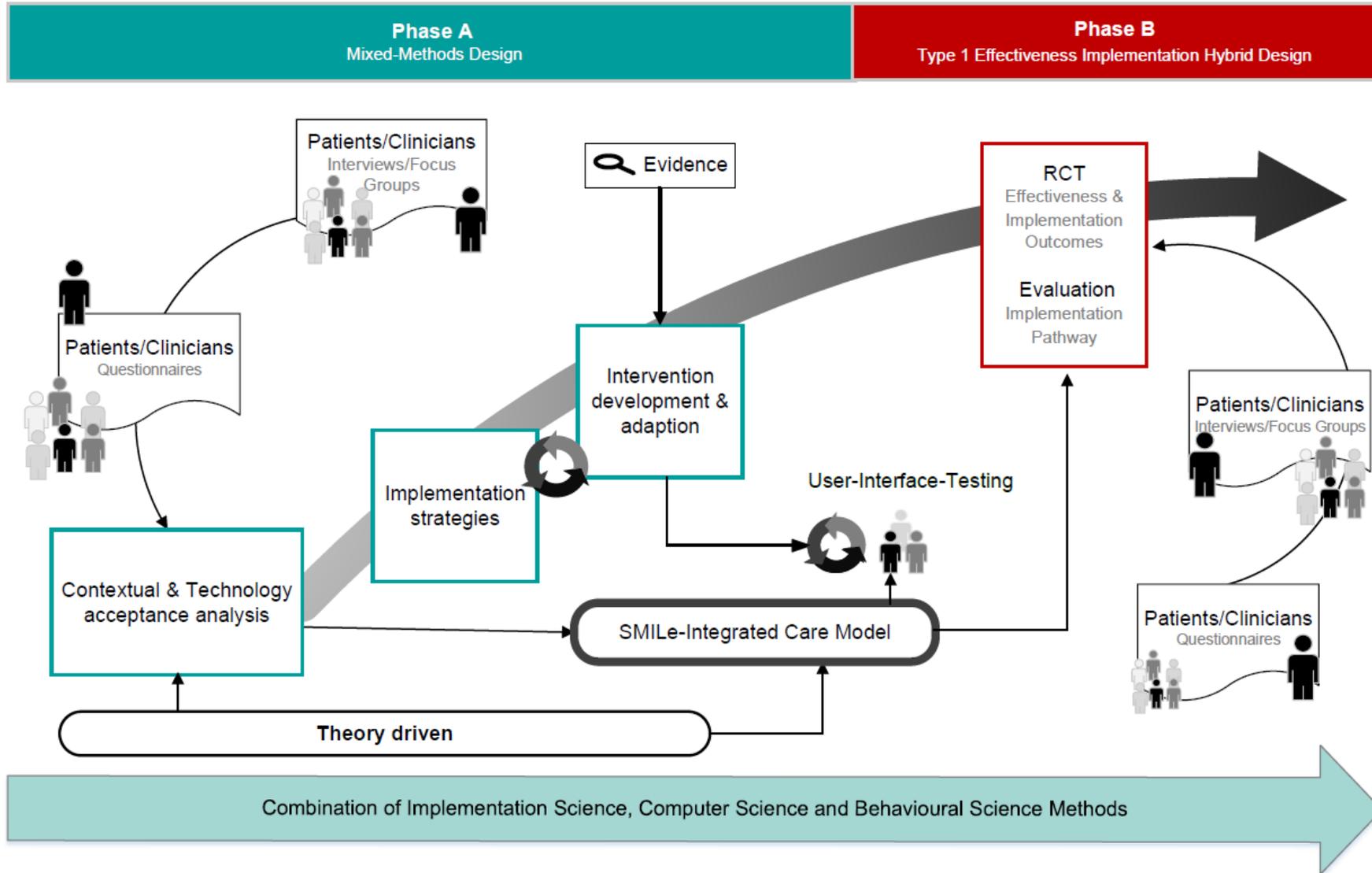
In **Chapter 5**, the article titled “Implementation Science Meets Software Development Techniques to create Software Components for an Integrated Model of Care for allogeneic **Stem** cell transplantation facilitated by **e**Health: The SMILe Study as an example” presents the software development process used for the SMILe-ICM's eHealth components. In addition to the computer science principles behind methodologies such as UCD and agile software development, it discusses the corresponding legal requirements.

### 1.4 Positioning the SMILe Project

This dissertation is embedded within the SMILe project (Allogeneic **Stem** cell transplantation facilitated by **e**Health embedded within an **I**ntegrated **C**are **M**odel – SMILe-ICM), a project of the University of Basel in collaboration with the University of Applied Sciences Augsburg and the participating clinical sites. SMILe is a multi-site, multistep implementation science project that currently involves five alloSCT centers: one in Germany (University Hospital Freiburg im Breisgau (FiB)), three in Switzerland (University Hospitals Basel (USB), Zürich (USZ) and Geneva (HUG)) and two in Belgium (University Hospital Leuven and Universitair Ziekenhuis Leuven (UZ Leuven)).

The SMILe project involves two phases: A) the **development** of the SMILe-ICM by combining implementation-, behavioral-, and computer science methods; and B) the **implementation** and **testing** of the SMILe-ICM, including evaluation of the implementation outcomes and implementation pathway (Figure 7).

Figure 7: Overview of the SMILe Project FiB



FiB was the first center to run the first step of Phase 1 (the contextual and technology acceptance analysis). This allowed us to build a first version of the SMILe-ICM, which could later be adapted to the needs of other participating centers according to their contextual analyses' findings.

**Phase A:** The contextual and technology acceptance analysis using an explanatory sequential mixed-methods design informing the development:

- Quantitative data collection (03-07/2017) involved a questionnaire survey of patients and clinicians involved in alloSCT care focusing on organizational structures, practice patterns in relation to chronic illness management, self-management and behavioral support, and technology openness in clinicians and patients (in line with the eCCM dimensions).
- Qualitative data (08/2017-01/2018) were collected via focus-group interviews with clinicians and individual interviews with patients. These focused on user needs and preferences as well as facilitators and barriers to an eHealth-facilitated ICM in alloSCT.
- Our contextual analysis' findings informed both our choices of setting-specific implementation strategies and the development of our eHealth-facilitated-ICM for FiB.
- Development of the SMILe-ICM FiB was based on external evidence, behavioral and computer science methods, and was driven by the findings of our contextual analysis (01/2018-07/2019).

**Phase B:** Implementation and testing of the SMILe-ICM in the first clinical setting (FiB):

- Preparation of the randomized controlled hybrid 1 effectiveness implementation trial (07-12/2019)
- Running of the SMILe randomized controlled hybrid 1 effectiveness implementation trial (01/2020 – 04/2022) with quantitative data collection at 8 time points within the first year post-alloSCT on summative and implementation outcomes
- Evaluating the SMILe-ICM using individual interviews with the first 10 participating patients (after 6 months within the study at the earliest) and focus group interviews focusing on the implementation pathway with all involved alloSCT clinicians at the end of the study (01/2021 – 10/2022).

In 2017, we started Phase A of SMILe at the FiB University Hospital. In 2016, during the preparation phase, a project group had been established and was meeting every 6 months. This group consisted of two nursing scientists from the University of Basel (one senior researcher /principal investigator and one junior researcher/PhD student), one senior software developer from the University of Applied Science Augsburg and five clinicians holding various positions within the FiB University Hospital: two senior

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attending stem cell transplant physicians, one nursing manager, two registered oncology nurses and one alloSCT APN from University Hospital FiB (local project leader), who was also a PhD student (University of Basel).

In parallel, a group of SMILe researchers with expertise in implementation science (nursing scientists), behavioral science (nursing scientist, psychologists) and computer science methods (programmers, usability experts, designers) was set up between the University of Basel, KU Leuven and the University of Applied Science Augsburg. The group met monthly while beginning to develop the content and preparing the digitalization of the SMILe-ICM eHealth components. Temporarily, a smaller subgroup of content and software developers and one clinician from FiB held bi-weekly meetings to perform discuss further steps such as the planning and conduction of usability tests or the implementation of the developed software components on their center's server infrastructure.

While the articles presented in chapter 3, 4 and 5 describe the SMILe-ICM's Phase A—the development phase—those presented in chapter 6 describe its implementation, testing and evaluation via a randomized controlled hybrid 1 effectiveness implementation design.

In **Chapter 6**, "Implementation and testing of an Integrated Model of Care in Allogeneic SteM Cell Transplantatlon faciLitated by eHealth - The SMILe project protocol for a hybrid-1 effectiveness-implementation science study" describes the methods employed to implement and test the SMILe-ICM in FiB. The care model's effectiveness will be tested regarding total healthcare utilization costs (primary outcome); re-hospitalizations, lengths of stay, medication non-adherence, treatment burden, health-related quality of life, graft-versus-host disease, re-hospitalization-free survival and survival. First year post-alloSCT implementation outcomes (i.e., feasibility, acceptability, appropriateness, fidelity) and the implementation pathway will also be evaluated.

### 1.5 Research gap and rationale for this dissertation

As noted above, although eHealth has a strong potential to improve outcomes in chronic illness, organ transplant and cancer patients, implementation of readily available applications in real-life settings frequently leads to adoption problems. To the best of our knowledge, no eHealth-facilitated ICMs for alloSCT care has been implemented and tested to date. Several arguments support the re-engineering alloSCT care towards an eHealth-facilitated-ICM via a combination of implementation science, behavioral science and computer science methods:

- First, alloSCT care is confronted with two major challenges: 1) steadily increasing numbers both of alloSCT procedures and of survival rates; and 2) the need for an ICM that addresses not only biomedical but also behavioral and psychosocial dimensions of alloSCT care. Still, reducing progression and occurrence of co-morbidities will depend on patients engaging in self-management behaviors, for which they need more structured support. We hypothesize that re-engineering alloSCT follow-up care—using the principles of CIM and facilitated by eHealth—will enhance this population’s quality of care, improve outcomes and might reduce costs.
- Second, international organizations such as the NIH’s Hematopoietic Cell Transplantation Late Effects Initiative have called for the development and research on novel and eHealth-facilitated ICMs to support self-management and delivery of targeted interventions for alloSCT patients. This call also aligns well with the European eHealth Action Plan and the objectives of the Digital Agenda for Europe, both of which are aimed at addressing and removing challenges to the care of chronically ill persons.
- Third, successful implementation of complex interventions such as eHealth-facilitated ICMs commonly fails for a lack of awareness of context-specific requirements. And when developing content for eHealth solutions, particularly regarding behavioral change components for eHealth solutions, the absence either of theoretical foundations or of an external evidence base is a major source of research waste. Further, particularly when shifting from pure face-to-face clinician consultations to software delivery, highly usable, sustainable software products with a high chance of uptake and use require the application of computer science methods including user-centered design and agile software development. We recommend a novel fusion of methodologies drawn from implementation science, behavioral science and computer science.

With the above points in mind, this dissertation will contribute from both a clinical and a methodological perspective. That is, we hypothesize that, once implemented, the

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SMILe-ICM will improve alloSCTs patients' outcomes; and the articles produced as part of the SMILe-ICM project will provide valuable guidance on the methodologies used. This combination of implementation science methods (included the use of contextual analyses both to inform choices regarding implementation strategies), behavioral theory-backed content, use-focused methods developed in computer science can be used as a blueprint for other researchers interested in developing, scaling-up or scaling-out eHealth-facilitated-ICMs.

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## Chapter 2

### Study Aims



### Study Aims

Given the gaps in the evidence regarding the need to re-engineer alloSCT care towards an eHealth-facilitated integrated care approach by combining implementation science, behavioral science and computer science methods, the aims of this dissertation were the following:

1. To identify the target organization's structural characteristics and practice patterns in view of chronic illness management; to assess how self-management and behavioral support is currently being supported; and to assess the technology openness of clinicians and alloSCT patients regarding eHealth use along the eCCM dimensions.
2. To develop the SMILe-ICM (allogeneic **Stem** cell transplantation facilitated by **e**Health embedded within an **I**ntegrated **M**odel of **C**are) by combining implementation science, behavioral science and computer science methods.
3. To test the SMILe-ICM effectiveness in view of total healthcare utilization costs (primary outcome), re-hospitalization rate, re-hospitalization lengths, medication non-adherence, treatment burden, health-related quality of life, incidence and grade of acute and chronic GvHD episodes, re-hospitalization-free survival and overall survival rate (secondary outcomes) in the first year post-alloSCT.

**Hypothesis:** We hypothesize that patients in the SMILe-ICM will have lower total healthcare utilization costs, a lower re-hospitalization rate, shorter re-hospitalization lengths, a lower medication non-adherence rate and less treatment burden, equal HRQL and equal medical outcomes (acute and chronic GvHD, re-hospitalization-free survival, overall survival) compared to the usual care alloSCT group.

4. To evaluate the implementation of the SMILe-ICM regarding feasibility, acceptability, appropriateness and fidelity and the implementation pathway.

## Chapter 3

### Clinicians and Patients Perspectives on Follow-up Care and eHealth support after Allogeneic Hematopoietic Stem Cell Transplantation: A Mixed-Methods Contextual Analysis as part of the SMILe Study

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### 3.1 Abstract

**Purpose:** We report on our contextual analysis’s methodology, as a first step of an implementation science project aiming to develop, implement, and test the effectiveness of an integrated model of care in SteM-cell transplantation facilitated by eHealth (SMILe).

**Methods:** We applied an explanatory sequential mixed-methods design including clinicians and patients of the University Hospital Freiburg, Germany. Data were collected from 3/2017 to 1/2018 via surveys in 5 clinicians and 60 adult allogeneic stem-cell transplantation patients. Subsequently, we conducted 3 clinician focus groups and 10 patient interviews. Data analysis followed a 3-step process: (1) creating narrative descriptions, tables, and maps; (2) mapping key observational findings per dimension of the eHealth-enhanced Chronic-Care Model; (3) reflecting on how findings affect our choice of implementation strategies.

**Results:** Current clinical practice is mostly acute care driven, with no interdisciplinarity and weak chronic illness management. Gaps were apparent in the dimensions of self-management support and delivery-system design. Health behaviors that would profit from support include medication adherence, physical activity and infection prevention. The theme “being alone and becoming an expert” underpinned patients need to increase support in hospital-to-home transitions. Patients reported insecurity about recognizing, judging and acting upon symptoms. The theme “eHealth as connection not replacement” underscores the importance of eHealth augmenting, not supplanting human contact. Synthesis of our key observational findings informed eight implementation strategies.

**Conclusion:** Stakeholders are willing towards a chronic care-focused approach and open for eHealth support. The contextual information provides a basis for the SMILe model’s development and implementation.

**Keywords:** allogeneic stem cell transplantation, integrated care, contextual analysis, implementation science, eHealth, user-centered design, chronic care model

### 3.2 Introduction

Advances in transplantation expertise have led to increasing numbers of allogeneic stem cell transplant (alloSCT) survivors.<sup>1</sup> Given that 70-90% of alloSCT recipients experience long-term complications, necessitating life-long follow-up, they can be considered as chronically ill.<sup>2</sup> Chronic graft-versus-host-disease (GvHD; 30-70%), endocrine (9-99%), cardiovascular (5-22%), or neurocognitive diseases (20-42%), many also suffer from fatigue (9-70%), depression (8-20%), emotional distress (22-43%), or low social support.<sup>3-5</sup> They also report health behavior challenges including medication non-adherence and physical inactivity, which increase their risk of poor long-term outcomes.<sup>6-8</sup> Finally, newly arising co-morbidities both reduce their quality of life and, compared to the general population, increase their risk of mortality within 15-20 years of transplantation by 20%.<sup>9</sup>

Internationally, transplant centers' resources are strained in view both of the growing number of alloSCT survivors and of their complex long-term needs, particularly concerning self-management support, care coordination and care continuity. As the prevailing care models focus predominantly on detecting and managing acute problems, they mostly lack an integrated care approach<sup>10, 11</sup>, i.e., one that addresses the entire care continuum- including the noted behavioral and psychosocial dimensions.<sup>4, 12</sup>

Integrated models of care are based on the principles of chronic illness management (CIM), of which the Chronic Care Model is the best known.<sup>13</sup> The Chronic Care Model (CCM) combines four building blocks: patient self-management support, decision support, clinical information systems and delivery system design. Driven by effective and productive interactions between prepared, proactive practice teams and informed, activated patients, the Chronic Care Model addresses complex care needs with a strong emphasis on patient outcomes. Evidence from other chronically ill populations, e.g., those with diabetes, heart failure or asthma, has demonstrated that care organized following CIM principles decreases mortality, improves health behaviors, social role functionality and treatment satisfaction, and improves economic outcomes (i.e., lower costs, fewer hospital admissions).<sup>14-16</sup> In general, concerning chronically ill populations, the more CCM building blocks of chronic care are implemented, the better the outcomes.<sup>17</sup>

In the last years, the CCM has been increasingly powered by eHealth. In 2015, Gee and colleagues conceptualized the eHealth-enhanced Chronic Care Model (eCCM).<sup>18</sup> EHealth, i.e., the use of information and communication technology for health, can potentially facilitate the implementation of integrated care models.<sup>19</sup> Recent evidence in cancer and solid organ transplant populations highlights the benefits of eHealth-powered care models regarding survival, re-hospitalization rates<sup>20, 21</sup>, knowledge<sup>22</sup>,

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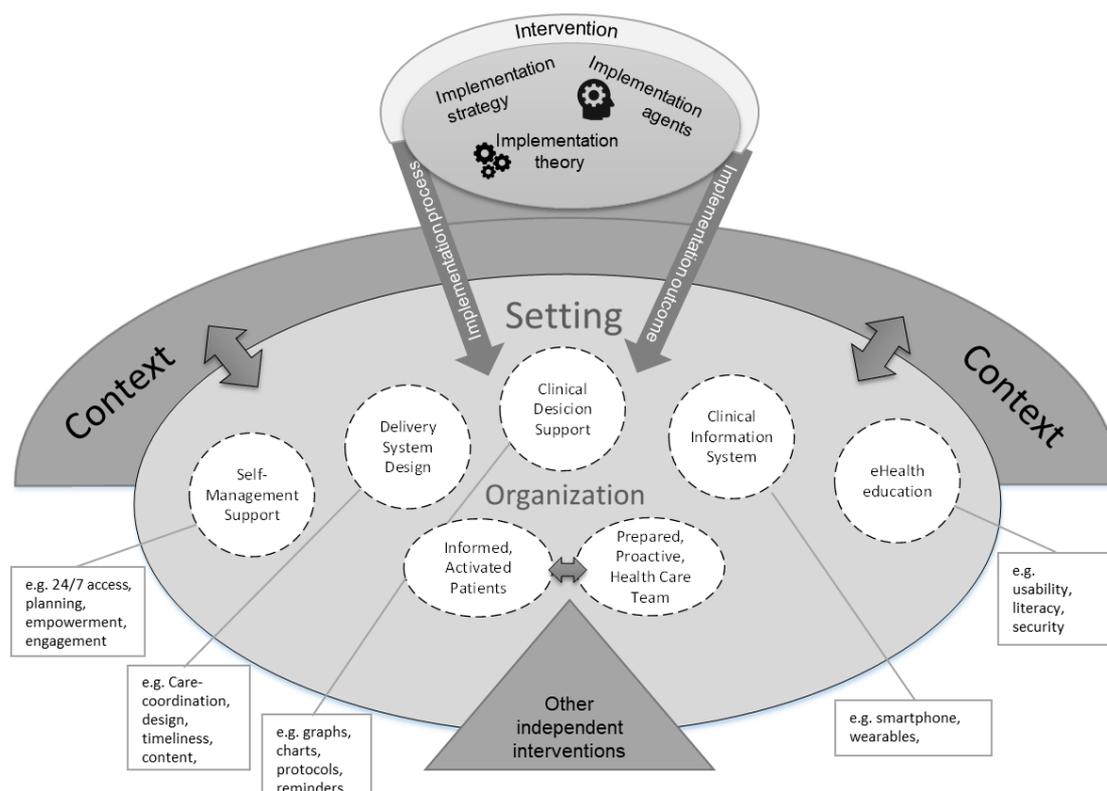
physical activity<sup>23,24</sup> medication adherence<sup>25</sup> and overall health care utilization.<sup>26</sup> Moreover, in cancer patients using electronic symptom monitoring combined with unstructured nurse support, Basch et al.<sup>21</sup> showed significantly improved quality of life, fewer re-admissions and improved survival. Still, while a similar care model tailored to the comprehensive care needs of alloSCT-patients would very likely improve their outcomes, none have yet been developed for this patient population.

The complexity of an intervention is commonly echoed – or amplified – in its implementation. As a result, the sustainability of eHealth is often suboptimal: studies have reported drop-out rates between 44% and 67%.<sup>27-29</sup> In fact, only 0.01% of available eHealth applications are sustainably used.<sup>30</sup> However, combining a user-centered design approach with implementation science methodology has a strong potential to overcome the observed issues with eHealth regarding both uptake and sustainability.<sup>31-</sup>  
<sup>33</sup> Implementation science “is the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services and care”.<sup>34</sup> Specifically, the strength of implementation science lies in its integration of numerous methodological considerations, including stakeholder involvement, contextual analysis or theory driven intervention development.<sup>35</sup>

Successful implementation of an intervention as complex as an eHealth-powered chronic care model begins with a thorough contextual analysis. Informed by multiple sources, including patients, caregivers and clinicians, the implementation team needs a solid theoretical framework upon which to assess and map relevant dimensions and factors that will later shape the project.<sup>36, 37</sup> Unfortunately, however, methodological guidance on how to conduct and use contextual analyses is scarce.

One of the theoretical frameworks to offer meaningful guidance for contextual analysis is the Context and Implementation of Complex Interventions (CICI) framework.<sup>38</sup> This model’s principal weakness is that it requires support from another model for such problems as where to position the contextual analysis, and says little about performing systematic, detailed assessments of prospective settings. For this task, the eCCM can guide the assessment of a setting, while helping to operationalize all necessary CIM dimensions.<sup>18</sup> Therefore, we embedded the eCCM dimensions (self-management support, delivery system design, decision support, clinical information systems and eHealth education) within the CICI framework (Figure 1).

**Figure 2:** eCCM embedded within the CICI framework



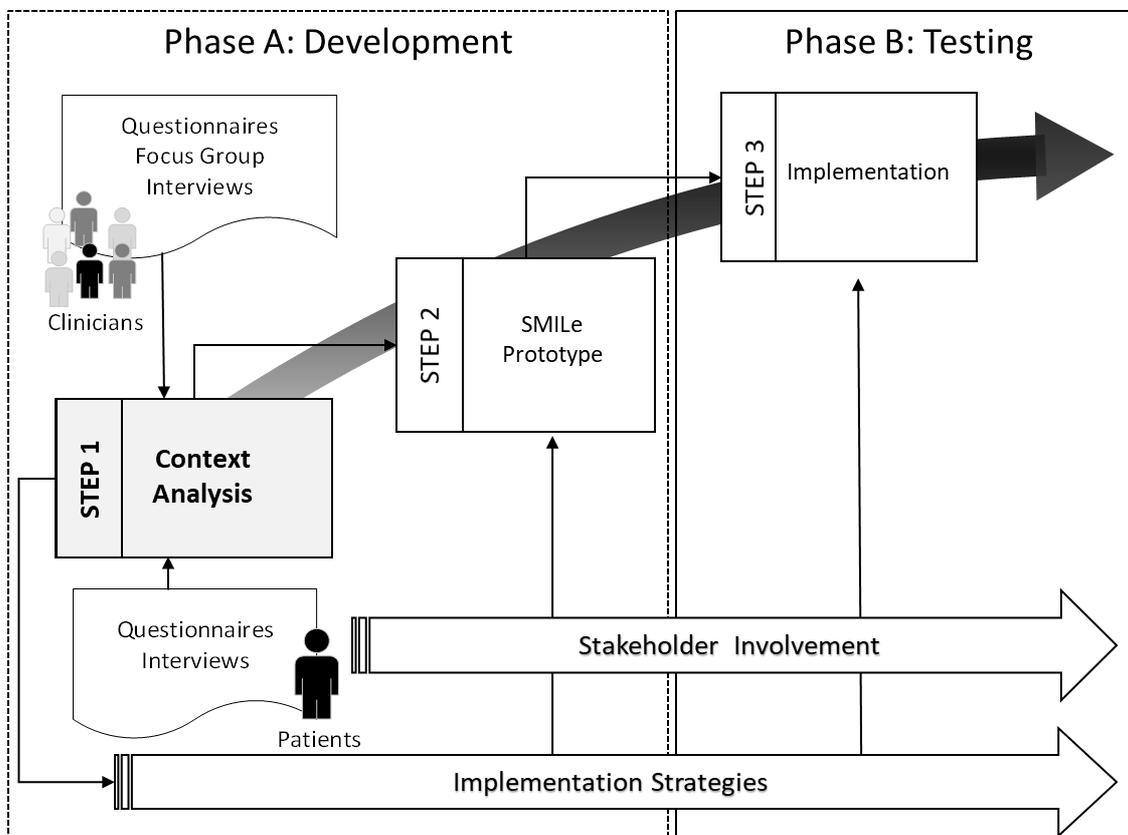
**Note:** Mapping the setting of an organization as part of the context where the setting is embedded, by using the eHealth enhanced Chronic-Care Model nested in the Context and Implementation of Complex interventions (CICI) framework. Implementation consists of implementation theory, implementation strategies, implementation agents, implementation process and implementation outcomes which facilitate the implementation into a specific setting.

To allow the richest yield of information to map a specific setting in terms of structural characteristics, practice patterns concerning CIM, and openness to technology, we used a mixed methods approach combining quantitative and qualitative methodology for data collection.

This study is the first step of a two-phase, multi-site implementation science project to develop (Phase A), implement, and test the effectiveness (Phase B) of an integrated model of care in allogeneic Stem-cell-transplantation facilitated by eHealth (SMILe; see Figure 2<sup>39</sup>). Reflecting these objectives, this report serves several aims: First, through its detailed description of the methodology underpinning of a contextual analysis, it provides a guideline to map any prospective context for the development of an intervention. Second, by summarizing the findings of the contextual analysis at our first participating center, it fulfills three minor aims: (1) to identify the target organization's structural characteristics and practice patterns in view of chronic illness management; (2) to assess how self-management and behavioral support is currently being supported;

and (3) to assess the technology openness of clinicians and alloSCT patients regarding eHealth use along the eCCM dimensions.

**Figure 2:** Overview SMILe project phases and steps



### 3.3 Methods

#### 3.3.1 Design and Setting

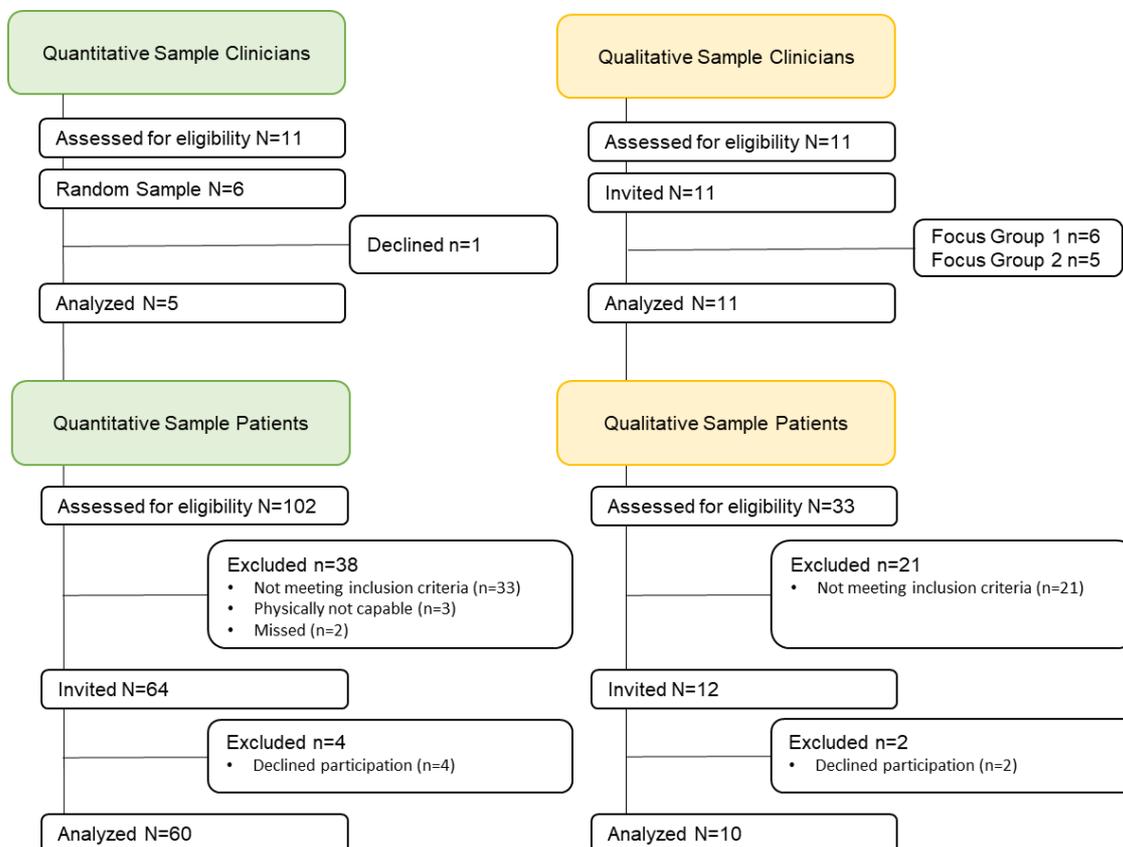
We applied a single-center explanatory sequential mixed-methods design using quantitative (QUAN) and qualitative (QUAL) methods guided by the dimensions of the eCCM. From one sample of clinicians and one of patients, we gathered quantitative and qualitative data. The study was conducted at the 1600-bed University Hospital Freiburg, Germany, one of the largest hospitals in southwest Germany. It was approved by the Ethical Committee of the University of Freiburg (EK 67/17). All participants provided written informed consent before contributing data.

#### 3.3.2 Clinician sample

The transplant director and a random sample of five clinicians were surveyed, followed by focus-group interviews with 11 clinicians (including those who completed the survey) (Figure 3). Three criteria determined eligibility for both the survey and the focus

group interview: 1) > 6 months' employment in the transplant center; 2) ≥ 50% in direct clinical practice; and 3) familiarity with post-transplant care.

**Figure 3:** Sampling procedure of clinicians and patients



### 3.3.3 Patient sample

We surveyed a convenience sample of 60 alloSCT patients during their regular outpatient clinic follow-up visits. Then, for the individual interviews, using purposive sampling based on age, gender and time after alloSCT, we added 10 who did not participate in the survey. For both samples, inclusion criteria were 1) transplantation and follow-up at the University Hospital Freiburg; 2) ≥18 years; 3) six weeks to three years post-SCT; and 4) ability to communicate in German. Based upon the treating physician's judgment, patients with any cognitive or physical condition that would impair adequate communication were excluded.

### 3.3.4 Quantitative variables and measurement

We assessed clinicians' and patients' demographic characteristics via a specially-developed self-report questionnaire. Building on our research group's previous work, we assessed the alloSCT center's structural characteristics, practice patterns regarding CIM, overall CIM level, technology openness (defined as mastery, i.e.,

## Chapter 3 – The contextual analysis

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patients' technology experience), acceptance (i.e., willingness and confidence to use eHealth), and perceived importance of eHealth for healthcare applications.<sup>40, 41</sup> Supplementary Table 1 provides the list of variables, the operational definitions, scoring, aggregation method and psychometric characteristics of the collected variables.

### *Structural/organizational characteristics of the SCT center*

Structural characteristics (the SCT center's organization and size) were assessed by the transplant director using six items from the alloSCT-adapted BRIGHT Transplant Director Questionnaire.<sup>40, 42</sup>

### *Practice patterns and overall CIM level*

Practice patterns were assessed at three levels – transplant director, clinician and patient – using 10 items from the BRIGHT questionnaires (Supplementary Table 1). The level of CIM was assessed from clinicians' and patients' perspectives. Clinicians completed the adapted 55-item CIMI-BRIGHT questionnaire<sup>43</sup> which is conceptually embedded in the WHO's Innovative Care for Chronic Conditions framework and operationalized based on the principles of CIM.<sup>44</sup> The total score is calculated as the mean of all item scores (range: 1–4), with higher scores indicating higher CIM levels.<sup>40, 45</sup> Patients also completed the 11-item PACIC (patient assessment of chronic illness care). For that, individual item scores are summed (range: 11–55), with higher values indicating higher patient-perceived CIM levels.<sup>45</sup>

### *Current self-management and behavioral support*

Additionally, using the 60 BRIGHT study self-report items (see Supplementary Table 1 for its content, scoring and interpretation), patients rated their self-management and health behaviors, as well as the degree of support they received from their team in following their therapeutic regimen.

### *Technology openness*

Patients' technology openness towards the use of eHealth across the various eCCM dimensions was assessed using an adapted 26-item self-report instrument developed by the PICASSO-Tx team.<sup>46</sup> Two items were added to evaluate patients' acceptance of symptom monitoring and data sharing with clinicians through eHealth applications (see supplementary Table 1 for scoring and interpretation).

### **3.3.5 Qualitative methods**

Guided by the eCCM, we used qualitative methods (i.e., clinician focus group, individual patient interviews) to map out the setting regarding relevant aspects of CIM and technological support. Both individual and focus-group interviews used open-ended questions based on an interview guide following the eCCM dimensions.<sup>18</sup> AlloSCT

follow-up care questions explored self-management-support (e.g., *How do you provide/perceive self-management support?*), delivery system design (e.g., *How do you experience care coordination?*), decision support (e.g., *How certain are your patients/you in making decisions when complications occur?*), clinical information systems (e.g., *What does eHealth mean to you?*), and eHealth (e.g., *What are your experiences with eHealth in supporting health or health behavior, what would be helpful?*). To facilitate understanding of the “eHealth” concept, a definition and examples of eHealth applications within healthcare were provided. Focus groups and interviews were audio recorded and transcribed.

### 3.3.6 Study procedures

The clinicians’ survey was conducted between end of March and end of April 2017, followed by the focus-group interviews between May and June 2017. The focus groups were led by a research associate (MK) and the first author (LL). From the end of June to the end of July 2017 the electronic health records were reviewed daily by the first author (LL) to identify patients eligible for the patient survey. All those fulfilling the inclusion criteria were asked to participate. From August 2017 to end of January 2018, the electronic scheduler was reviewed once weekly to identify eligible patients for the qualitative interviews. Individual interviews were conducted by one researcher (MK), in a separate clinic room, immediately after the subject’s outpatient visit.

### 3.3.7 Data Analysis

As this study was intended to be the basis for an implementation science study through an eCCM-guided contextual analysis, we will report our findings with the goal of making the invisible visible. Our data analysis process followed a three-step process. First, we developed descriptive tables for the QUAN data, using narrative descriptions and a meta-map for the QUAL eHealth support data (Supplementary Tables 2, 3, 4, Fig. 1). For this purpose, quantitative data were analyzed descriptively, using appropriate descriptive statistics as appropriate for data measurement levels and distributions (means, SDs, medians, IQRs, frequencies). After calculation of the total CIMI-BRIGHT and PACIC scores, Likert Scales were dichotomized (often and almost always= yes) and proportions for each variable displayed based on total N per question, sorted by eCCM dimension. Analysis was done using SPSS 24.

Qualitative data were analyzed using two methods. For the clinician focus groups, mind-mapping was used.<sup>47</sup> This method allows an ongoing discussion on the evolving map, to which emerging themes can be added. Once data collection was completed, mind maps of each focus group were merged into a single meta-map. The individual interviews with patients were transcribed verbatim and imported into MAXQDA

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(VERBI Software) by a research associate (MK). Data were iteratively analyzed and discussed according to Braun and Clarke's six thematic analysis steps: familiarization with the data, generation of initial codes, searching for themes, reviewing themes, defining and naming themes, and writing the report.<sup>48</sup> The deductive analysis followed the eCCM dimensions and was accompanied by meaningful quotes from the patient interviews.

Second, we mapped all key contextual findings – both QUAN and QUAL – according to the corresponding eCCM dimensions, side by side within a joint display. This led to a synthesis and implications regarding the first SMILe prototype. The third and final step included reflection on how the synthesized findings could inform the choice of implementation strategies most appropriate for the target context.

### 3.4 Results

We conducted 3 clinician focus-groups (N=11; mean duration 56 min. (SD 11 min.)) and ten individual patient interviews (N=10; mean duration 71 min. (SD 22 min.)). Table 1 provides detailed information on the clinicians' and participants' demographic characteristics; Table 2 shows the identified key contextual QUAN and QUAL findings regarding the organization's structural characteristics, practice patterns and technology openness – mapped according to their corresponding eCCM dimensions and relevance for intervention development, presented within a joint display.

#### 3.4.1 Structural characteristics of the allo-SCT center

The University Hospital Freiburg, located in southern Germany, has 18 beds allocated to alloSCT. Germany's compulsory universal health insurance covers most alloSCT costs. The hospital started its transplant program in 1989 and now performs around 100 adult alloSCTs annually. The outpatient clinic follows up 800-1000 alloSCT patients – accounting for about 3000 visits – per year.

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**Table 1:** Clinicians and Patients demographics of quantitative (QUAN) and qualitative (QUAL) samples

<b>Clinicians</b>		<b>QUAN (N=5)</b>		<b>QUAL (N=11)</b>	
<b>Sex; n (%)</b>	Male	2	(40%)	5	(45%)
<b>Age; Mean (SD)</b> /range		45.6	(10)	47.8	(17)
		31-58		30-61	
<b>Physician</b>		3		6	(55%)
<b>Registered Nurse</b>		2		5	(45%)
<b>Working experience</b> (median years/range/IQR)		21	4-34	17.5	2-25
		20.5		11.5	
<b>Patients</b>		<b>QUAN (N=60)</b>		<b>QUAL (N=10)</b>	
<b>Sex; n (%)</b>	Male	36	(60)	6	(60)
<b>Age; Mean (SD)</b> /range		52	(15)	50.2	(16)
		21-76		21-75	
<b>Time after alloSCT;</b> Mean (SD)/range	(months)	15.8	(9.7)	16.5	(13)
		3-36		2-36	
<b>Marital status;</b> <b>n (%)</b>	Single	12	(20.0)	2	(20)
	Married/living with partner	41	(68.3)	8	(80)
	Divorced/separated	5	(8.3)		
	Widowed	1	(1.7)		
	Missing	1	(1.7)		
<b>Highest educational degree; n (%)</b>	Primary school	8	(13.1)	1	(10)
	Secondary school	10	(16.3)	3	(30)
	Apprenticeship	25	(42.5)	5	(50)
	University degree	15	(25.0)	1	(10)
	Missing	2	(3.1)		
<b>Employment;</b> <b>n (%)</b>	None	37	(61.7)	9	(90)
	Part time	5	(8.7)	1	(10)
	Full time	13	(21.7)		
	Missing	5	(7.9)		
<b>Reason for no employment;</b> <b>n (%)</b>	Student	2	(3.4)	1	(10)
	Unable to work (temporarily)	19	(31.6)	5	(60)
	Retired	18	(30.0)	3	(20)
	Missing/double/not applicable	21	(35.0)	1	(10)

**Note:** alloSCT=allogeneic hematopoietic stem cell transplantation

### 3.4.2 Practice patterns and CIM level

At transplantation, patients are hospitalized a mean of 35 days (5 weeks). After the stem cells have engrafted, and peripheral blood values and general physical condition are stable, patients are discharged. After leaving the transplant center, most attend a 3-week inpatient rehabilitation program. Patients return for follow-up 1-2 times per week for the first 3 months, then monthly until 6 months post-SCT. Provided their condition remains stable, follow-up intervals gradually increase to once yearly after five years. Facilitating continuity of care, each patient is usually assigned the same attending physician, each of whom has a fixed consultation day. In the event of complications, patients are instructed to call the outpatient clinic or emergency room directly. As the current follow-up model focuses primarily on medical aspects of alloSCT, with no structured self-management or behavioral support and no nurse interventions, clinicians

describe it as mainly physician-centered. Clinicians spend a mean of 19 minutes (SD 8.5 min.) with each patient per visit. No routine formal psychiatric, psychological, social or financial evaluation is performed before or after alloSCT.

As clinicians frequently gave conflicting answers, their CIM ratings showed high variability (overall mean CIMI-BRIGHT score: 2.74, possible range: 0-4, SD 0.41). Fifteen critical items showed CIM deficits, i.e., < 50% positive responses. These related to four of the five CIM dimensions: self-management support (8 items), followed by delivery system design (3 items), clinical decision support (3 items) and use of clinical information systems (1 item) (see supplementary Table 2 for details).

Patients (N=60) reported spending a mean of 22 minutes (SD=11.7) with their transplant team at each follow-up appointment. The mean overall patient-perceived CIM rating was 32.6 (range: 11–55, SD: 10.8) (see Supplementary Table 3 for details).

### **3.4.3 Current self-management and behavioral support in view of CIM and technology openness, by eCCM dimension - QUAN and QUAL results**

#### *Dimension of self-management support: clinicians*

According to our QUAN results, 75% of clinicians report not having enough time to support patients with their self-management, with 67% of clinicians feeling unable to discuss with patients how they manage their treatment plan or specific self-management behaviors (see Supplementary Table 2 for details). In the focus groups, clinicians noted that adequate physical activity, application of infection prevention measures, and excellent adherence to immunosuppressive medication is crucial for long-term outcomes; however, they frequently see patients who struggle to perform these behaviors. Patients' insecurity regarding recognizing, judging and acting upon new symptoms was deemed the most crucial problem. Clinicians explained that, as fear of re-hospitalization frequently causes patients to report new symptoms too late for timely treatment adaptations, they see eHealth as a valuable tool to support patients in assessing, interpreting and acting upon their symptoms. For example, using eHealth to monitor symptoms, complications such as GvHD could be detected earlier and better controlled. Further, they acknowledged a role for eHealth in supporting health behaviors such as medication adherence or physical activity. Concerns included the lower reliability of patient-reported symptoms and the possibility that some patients would find eHealth use burdensome (Supplementary Figure 1).

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**Table 2:** Joint display of the key contextual observations from clinicians and patient’s perspective: structural characteristics and practice patterns in view of CIM including level of CIM at organizational level and within the eCCM dimensions (self-report on self-management/health behavior and perceived support; technology openness)

		Transplant Director & Clinicians		Patients		Synthesis & Implications for Intervention
		QUAN	QUAL	QUAN	QUAL	
Organizational level		-3800 follow-up visits per year -no interdisciplinarity -inconsistency how clinicians evaluate care processes <b>-CIMI BRIGHT score of 2.74</b> -existing electronic records -no system available to monitor pts. at home	-one attending physician per working day -nutritional counseling before discharge -clinicians state that guidelines are available and used in clinical practice	<b>PACIC score of 32.6</b>	perceive that physicians are tightly scheduled	-gaps in CIM as no interdisciplinarity -low to mid level of CIM  The intervention should facilitate inter-disciplinarity following the principles of CIM
	Self-Management support (SM-S)  Practice Pattern	<b>33% of clinicians</b> -check if pts. are dealing effectively with treatment plan -asks pts. on their SM efforts -review pts. SM performance -follow-up after new SM goal -assess individual concerns or goals <b>25% of clinicians</b> -have time for SM-Support -refer to community services helping to self-manage care at home -works directly with these agencies	-physical activity, infection prevention, adherence to immunosuppressive medication are most important health behaviors -clinicians observe that pts. struggle with being physically active, adhering to infection prevention measures and prescribed medication -structured SM support is limited to inpatient time -some physicians already use simple, unstructured behavioral interventions (e.g. reminder system for medication intake) -clinicians are satisfied with own availability for pts. -clinicians observe insecurity of pts. in recognizing judging and acting upon symptoms	<b>-78% of pts.</b> are not adequately physically active -reported various problems of taking immunosuppressive medication as prescribed (e.g. 21% forget to take them) <b>-45.8% of pts.</b> have nobody helping to read health related materials <b>18.6% of pts.</b> have problems to understand health-related information <b>-pts.</b> Health literacy of <b>3.41</b> <b>-38.9% of pts.</b> were given choices about treatment <b>-35.1% of pts.</b> were asked how alloSCT affects their life <b>-26.6% of pts.</b> were asked about health behaviors <b>-16.3% of pts.</b> received help to plan ahead <b>-15% of pts.</b> were encouraged going to self-help group <b>-12.7% of pts.</b> received a treatment plan fitting to their daily life	<b>“being alone- and becoming an expert”</b> -expressed a need for more informational, emotional and physical support  -felt physically exhausted  -follow-up reduces anxiety as pts. know that everything is all right  -would like SM-S regarding infection prevention, medication intake, symptom assessment and management  -became experts over time in managing symptoms	Congruency between clinicians and patients about gaps in SM-Support  The intervention should include structured behavioral, psycho-social and self-management support elements, building on principles of CIM. i.e regarding: Medication adherence, Infection prevention, physical activity, symptom recognition.

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		Transplant Director & Clinicians		Patients		Synthesis & Implications for Intervention
		QUAN	QUAL	QUAN	QUAL	
	Technology Openness		-see potential support medication adherence and physical activity by technology -technology could empower pts.	- <b>69.1% of pts.</b> Try out new technologies - <b>63.7% of pts.</b> easily get used to new technologies <b>56.2% of pts.</b> would like to get electronic feedback to promote favorable health behavior or on symptom development	-would benefit from a monitoring element supervising medical, behavioral and symptom related signs combined with information platform to support symptom recognition	Congruence between clinicians and patients about benefits of technology to promote health behavior or symptom monitoring and management.
Delivery System Design	Practice Pattern	<b>25% of clinicians</b> -are given incentives for effective clinical processes and improved outcomes  <b>20% of clinicians</b> -state that the SCT follow-up team is based on interdisciplinary team care  <b>0% of clinicians</b> -state that there is a specific long-term care-coordinator	-clinicians are satisfied with own continuity of care  -clinicians state that there are long waiting times	-pts. spend in mean <b>22 min</b> with transplant team at follow-up  - <b>93%of pts.</b> are satisfied how care is organized	<b>“having someone accompanying me”</b> -pts. describe transition phase as most distressing, felt left alone  -felt challenged by managing household and coordinating appointments  -depict the need for a more easy reachable and accompanying person	Dis-congruency as clinicians are satisfied and pts. perceive gaps in chronic care delivery. Pts. state a need for an easy reachable person.  Continuity of care could be realized by eHealth powered integrated care model with care-coordination.
	Technology Openness		-electronic guideline reminders (e.g. vaccination, bone marrow biopsies) would be helpful -electronic monitoring of pts. to identify complications early	- <b>70.4% of pts.</b> would use a health application from the hospital,  - <b>61.7%</b> on own smartphone -With a <b>mean of 8.05, pts.</b> state that it is important to develop new technologies supporting health behaviors	-technology would need to be connected to a person within the transplant center to increase acceptance	Technology can be used to power an integrated care model and connects pts. Virtually to the SCT-center. Technology part needs to be provided by the hospital.

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		Transplant Director & Clinicians		Patients		Synthesis & Implications for Intervention
		QUAN	QUAL	QUAN	QUAL	
Clinical Decision Support	Practice Pattern	<p><b>25% of clinicians</b> -state that the information system is used to give feedback to individual clinicians -state that the information system gives feedback about quality of care/areas of improvement</p> <p><b>0% of clinicians</b> -state that the information system flags pts. when overdue for follow-up</p>	-Clinicians observe problems in adherence with recommendations		<p>-describe insecurity in recognizing and judging upon new symptoms when discharged</p> <p>-would benefit from decision support when to contact the transplant center</p>	<p>Congruency in the perception of insecurity in recognizing, judging and acting upon new symptoms.</p> <p>Congruency that technology could support recognizing, judging and acting upon new symptoms. SMILe should include feedback loops allowing to empower patients and visualization over time for treatment decisions by clinicians</p>
	Technology Openness		<p>-state that pts. would benefit from technology support in interpreting their symptoms</p> <p>- electronic symptom monitoring would help identify complications in the home setting</p> <p>-concerns that pts. could feel overwhelmed by entering data or dealing</p>		-Technology could support symptom assessment and decision making how to act upon	
Clinical Information System	Practice Pattern	<p><b>0% of clinicians</b> -state that the information system is used to monitor pts. at home</p>	-work with electronic medical records	<b>-55% of pts.</b> are confident in filling in medical documents		<p>Congruency that technology needs to be connected to a person in the Tx center, overseeing incoming data and judging when a physician needs to be involved. Interoperability as important factor for acceptance of technology. Technology should connect end- users and be integrated in existing systems.</p>
	Technology Openness		<p>-express a need for interoperability the new technology with existing systems in the hospital</p> <p>-they would need a person looking at incoming values and decide when a physician needs to be included. They cannot invest more time</p> <p>-see benefit of timeliness data availability</p>	<p><b>-47% of pts.</b> would send data upon request</p> <p><b>-63% of pts.</b> would be willing to share their data with clinicians and</p> <p><b>-57.2% of pts.</b> would feel more secured</p> <p><b>-47% of pts.</b> would use step counters</p> <p><b>-40% of pts.</b> would use electronic symptom monitoring</p>	<p><b>“eHealth as connection not replacement”</b></p> <p>-technology should be connected to a person within the hospital and located in the clinic information system</p> <p>-should also display lab values</p>	

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		Transplant Director & Clinicians		Patients		Synthesis & Implications for Intervention
		QUAN	QUAL	QUAN	QUAL	
eHealth education	Practice Pattern		<ul style="list-style-type: none"> <li>- Not familiar with technology monitoring patients-</li> <li>-technology should not replace human contacts</li> </ul>		<ul style="list-style-type: none"> <li>-technology as additional element in follow-up care,</li> <li>- it should not replace human contacts</li> </ul>	Congruency that technology should not replace human contacts A technology-delivered model of care needs to include both, human aspects and technology.
	Technology Openness		state that good usability of a new technology is important	<ul style="list-style-type: none"> <li>-86% of pts. Have WLAN -</li> <li>-78.3% of pts. Own a smartphone</li> <li>-97.9% will also use it in future</li> </ul>	<ul style="list-style-type: none"> <li>-patient were open towards eHealth</li> <li>-good usability of the technology is needed</li> </ul>	Congruency that a User-Centered Design is crucial.

Note: CIM= chronic illness management; SM-M= self-management support; pts.= patients, SMILe= integrated model of care for allogeneic Stem cell transplantation facilitated by eHealth

### *Dimension of Self-Management Support: patients*

The questionnaire responses revealed that 78% of patients struggled in performing adequate physical activity and had problems adhering to their immunosuppressive regimes (e.g., 21.6% at least occasionally forget to take them). Having nobody to help them read health-related information was reported by 45.8%; and 18.6% did not understand the written information provided. Overall, 73.4% reported not being asked how alloSCT affects their daily life; and only 12.7% received treatment plans tailored to their daily life. Just over 69% would be open to try new technologies; and 56.2% would like to receive electronic feedback supporting positive health behaviors (Supplementary Table 3).

*“Being alone – and becoming an expert”* was a major theme within the eCCM dimension of *self-management support*. Patients described the transition from full support to weekly visits as the most distressing treatment phase: *“The attendance by medics and staff is excellent. But then – pow! – it ends and you’re left all alone”* (male, 60-70 years, 6 months post-SCT). In their first 6 months post-alloSCT, all patients experienced several physical limitations, often including tiredness or exhaustion. Even simple activities (e.g., showering, cooking, brushing teeth) were perceived as burdensome and demanding. They further expressed a need for additional information and more emotional, physical and social support to master the demands of post-SCT life. Most also commented that they were unable to adapt the information provided during their inpatient stay to life at home. This led to wishes for increased self-management support regarding infection prevention measures, medication intake, assessment of and appropriate reactions to changes in symptoms, long-term outcomes, possible courses of therapy and follow-up. To overcome these knowledge deficits, patients bought books, asked their peers or sought information on the internet, but for some, it was difficult to identify trustworthy and valid information via internet searches.

Unfortunately, the copious information available online often *“doesn’t help at all and that would make you mad. Too much information”* (male, 60-70, 36 months post-SCT). However, patients mentioned not daring to ask for support or information, assuming that the attending physicians’ schedules would be too busy: *“No. No, that’s difficult with ... the senior physician. ...Well, he’s got a tightly synchronized day even without me. And I think that he’d barely be available for patients outside of consultation hours”* (male, 50-60 years, 24 months post-SCT).

Patients felt especially insecure in recognizing and evaluating new symptoms: *“No idea what’s relevant and what’s not”* (male, 40-50 years, 3 months post-SCT). When concerned, some patients immediately contacted a physician; some waited for their next scheduled appointment; and some, fearing re-hospitalization, never reported their

concerns. Overall, then, the prospect of 24-7 at-home technological support to assess and judge the severity of symptoms was considered useful. *"Yes that would help me decide whether or not to come immediately"* (female, 20-30 years, 3 months post-SCT). Most said they would find a monitoring element helpful to track medical, behavioral or symptom-related signs, combined with an information platform to support symptom recognition or health behaviors, e.g., listing *"immune response[s] or other reactions such as a rash ... and how to respond to...[them]"* (female, 40-50 years, 5 months post-SCT).

Patients were also challenged in managing their households, coordinating their appointments and following the instructions concerning medication taking or regular physical activity *"I had many appointments, when I was back home...family practitioner, physiotherapist, outpatient clinic...and my children. I was so completely done and weak that it turned out to be a huge challenge. You see your day planner and you feel that you are too weak to manage...you need to be careful with your energy"* (female, 30-40 years, 5 months post-SCT).

The longer patients had to manage their post-SCT symptoms and self-management tasks, the more they felt their expertise growing. And as their experience and knowledge increased, they gained confidence assessing and managing their symptoms: *"You kind of get a feeling of whether you should give them a call or not, because I always had so many adverse effects"* (female, 20-30 years, 9 month's post-SCT). Additionally, by one year post-transplantation, increased physical stamina and decreased self-management demands resulted in reduced support needs.

### *Dimension of delivery system design: clinicians*

Of the five clinicians who completed questionnaires, four noted that no interdisciplinary team approach had been implemented and that no long-term care coordinator was available (Supplementary Table 2). The focus group interviews revealed that, to facilitate continuity, participating clinicians (N= 11) always try to ensure that patients are followed up by the same physicians. They would see an eHealth support system that enabled clinicians to monitor their patients from a distance *"as a long leash to the transplant center"*, but that at the same time would allow for risk-adjusted individual follow-up (Supplementary Figure 1).

### *Dimension of delivery system design: patients*

Regarding delivery system design, the questionnaire data showed that 93% of patients are satisfied with care organization and 70.4% would be open to use an eHealth application provided by the hospital (Supplementary Table 3). In the qualitative interviews, the theme of *"having someone accompanying me"* emerged in this eCCM dimension. Patients perceived follow-up as important and described it as a source of reassurance in terms of infection and disease control. Extending intervals between

follow-up visits intensified anxiety and concerns: *"This time, during the three weeks, my head was rather preoccupied with whether everything was okay"* (female 60-70 years, 6 months post-SCT). Although they felt well cared-for during outpatient visits, they voiced a need for an easily reachable, trustworthy professional familiar with their individual situation able to support them via technology: *"Just someone who accompanies you a bit on that path"* (male, 50-60 years, 4 months post-SCT). Several patients expressed a wish to have their relatives more involved in their follow-up care, as many had difficulty understanding their conditions and challenges, leading to emotional conflicts that burdened their partnerships: *"I was just done when I got home from the stem-cell transplantation. And my wife couldn't understand. ... Only after she'd talked to a medic did I realize: now something's changed"* (male, 40-50 years, 3 months post-SCT). Yet, patients also realized that their relatives also had to handle additional worries and burdens.

### *Dimension of clinical decision support: clinicians*

The QUAN results showed that, although the team was already working with electronic health records (100%), the system did not flag patients who were overdue for their appointments; nor did it provide feedback about the quality of care provided (75%, Supplementary Tab. 2). In the focus groups, clinicians agreed that, by facilitating faster and better-targeted follow-up, remote electronic patient monitoring would support both diagnostic and treatment decisions (Supplementary Fig. 1).

### *Dimension of clinical decision support: patients*

No quantitative questions in the used questionnaires addressed the dimension of clinical decision support. Regarding the qualitative results, those concerning symptom recognition, judgment and decision support overlap those of the self-management support dimension.

### *Dimension of clinical information system: clinicians*

All clinicians confirmed the absence of any system to monitor patients at home. In the focus groups, they appreciated the potential benefits of such a system, particularly to provide remote health data (see also the dimension of self-management support), but highlighted the importance of interoperability with existing electronic systems. Clinicians emphasized that they cannot invest additional time learning a new system. They agreed that, in addition to fulfilling the need for a trustworthy professional to monitor and screen incoming data, a nurse-counselor would also be able to identify potential threats and provide triage (Supplementary: Table 2, Figure 1).

### *Dimension of clinical information system: patients*

About 63% of patients surveyed would be willing to share their health data with the transplant team. Of these, most (57.2 %) believed this would increase their feeling of security. In total, 70.4% would use a health application provided by the hospital. However, in the qualitative interviews, the theme of “*eHealth as connection not replacement*” underpinned the role of eHealth as a supplementary tool, not something to replace human care. The principle that human contact remains crucial in follow-up care is very strong, especially among the more recently transplanted patients: “*You still have an unpleasant feeling about that [symptom] and want to see the doctor in order to know that everything’s alright*” (female, 20-30 years, 3 months post-SCT).

In general, patients were open towards the idea of eHealth support: in the interviews nine out of ten rated eHealth support in alloSCT follow-up care as positive: “... *I’d be positive if something like that [technological support] existed*” (male, 50-60 years, 24 months post-SCT). They also expressed a wish for functionalities such as a lab value diary, their current medication plan and a calendar to display upcoming outpatient appointments, diagnostics or vaccinations. Fewer than half would use stand-alone step counters (47%) or electronic symptom diaries (40%); however, if connected to the hospital and able to share data with clinicians, on a scale from 0 to 10, their mean rated value of such new technologies was 8 (Supplementary Table 3).

### *Dimension of eHealth education: clinicians and patients*

For clinicians, not only would the technology have to be highly usable/intuitive, but above all it should never be seen as a replacement for human contact (Supplementary Figure 1). As all patients (N=58) owned at least one computer-enabled electronic device – a smartphone being the most common (78.3%) – the prevalence of technology experience was 100% (Supplementary Table 4). In order to support uptake and use of an eHealth technology, patients believed any new eHealth application would also require a user-friendly design: “*Well yes. You don’t want to break off your fingers. Well, in this phase the eyes are dry, your motor function is limited. So, it needs to be simple to use*” (male, 50-60 years, 24 months post-SCT). Conversely, usability issues such as a non-intuitive interface, the use of medical terminology and a lack of data protection standards were all noted as barriers to technology use.

### **3.4.4 Contextually informed implementation strategies**

Based on our synthesis of the key contextual findings, we choose eight of the Powell et al.’s 73 recommended implementation strategies <sup>49</sup> to facilitate the first implementation of our proposed eHealth-powered model of integrated care in a transplant center. For instance, combined with its lack of interdisciplinarity, this context’s

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low level of CIM may call for the creation of new clinical roles (e.g., integration of advanced practice nursing roles) or revision of existing roles to provide the needed self-management and behavioral support, which in turn will demand further strategies, e.g., to access the necessary funding (see Table 3 for all chosen strategies). By evaluating the outcomes and processes of usual care and collecting stakeholder opinions within this contextual analysis, we have already applied one important implementation strategy – that of conducting a local needs assessment. The findings of the contextual analysis clearly indicate a need both to devise further implementation strategies and to tailor those strategies to the target context (Table 3).

**Table 3:** How the synthesis of the key contextual observations (Table 2) informs possible implementation strategies

	Synthesis	Implementation strategies
SM-S	Congruency about gaps in Self-Management Support and benefits of eHealth support.	<ul style="list-style-type: none"> <li>● <b>Obtain and use patients/consumers and family feedback</b> Use data of contextual analysis to re-engineer the current model of care.</li> </ul>
DSD	<p>Dis-congruency between clinicians and pts. in terms of current care model.</p> <p>Low levels of CIM, indications that there are gaps in chronic care delivery.</p> <p>Pts. state a need for an easy reachable person.</p> <p>Continuity of care could be realized by eHealth powered integrated care model with care-coordination connecting pts. to the SCT-center.</p> <p>Technology part needs to be provided by the hospital.</p>	<ul style="list-style-type: none"> <li>● <b>Conduct educational meetings</b> Inform and educate clinicians and other relevant stakeholder about pts. feedback.</li> <li>● <b>Conduct local consensus discussions</b> Discuss how dis-congruence can be overcome, give feedback on CIM levels</li> <li>● <b>Create new clinical teams</b> As physicians are tightly scheduled with &gt;3000 visits per year, the current follow-up care team can be expanded by new roles (e.g. APNs) to allow more interdisciplinarity.</li> <li>● <b>Revise professional roles</b> Assess if available nurses can be further developed to advanced roles and included in the follow-up of alloSCT pts. Providing structured behavioral and SMS interventions are a core competency of nurses.</li> <li>● <b>Develop educational materials</b> Advanced Nurses involved in follow-up care need protocols which interventions need to be delivered and when.</li> <li>● <b>Access new funding</b> Access new funding to allow role revisions and development of new clinical teams.</li> <li>● <b>Obtain and use patients/consumers and family feedback</b> Use data of contextual analysis to re-engineer the current model of care. And design content of technology.</li> </ul>

	Synthesis	Implementation strategies
CDS	<p>Congruency in the perception of insecurity in recognizing, judging and acting upon new symptoms.</p> <p>Congruency that technology could help to overcome these deficits.</p>	<ul style="list-style-type: none"> <li>• <b>Conduct local consensus discussions</b> Clinicians need to be involved and find a consensus when designing a technology supporting symptom assessment; rating and decision support what to do.</li> <li>• <b>Develop educational materials</b> A protocol guiding the decision upon symptoms, needs to be developed based on the consensus decision from clinicians to guide the technology development.</li> </ul>
CIS	<p>Congruency that technology is connected to a person in the Tx center</p> <p>Interoperability as important factor for acceptance of technology.</p>	<ul style="list-style-type: none"> <li>• <b>Create new clinical teams</b> As physicians are tightly scheduled, the current follow-up care team can be expanded by new roles (e.g. APNs) to allow eHealth driven care-coordination</li> <li>• <b>Inform local opinion leaders</b> Constantly inform and include different stakeholders at higher levels (e.g. transplant director, director of clinical data center, nursing director) to facilitate acceptance and option of interoperability.</li> </ul>
eHed	<p>Congruency that a User-Centered Design is crucial.</p> <p>An eHealth-delivered integrated model of care needs to include both, human aspects and technology.</p>	<ul style="list-style-type: none"> <li>• <b>Obtain and use patients/consumers and family feedback</b> Use data of contextual analysis to design technology and apply a user-centered design process with ongoing usability tests to obtain continuous feedback.</li> <li>• <b>Create new clinical teams</b> As physicians are tightly scheduled, the current follow-up care team can be expanded by new roles (e.g. APNs) to allow eHealth driven care-coordination</li> </ul>

Note: SM-S= self-management support; DSD=Delivery System Design; CDS=Clinical Decision Support; CIS=Clinical Information System, eHed=eHealth education

### 3.5 Discussion

Although eHealth-delivered integrated care models are emerging in chronically ill populations, none yet exist, to our knowledge, in the alloSCT setting. This mixed-method study focused on the methodology of a contextual analysis prior to implementing of an eCCM-based integrated care model within our setting. This report demonstrates how that analysis can inform not only our content and development processes but also our choices regarding implementation strategies.

Most studies reporting on contextual analysis focus exclusively on facilitators and barriers of implementation. Few are embedded in theoretical models and even fewer use mixed-methods techniques or combine theoretical underpinnings.<sup>50-52</sup> To our knowledge, the presented method – combining implementation science theory with a clinically relevant model (the eCCM) to illustrate each step of our setting-specific contextual analysis – has not been described before. Reflecting both our insights concerning this

composite methodology and on our results, the report offers valuable guidance on how to approach an implementation science driven intervention development.

As an in-depth contextual analysis represents a considerable investment of resources, especially time, interventions are commonly implemented with no formal assessment of how they will fit the target context.<sup>53</sup> This impacts sustainable implementation<sup>54</sup> leading to limited adoption or early de-implementation.<sup>29</sup> To be clear, it cannot be assumed that any complex intervention – and certainly not one as complex as a care model – can easily be implemented into daily clinical practice.<sup>35</sup> Successful implementation methodology supports translation from the controlled context of a trial to a comparatively chaotic, resource-competitive clinical setting.<sup>55</sup> So while poor adoption of potentially beneficial eHealth interventions into chronic illness contexts reflects a lack of perceived benefit, it also reflects developers' failure to tailor their solutions specifically to their target populations.<sup>54</sup> Successful implementation of interventions in complex settings, e.g., a healthcare system, demands a comprehensive knowledge of the target context. However, especially regarding self-management and eHealth support expectations, different chronic illness populations' needs and abilities vary widely.<sup>56</sup> In response to that variation, the marriage of implementation science methods to user-centered design processes is a dynamic match: implementation science calls for and guides contextual analyses; following user-centered design principles, developers can tailor the potential solution to the stakeholders' needs and preferences.

### 3.5.1 Clinicians and Patients Perspective on practice pattern in view of CIM

High congruence between our clinicians' and patients' perspectives on CIM practice patterns resulted frequently in similar statements. Both groups saw the widest gaps in the most important dimensions – self-management support and delivery system design. However, concerning the latter, while clinicians were satisfied with care organization and provision, patients experienced gaps in care delivery, leading to unmet needs. This disagreement might have resulted from different perspectives regarding daily life support needs. Our mean PACIC and CIMI BRIGHT scores (respectively 2.74 and 32.6) were low compared to those from solid organ transplant centers<sup>45</sup> indicating that investment is needed to improve CIM to a clinically meaningful level. As evidence also shows that the more CCM dimensions are addressed, the better the outcomes<sup>17, 44</sup> it may also be necessary to focus more on those.

Our results also confirm previous findings that alloSCT-patients' support needs are highest in the first months post-transplantation, while they adjust to the transition from in- to outpatient care.<sup>57</sup> Despite frequent outpatient appointments, both clinicians and patients described CIM gaps regarding self-management or behavioral support: both noted patients' problems recognizing, judging and acting upon new symptoms,

inadequate physical activity, medication non-adherence and problems with infection prevention measures in the early months post-discharge, i.e., following discharge, this population needs more support to gain confidence and expertise, particularly regarding symptom management.

### **3.5.2 Clinicians' and patients' perspectives on eHealth support**

Clinicians mainly described potential benefits of using technology to support health behaviors and to monitor early signs of complications. They also reported concerns regarding both human replacement and the lack of additional resources to monitor electronically collected data.

While most patients were already quite familiar with technology, a slight majority of 52% stated that, while technologies such as activity trackers were associated with the hospital, which increased their perceived importance, they would be unwilling to use them as stand-alone devices. Patients also expressed the fear that technology would replace human contacts. As noted above, and as was observed in a previous study in cancer patients<sup>58</sup>, uptake and use of an eHealth-powered care model will demand easy, direct access to a trustworthy professional within the transplant center. Electronic symptom monitoring was perceived as helpful in managing symptoms and patients felt more secure knowing a person would be watching over them, i.e., the human component remained a vital element. In support of this principle, Mooney et al.<sup>59</sup> reported better outcomes when combining electronic symptom monitoring with nurse practitioner interventions. They concluded that a technology's efficacy and success depends largely on its link to timely and personal health care provider responses. Without that link, it is unlikely that a stand-alone technology that covers only one dimension of eCCM – as this does – could adequately support highly burdened cancer or alloSCT patients.

### **3.5.3 Implications for the first SMILe prototype and potential implementation strategies**

Our contextual analysis provided information essential to the intervention elements of the first eHealth-delivered integrated care model for alloSCT patients (Table 2). As the current system's CIM level require improvement, structured behavioral, psychosocial and self-management elements building on the principles of CIM should be included.<sup>17</sup> Our results show that interventions are needed for medication adherence, infection prevention, physical activity and symptom recognition.

While eHealth can meet these needs, while improving continuity of care and allowing remote patient monitoring between clinic visits, it cannot replace human interaction. Physicians' tight scheduling prevents them either from delivering structural self-management and behavioral support interventions or from monitoring eHealth

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systems. However, as these types of interventions typically involve nursing competencies, advanced practice nurses would be ideal to deliver most or all needed support within an integrated interdisciplinary care approach.

This study has several limitations. First, while our samples provided us with relevant information, they were rather small. Second, resource limitations precluded home visits, which might have provided a broader understanding of patients' post-alloSCT situations. As Vanhoof et al.<sup>60</sup> gained rich insights into patients' needs by conducting contextual in-home interviews, future studies should consider using this method. Further, the lack of a gold standard methodology for contextual analyses including QUAN and QUAL methods indicates a clear need for future research. Therefore, based on previous work by Stange et al.<sup>61</sup> we are currently developing the Basel Approach for Contextual Analysis (BANANA). Building on to perform a contextual analysis consisting of following steps (1) choice of a theoretical framework underpinning analysis of context and a setting specific theory for increased granularity; (2) use of available empirical evidence on relevant contextual information; (3) involvement of multilevel stakeholders; (4) collection and analysis of data by applying mixed methods; (5) determine contextual and setting factors' relevance for implementation strategies, outcomes and intervention co-design; (6) publication of findings of contextual analysis by using appropriate guidelines.<sup>62</sup>

This study's greatest strength is its comprehensive method-driven approach to mapping out the target setting before beginning development of a care model. This allows development of a setting-specific prototype and strategies to support sustainable implementation in clinical practice. Although we used a monocentric population, our methodology can easily be applied to other settings in which evidence-based interventions will be implemented.

### 3.6 Conclusions

This study provides important information for re-designing alloSCT care from the current acute-care perspective towards an eHealth-facilitated integrated chronic care approach. As alloSCT patients are at a high risk for chronic long-term complications, they require comprehensive, proactive follow-up care that integrates behavioral and psychosocial support to improve long-term outcomes. And while we are certain that, across countries, diseases and settings, the future of health care will include eHealth, we cannot successfully implement any care model into a clinical setting without knowing the context and end-users' needs and preferences.

This report describes the methodological approach and findings of a mixed-methods examination and mapping-out of our target context as it applies to a single

organizational setting. Our findings concern structural characteristics, CIM-related practice patterns and technology openness from the perspectives of clinicians and patients. They have also allowed us to synthesize further findings with implications either for the intervention itself or for our choice of strategies regarding the new care model's implementation. Overall, these results will directly inform the development of the SMILE eHealth-delivered integrated model of alloSCT care.

### 3.7 References

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3.8 Supplementary Material

**Supplementary Table 1:** Assessed variables, measurements, scoring, definitions and psychometrics where applicable

Variables	Instrument/measurement Values/scoring/conceptual definition	Psychometrics
<b>Demographics</b>		
Clinicians: age, gender, work experience		
Patients: Age in years, gender, marital status, educational level, employment status, status of immunosuppressant intake		
<b>Organizational level</b>		
<b>Stem cell transplant center's structural characteristics</b>		
Transplant Director Questionnaire	BRIGHT transplant director questionnaire <sup>1,2,5</sup> items 1) Type of SCT center- 2 response options: 1) University or 2) regional, community or other hospital; dichotomous variable 2) Location of the SCT program - 2 Options: 1) urban, or 2) suburban or rural; dichotomous variable 3) Years since start of the SCT program - Time in years between start date of the transplant program and the date of the start of the BRIGHT data collection in a given center; continuous variable 4) N of patient who are 1-year post SCT and followed-up - Number of patients regularly being followed up; Continuous variable 5) Center size – how many SCT have been performed in the last 5 years- Categories based on total number: small (< 75), medium (75-100), or large (> 100) center 6) Multidisciplinarity of the team in follow-up = at least one physician, one nurse and one other discipline, 1 item: describe the members of your team (routinely involved or consult only), Various disciplines listed; check box to be ticked if discipline is part of the team, dichotomous score multidisciplinarity (yes/no)	No information
<b>Practice patterns</b>		
Transplant director Questionnaire	BRIGHT transplant director questionnaire,8 items 1) Length of hospital stay after alloSCT- 1 item, average length of stay after alloSCT in days; Continuous variable 2) Number of yearly visits scheduled for patients after alloSCT – 3 items number of visits in the first year, between 1 and 2 years; and beyond 3 years	No information

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	<p>3) Formal mental health or psychological evaluation before alloSCT – 1 item, yes/no, dichotomous score</p> <p>4) Formal financial-social evaluation before alloSCT- 1 item yes/no, dichotomous score</p> <p>5) Are patients followed-up by the same clinician when visiting the outpatient clinic –1 item, 3-point Likert scale ranging from '1= always or nearly always' to '3 rarely or never'; Ordinal variable</p> <p>6) Who is the initial contact in case of after hour questions or emergencies – 1 item, yes/no</p>	
Clinicians	<p>BRIGHT clinician Questionnaire <sup>2</sup>; 2 items</p> <p>1) Transplant clinic has a long-term care-coordinator - Care coordinator can be an advanced practice nurse, a transplant coordinator or a social worker, 1 item Response option: yes/no; Dichotomous score</p> <p>2) Having an Advanced Practice Nurse with specialization in alloSCT - 1 item Response option: yes/no; Dichotomous score</p>	
Clinicians and patient's questionnaire	<p>Time spend with the transplant team during follow-up Patient's perspective, 1 item each; self-report (written) questionnaire average time per patient in minutes; Continuous variable</p>	No information
<b>Level of Chronic Illness Management (CIM)</b>		
Clinicians' perspective	<p>CIMI-BRIGHT 55 items <sup>2</sup>, with the dimensions of:</p> <p>1) Self-management Support (19 items)</p> <p>2) Delivery System Design (20 items)</p> <p>3) Clinical Decision Support (10 items)</p> <p>5) Clinical Information System (6 items)</p> <p>5-point Likert scale ranging from '1= strongly disagree' to 4= strongly agree'; (5=don't know; set to missing). Higher scores correspond with higher level of chronic illness management implemented. Total score ranging from 0-4</p>	<p><b>Content validity:</b> Scale content validity= 0.86</p> <p><b>Interrater reliability</b> pilot tested: ranging between 75% and 85% 52 of originally 55 items retained in a unidimensional scale, with a Cronbach's alpha of 0.94 <sup>3</sup></p>
Patients' perspective	<p>Short version of the Patient Assessment of Chronic Illness Care (PACIC) <sup>4</sup> instrument, 11-items with the dimensions of:</p> <p>1) Self-Management Support (8 items)</p> <p>2) Delivery System Design and Clinical Decision Support (1 items)</p> <p>3) Most CCM components (2 items)</p> <p>5-point Likert scale ranging from '1= almost never' to '5= almost always'; often-almost always were considered as yes. Total score ranging from 11 to 55.</p>	<p>Unidimensional scale, with a Cronbach's alpha of 0.88 <sup>3</sup></p>

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Patient level		
Patients Self-Report on Self-Management and Health Behaviors		
Level of physical activity	Brief Physical Activity Assessment tool <sup>6</sup> , patient self-report; 2 items, dichotomous score (yes/no). Sufficiently active: ≥ 3x/week 20 min. of vigorous AND/OR ≥ 5x/week 30 min. of moderate physical activity	<b>Criterion validity</b> K statistic 0.14-0.40 <b>moderate inter-rater reliability</b> (κ= 0.53, 95% CI= 0.33-0.72)
Currently smoking	Swiss Health survey <sup>8</sup> ; 1 item; self-report; dichotomous score (yes/no)	No information
Level of alcohol consumption	BRIGHT patient self-report; 2 Items; (drinking alcohol (yes/no; if yes, number of alcoholic drinks per week). Ordinal scoring: non-drinker; moderate drinker (1 drink/day (women), 2 drinks/day (men)), or heavy drinker (>1 drink/day (women), >2 drinks/day (men)	No information
Sun protection measures	Swiss study on health of people with cancer, leukemia, tumor in childhood <sup>7</sup> and Cambridge University Hospitals' perception of skin cancer in transplant recipients scale <sup>5</sup> ; 8 items; 'Yes/No' and 5-point Likert scale ranging from '1= never' to '5= always'; Non-adherent= never protect or most of the time no protection against sun or use sunscreen SPF ≤ 30/no sunscreen if advised by the transplant team to protect against the sun.	Unidimensional scale, Cronbach's alpha of 0.59
Adherence to food recommendations	BRIGHT patient self-report, adapted to alloSCT setting; 6 Items, 5-point Likert scales: never, seldom, sometimes, often, always; often-always considered as yes.	No information
Barriers of taking IS` as prescribed	BRIGHT patient self-report 28 Items, 5-point Likert scales: never, seldom, sometimes, often, always; often-always considered as yes.	19 items unidimensional scale, Cronbach's alpha 0.89
Importance and confidence of taking IS`	BRIGHT patient self-report 2 Items, 10-point Likert scales: 0= not at all important/confident- 10 extremely/confident.	No information
Adherence to appointment keeping	BRIGHT patient self-report; 1 Item, 5-point Likert scale: 1= never missed to 6= last 5 appointments missed.	No information
Member of a Patient organization	BRIGHT patient self-report; 1 Item, yes/no	No information
Health Literacy	BRIGHT patient self-report; 1 Item, How confident are you filling out medical forms by yourself, 5-point Likert scale: 1= none of the time to 5= all of the time. Score between 0 and 2 considered as low health literacy	Concurrent validity: with the Short Test of Functional Health Literacy in (AUC=.72-.74; with the Rapid Estimate of Adult Literacy in Medicine (AUC=.81-.84)

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<b>Patients perspective on Self-Management Support</b>		
Patients have been advised by the transplant team to be physically active	BRIGHT patient self-report; 1 item, yes/no	No information
Patients have been advised by the transplant team to cut down alcohol intake	BRIGHT patient self-report; 1 Item, yes/no	No information
Patients have been advised by the transplant team to protect against sun	BRIGHT patient self-report; 1 Item, yes/no	No information
Patients have been advised by the transplant team to follow a specific diet	BRIGHT, 1 item, yes/no	No information
Transplant team discussed intake of IS with the patient`	BRIGHT patient self-report; 1 Item, yes/no	No information
Frequency of having help to read health-related materials	BRIGHT patient self-report; 1 Item, 5-point Likert scale: 1= none of the time to 5= all of the time.	No information
Problems in understanding health related information	BRIGHT patient self-report; 1 Item, 5-point Likert scale: 1= none of the time to 5= all of the time.	No information
<b>Patients technology openness on Self-Management support</b>		
Open towards new technologies	PICASSO TX Questionnaire patient self-report; 2 Items, 5-point Likert scales: never, seldom, sometimes, often, always; try out and easily master new ICTs	No information
Willingness to receive feedback about performance	PICASSO TX Questionnaire patient self-report; 1 Item, 5-point Likert scales: never, seldom, sometimes, often, always	No information
Preferred device for e.g. reminders,	PICASSO TX Questionnaire patient self-report; 1 Item, 5-point Likert scales: never, seldom, sometimes, often, always	No information
Preference of device	PICASSO TX Questionnaire patient self-report; 2 Items assessing preference for medication reminder, information seeking	No information
Use of health applications	PICASSO TX Questionnaire patient self-report; 1 Item, yes/no, if yes indicate which ones.	No information
<b>Patients technology openness on Delivery System Design</b>		
Willingness to use a health application of the SCT center	PICASSO TX Questionnaire patient self-report; 1 Item, 5-point Likert scales: never, seldom, sometimes, often, always	No information
Preferred device for health application	PICASSO TX Questionnaire patient self-report; 2 Items, 5-point Likert scales: never, seldom, sometimes, often, always; own device/device provided by hospital	No information

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Perceived importance of technology in terms of behavior support, monitoring or data sharing with clinicians	PICASSO TX Questionnaire patient self-report; 1 Item; Investigator developed 2 Items, Visual Analogue Scale, 0= not at all important-10 extremely; continuous variable	No information
<b>Patients technology openness on Clinical Decision Support</b>		
Increased confidence by data sharing	PICASSO TX Questionnaire patient self-report; 1 Item, 5-point Likert scales: never, seldom, sometimes, often, always	No information
<b>Patients technology openness on Clinical Information System</b>		
Willingness to use eHealth for tracking health behavior	PICASSO TX Questionnaire patient self-report; 3 Items, 5-point Likert scales: never, seldom, sometimes, often, always; tracking activity, medication intake, symptoms	No information
Data transfer preferences	PICASSO TX Questionnaire patient self-report; 2 Items, 5-point Likert scales: never, seldom, sometimes, often, always; automatic/ at request	No information
Data sharing with clinicians	PICASSO TX Questionnaire patient self-report; 1 Item, 5-point Likert scales: never, seldom, sometimes, often, always	No information
<b>Patients technology openness on eHealth education</b>		
Ownership, experience, use, purpose, handling of electronic devices	PICASSO TX Questionnaire patient self-report; 5 Items per device (Mobile phone, smartphone, Tablet PC, Laptop, Desktop PC, Smartwatch, Internet),	No information
Internet access, type of connection	PICASSO TX Questionnaire patient self-report; 1 Item,	No information

**Note:** IS= Immunosuppressant's; alloSCT= allogeneic hematopoietic stem cell transplantation

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**Supplementary Table 2:** Clinicians' perspective on practice pattern in view of CIM (values in bold = items with less than 50% positive answer)

Dimensions	Items	Results	
		N (5)	Yes n(%)
<b>Level of chronic illness management (CIM) according to the dimensions of the eCCM</b>			
<b>Self-Management Support</b>	1. Healthcare workers have enough time to assess, educate and support patients in self-management (e.g. medication taking, smoking, physical activity, sun protection, diet)	5	<b>1 (25)</b>
	2. The transplant team routinely works with patients to identify clear, measurable and workable self-management goals	4	2 (50)
	3. The transplant team helps all patients set up action plans for medication adherence	5	4 (80)
	4. Before making or changing a treatment plan, the transplant team discusses the alternatives with the patient and asks them about their preferences	4	4 (100)
	5. The transplant team lets patients decide on the treatment options they prefer	4	4 (100)
	6. The transplant team lets patients decide on self-management goal(s)	3	3 (100)
	7. We always ask patients if they agree with their treatment plans	4	4 (100)
	8. The transplant team routinely assesses obstacles patients believe prevent them from following their treatment plans	3	3 (100)
	9. The transplant team routinely assesses each patients' ability to follow the agreed treatment plan	4	3 (75)
	10. The transplant team checks during follow-up if patient is dealing effectively with the treatment plan	3	<b>1 (33)</b>
	11. The transplant team gives each patient a copy of the agreed treatment plan, including information on self-management	4	4 (100)
	12. The transplant team routinely asks patients to report on their self-management efforts	3	<b>1 (33)</b>
	13. The transplant team routinely uses interpreters for foreign language patients	4	3 (75)
	14. During follow-up visits, the transplant team routinely reviews, together with the patient, data on self-management	3	<b>1 (33)</b>
	15. The transplant team routinely conducts follow-up contacts within 2 weeks for all patients who have set a new self-management goal	3	<b>1 (33)</b>
	16. The transplant team routinely follows up with the patient within 2 weeks on all patients who have started a new medication regimen	4	2 (50)
	17. The transplant team routinely assesses patients for their individual concerns or goals	3	<b>1 (33)</b>
	18. The transplant team routinely refers patients to community services that can help them self-manage their care after leaving the hospital	4	<b>1 (25)</b>
	19. If the transplant team refers patients the team routinely works directly with these agencies to coordinate care for individual patients	4	<b>1 (25)</b>
	20. If the transplant team refers patients we routinely follow up with patients to assess their progress	4	3 (75)

## Chapter 3 – The contextual analysis

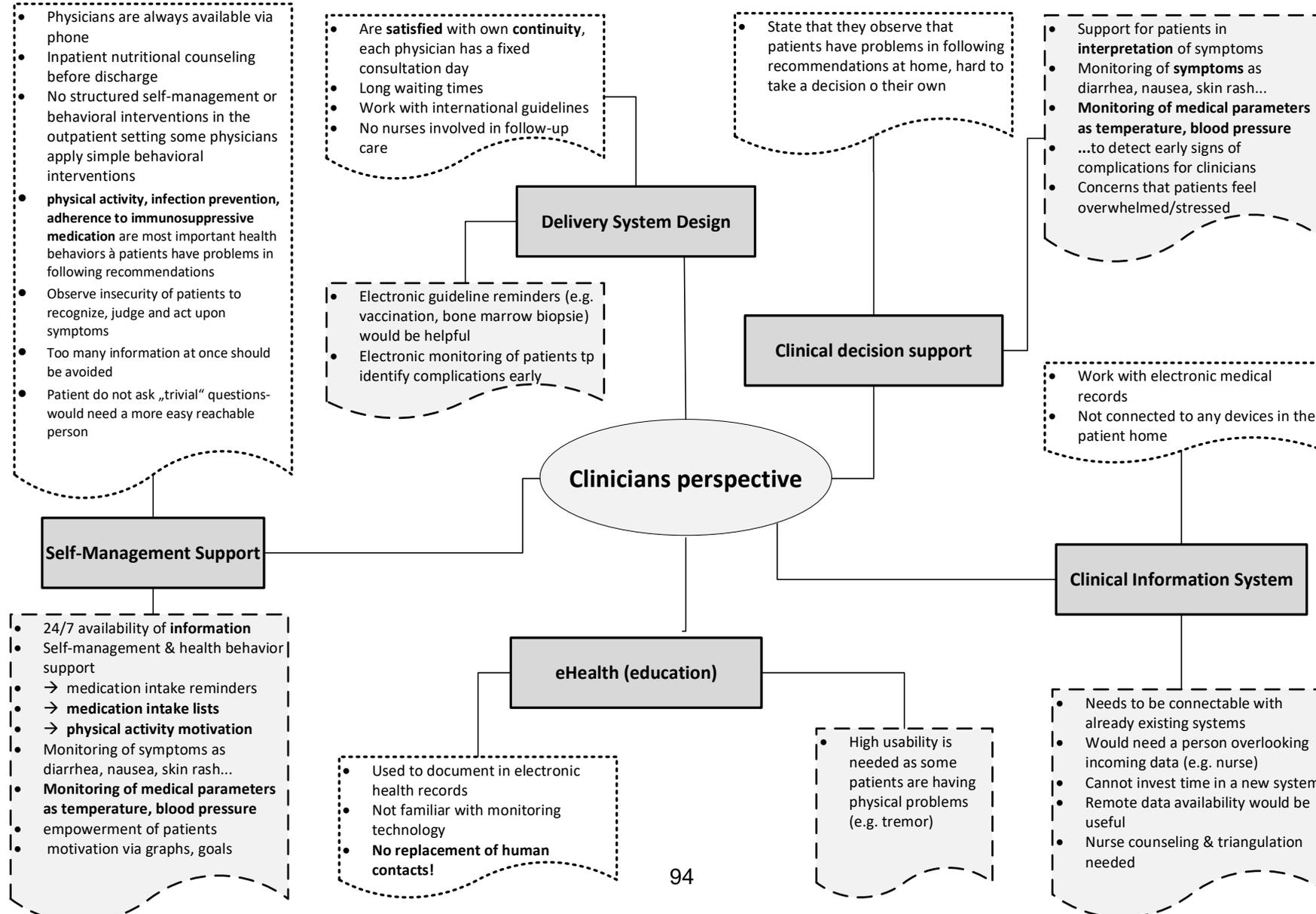
Dimensions	Items	Results	
		N (5)	Yes n(%)
<b>Delivery System Design</b>	21. Inpatient and outpatient services are coordinated	5	4 (80)
	22. Services are coordinated across different healthcare providers	4	2 (50)
	23. Services are coordinated over time	4	2 (50)
	24. There is a specific long-term care coordinator	5	<b>0 (0)</b>
	25. Patients are strongly encouraged to see the same healthcare workers over time	3	3 (100)
	26. Patients are assessed when they have concerns/questions beside appointments	4	4 (100)
	27. Outpatient follow-up appointments are scheduled with patients at the end of visit	5	5 (100)
	28. Patients who cancel their follow-up visits are contacted to reschedule	5	5 (100)
	29. Patients who cancel their follow-up visit are contacted to identify & solve problems that prevent them from their visits	5	5 (100)
	30. Healthcare workers are given incentives for effective processes or improved outcomes	4	<b>1 (25)</b>
	31. Patients are given incentives for effective self-management and improved outcomes	3	2 (66)
	32. Senior and other influential leaders clearly help improve the quality of care	5	4 (80)
	33. The transplant program has a system for routinely monitoring the quality of care	3	2 (66)
	34. The transplant program has a highly organized quality improvement process	3	2 (66)
	35. All members of the transplant program's team routinely take part in quality improvement	4	2 (50)
	36. The achievements of quality improvement processes are reported to the public	2	1 (50)
	37. The transplant program is based on a system of interdisciplinary team care	5	<b>1 (20)</b>
	38. Team members are given roles and responsibilities for tasks according to their professional strengths and abilities	4	3 (75)
	39. Clinicians' time is freed by shifting routine jobs to clinical assistants	3	2 (66)
	40. Each member of the healthcare team is respected for his/her unique areas of expertise and contributions to overall patient care	3	3 (100)
<b>Clinical Decision Support System</b>	41. Written guidelines for care are easily available	5	5 (100)
	42. Written guidelines for care are supported by education/courses	2	2 (100)
	43. Written guidelines for care are built into care through prompts/reminders	3	2 (66)
	44. Care guidelines are built into the information system through computerized prompts/reminders	4	3 (75)
	45. The transplant team's information system automatically gives healthcare workers specific guidance for individual patient care (e.g. reminders for visit, blood test)	4	2 (50)
	46. The transplant team's information system automatically flags patients who are overdue for routine follow-up	4	<b>0 (0)</b>
	47. The transplant team's information system is used to give feedback to individual healthcare workers	4	<b>1 (25)</b>
	48. The transplant team's information system is used to give feedback to the transplant team about the quality of care they are delivering and identify areas for improvement	4	<b>1 (25)</b>
	49. The transplant team's information system is used to give information about trends in the transplant population	4	2 (50)

## Chapter 3 – The contextual analysis

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Dimensions	Items	Results	
		N (5)	Yes n(%)
<b>Clinical Information Systems</b>	50. Patients have access to their medical records or personal health records	4	4 (100)
	51. Electronic medical records are available to all members of the transplant team	4	3 (75)
	52. Electronic medical records are used by all members of the transplant team	3	3 (100)
	53. The same information about individual patients is accessible in- and outpatient	3	2 (66)
	54. The transplant team uses information systems to monitor patients at home	4	<b>0 (0)</b>
	55. The transplant team uses information systems for research purposes	4	4 (100)

**Supplementary Figure 1:** Meta-Map about main topics in terms of current practice pattern (dotted lined boxes) and possible eHealth support (dashed lined boxes) from the clinicians focus groups per dimension of the eCCM



## Chapter 3 – The contextual analysis

**Supplementary Table 3:** Patients' perspective on practice pattern in view of CIM and self-reflection on self-management and behavior

Variables	Answer options	Results	
		N	Yes n (%)
<b>Practice Pattern</b>			
Time spend with transplant team during follow-up	Estimated minutes without waiting time ( <b>mean/SD</b> )	58	22 Min. (11.7)
<b>Level of Chronic Illness Management (CIM)</b>			
Self-Management Support  Delivery System Design/ Clinical Decision Support	Given a copy of treatment plan	57	37 (64.9)
	Helped to set specific goals to improve my eating or exercise	57	30 (52.6)
	Given choices about treatment	54	21 (38.9)
	Asked how the alloSCT affect my life	57	20 (35.1)
	Asked question about my health behavior	57	16 (26.6)
	Helped to plan ahead even for hard times	55	9 (16.3)
	Encouraged to go to group help to cope with transplantation	57	9 (15)
	Made a treatment plan fitting to daily life	55	7 (12.7)
Most CCM components	Satisfied how my care is organized	56	52 (92.9)
	Told me how other medical disciplines help my treatment	56	19 (33.9)
<b>Patient Self-Report on Self-Management and Health Behaviors</b>			
Level of physical activity	≥ 3x/week 20 min. of vigorous physical activity	54	12 (22.2)
	≥ 5x/week 30 min. of moderate physical activity	55	10 (18.2)
Currently smoking	Currently smoking	59	6 (10.2)
Level of alcohol consumption	Alcohol drinking	58	30 (50.8)
	>3-4 per/week	58	4 (8.6)
Use of sun protection measures	Use of sun blocker	56	38 (66.7)
	Wearing a hat or clothes with long sleeves	56	40 (62.1)
	Staying in the shade	56	52 (89.7)
	Sensitive to day time and sun exposure	56	44 (78.6)
	Get sunburned	59	6 (10.2)

## Chapter 3 – The contextual analysis

Variables	Answer options	Results	
		N	Yes n (%)
Adherence to food recommendations	Resign grapefruit	51	48 (94.1)
	Resign raw-milk-cheese	53	49 (92.4)
	Eat intact fruits and vegetables	49	45 (91.8)
	Prepare food fresh	52	49 (94.3)
	Resign raw fish	52	51 (98.1)
	Eat only well boiled eggs	51	51 (100)
Problems of taking IS as prescribed (most frequent problems out of 28 listed)	Forget to take them	60	12 (21.6)
	Bad taste	60	7 (12)
	Problems with swallowing	60	6 (10)
	Taking too many drugs at same time	60	5 (8)
	Side-effects as nausea	60	4 (7)
	Feel too sick	60	4 (7)
	Fall asleep or oversleep	60	3 (5)
Importance and confidence of taking IS	Importance of taking immunosuppressant's (mean/SD)	50	9.14 (1.4)
	Confidence of taking immunosuppressant's (mean/SD)	49	9.16 (1.4)
Adherence to appointment keeping	Never missed	59	57 (96.6)
	Once		2 (3.4)
Member of a patient organization	Member of a patient organization	59	6 (10.2)
Confident in filling in medical documents	None of the time	56	9 (16.1)
	A little to some of the time		16 (28.6)
	Most to all of the time		31 (55.4)
Health literacy	Total score	56	3.41
<b>Patient perspective on Self-Management Support</b>			
Advised by the transplant team	To be physically active	58	57 (98.3)
Patients have been advised by the transplant team	To cut down alcohol intake	58	29 (50)
Patients have been advised by the transplant team	To protect against sun	59	56 (94.9)
Patients have been advised by the transplant team	To follow a specific diet/food recommendation	56	52 (92.7)
Transplant team discussed	The intake of IS	58	55 (94.8)
Frequency of having someone's help reading health-related materials	None of the time	59	27 (45.8)
	A little to some of the time		23 (39)
	Most to all of the time		9 (15.3)

## Chapter 3 – The contextual analysis

Variables	Answer options	Results	
		N	Yes n (%)
Problems in understanding health related information	None of the time A little to some of the time Most to all of the time	59	17 (28.8) 31 (52.5) 11 (18.6)
<b>Patients technology openness on Self-Management support</b>			
Open towards new technologies	I try out new technologies Mostly I get quickly used to new technologies	55 55	38 (69.1) 35 (63.7)
Willingness to receive feedback about performance	I would agree to get feedback on my progress, symptoms or health behavior Smartphone Tablet Computer SmartWatch	48 40 42 31	27 (56.2) 14 (35) 15 (42.2) 1 (3.2)
Preferred device for e.g. reminders, overview of symptom development	Smartphone Tablet Computer SmartWatch Other (e.g. alarm clock, mobile phone)k	49	35 (71.4) 4 (8.3) 3 (6.1) 1 (2) 6 (12.2)
Preference of device	Which device would you prefer for searching information in the internet? Smartphone Tablet Computer SmartWatch	49	8 (17.4) 8 (17.4) 23 (58.7) 0 (0)
Use of health applications	Do you use apps to support you in a healthy lifestyle?	52	12 (23.1)
<b>Patients technology openness on Delivery System Design</b>			
Willingness to use a health application of the hospital	Would you use an available health application provided by the hospital? ○ With your smartphone ○ With a smartphone provided by the hospital ○ With your tablet ○ With a tablet from the hospital	54 47 44 43 45	38 (70.4) 29 (61.7) 11 (25) 17 (18.6) 14 (31.1)
Perceived importance (mean/SD)	<ul style="list-style-type: none"> <li>To what extend is it important that new technologies are developed to support health behavior e.g. physical activity, healthy eating</li> <li>To what extend is it important that new technologies are developed that collect vital signs and symptoms and give automated feedback on the entered data?</li> </ul>	58 57	8.05 (2.3) 7.3 (2.6)

## Chapter 3 – The contextual analysis

Variables	Answer options	Results	
		N	Yes n (%)
	<ul style="list-style-type: none"> <li>To what extent is it important that new technologies are developed that allow clinicians to monitor your vital signs, symptoms, medication intake or physical activity?</li> </ul>	57	7.0 (2.8)
<b>Patients technology openness on Clinical Information System</b>			
Increased confidence by data sharing	The knowledge that nurses and physicians can see my data gives me security	56	32 (57.2)
Willingness to use eHealth for tracking health behavior	Would you be willing to use: A step counter to measure your physical activity?	57	27 (47.4)
	A medicine box which detects if you take you medication?	58	25 (43.1)
	An electronic symptom questionnaire asking for symptoms?	57	23 (40.4)
Data transfer preferences	Health data should be sent at request	53	25 (47.2)
	Health data should be sent automatically	51	16 (31.4)
Data sharing with clinicians	Clinicians can see my data to monitor my e.g. vital signs, symptoms or health behavior	57	36 (63.1)
<b>Patients technology openness on eHealth education</b>			
Ownership, experience, use, purpose, handling of electronic devices and internet	See Supplementary Table 4		
What type of connection do you use at home to access the internet	Fixed-line connection	49	44 (89.8)
	<ul style="list-style-type: none"> <li>LAN as internet access</li> </ul>		4 (9.3)
	<ul style="list-style-type: none"> <li>WLAN as internet access</li> </ul>		37 (86)
	Only mobile connection		5 (10.2)

**Note:** IS= Immunosuppressant's; alloSCT= allogeneic hematopoietic stem cell transplantation, CCM

### Chapter 3 – The contextual analysis

**Supplementary Table 4: Devices owned, used and handled by patients in %, N=58 (multiple answer options possible)**

Device	Own	Experience		Use (at least daily)						Handling				
		0-3 years	>3 years	Calls	SMS	Messages	Internet	Email	other	Get on well	Confident	Makes life easier	Future use	Others want me have it
Smartphone	78.3	54.7	42.6	56.5	31	87	58.7	52	18.2	91.5	90	85	97.9	47
Laptop	61.7	38.9	61.1	NA	NA	NA	40	29	18	94.4	91	72.2	97	35
Computer	43.3	8	92	NA	NA	NA	60	68	NA	95.8	95.8	87.5	100	47.6
Tablet	40	66.7	33.3	NA	NA	31	58.3	40.9	33.3	92	92	83	92	34
Cell phone	36.7	16.7	83.3	50	22.7	NA	NA	NA	56	100	90.5	76.2	100	76.2
SmartWatch	5	100	0	25	0	0	0	0	66.7	100	100	100	100	0
Internet	91.2	7.7	92.3	NA	NA	38	NA	24	14	100	90	84.1	100	40

**Note:** messages include e.g. WhatsApp, Twitter; Internet includes messages (38 %), email (24 %), social networks (22 %), chat (e.g. Skype/Facetime) (12 %) and information seeking (12 %); NA=not applicable

## Chapter 4

### Development of an Integrated Model of Care for allogeneic SteM cell transplantation facilitated by eHealth – The SMILe Study

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Submitted to Supportive Care in Cancer

### 4.1 Abstract

**Purpose.** Allogeneic stem cell transplantation would benefit from re-engineering care towards an integrated eHealth-facilitated care model. With this paper we aim to: 1) describe the development of an integrated care model (ICM) in allogeneic **Stem**-cell-transplantation facilitated by **e**Health (SMILe) by combining implementation, behavioral and computer science methods (e.g., contextual analysis, Behavior Change Wheel, and user-centered design combined with agile software development); and 2) describe that model's characteristics and its application in clinical practice.

**Methods:** The SMILe intervention's development consisted of four steps, with implementation science methods informing each: 1) planning its set-up within a theoretical foundation; 2) using behavioral science methods to develop the content; 3) choosing and developing its delivery method (human/technology) using behavioral and computer science methods; and 4) describing its characteristics and application in clinical practice.

**Results:** The SMILe intervention is embedded within the eHealth Enhanced Chronic Care Model, entailing four self-management intervention modules, targeting monitoring and follow-up of important medical and symptom-related parameters, infection prevention, medication adherence and physical activity. Interventions are delivered partly face-to-face by a care-coordinator embedded within the transplant team, and partly via the SMILeApp that connects patients to the transplant team, who can monitor and rapidly respond to any relevant changes within one year post-transplant.

**Conclusion.** This paper provides stepwise guidance on how implementation, behavioral and computer science methods can be used to develop interventions aiming to improve care for stem cell transplant patients in real-world clinical settings. This new care model is currently being tested in a hybrid I effectiveness-implementation trial.

**Keywords:** allogeneic stem cell transplantation, eHealth, integrated care, implementation science, behavioral science, user-centered design, agile software development, intervention development

### 4.2 Introduction

Although allogeneic stem cell transplantation (alloSCT) recipients' survival has improved over recent years, significant risks remain for short and long-term complications.<sup>1, 2</sup> Moreover, non-adherence to their therapeutic regimens is common, and can negatively affect long-term outcomes.<sup>3-5</sup> Including psychosocial issues, alloSCT patients' comprehensive care needs demand self-management interventions embedded in an integrated care model (ICM).<sup>6</sup> Based on chronic illness management principles, using multidisciplinary team-based approaches spanning settings and care levels,<sup>7</sup> ICMs strengthen person-centered care, potentially improving medical, behavioral and economic outcomes.<sup>8</sup>

One excellent example is the Chronic Care Model (CCM). Its four inner dimensions—self-management support, decision support, clinical information systems and delivery system design—guide the reengineering of acute-care-oriented models towards chronic care principles.<sup>9</sup> The more are combined, the stronger the effect.<sup>10</sup> Considering healthcare's increasing digitalization, the updated eHealth Enhanced Chronic Care Model (eCCM) explains how to strengthen all four dimensions via digitalization.<sup>11</sup> Systematic reviews and meta-analyses indicate that eHealth-facilitated ICMs improve biomedical, behavioral, psychosocial<sup>12-14</sup> and economic outcomes.<sup>14, 15</sup> In organ transplant recipients, these include improved medication adherence<sup>16</sup> and reduced re-hospitalizations.<sup>17</sup> In cancer patients, eHealth-facilitated care models integrating two or more eCCM dimensions led to, e.g., reduced symptom burden<sup>18</sup>, re-hospitalizations, improved survival, quality of life<sup>19, 20</sup> and physical activity.<sup>21</sup>

Regarding SCT care models, the only two RCTs focused respectively on one and two eCCM dimensions. For the first, Bryant et al.<sup>22</sup> implemented electronic patient-reported outcomes into routine care during the first two weeks post-SCT (n=45 autologous; n=31 allogeneic), followed by tailored self-management support leading to reduced peak symptom burden ( $p=0.03$ ). In the second, Syrjala et al.<sup>23</sup> found that for survivors >3 years post-SCT (n=182 autologous; n=566 allogeneic), online self-management and decision support led to reduced treatment distress ( $p=0.032$ ). However, both trials focused on very specific treatment phases; and neither was conceptually embedded in an ICM or comprehensively addressed multiple eCCM dimensions.

Moreover, implementing eHealth-facilitated ICMs into routine care is often problematic.<sup>24</sup> Adoption and sustainment problems commonly prevent eHealth applications' integration in established care models, with 44% to 67% of patients discontinuing the use.<sup>25-27</sup> Explanations include poor fit to context-dependent variables,

deficits regarding behavioural effectiveness, and problems with the technology not meeting users' needs.<sup>28</sup>

Combining implementation (e.g., contextual analysis), behavioral (e.g., behavior change theories) and computer science methods (e.g., agile software development, user-centered design) to develop eHealth-facilitated interventions could solve such problems.<sup>28-30</sup> Implementation science sets the long-range goal—sustainably improving the quality and effectiveness of patient care.<sup>31</sup> This means integrating methodological considerations such as stakeholder involvement, contextual analysis and the choice and application of context-adapted implementation strategies.<sup>32</sup> Combined with a theory-guided content development using behavioral science and by developing the necessary technology around end-user needs and preferences using agile software development processes, maximize its usability and accessibility.<sup>28, 30, 33</sup> For eHealth component production, this combination promises fast, iteratively improved software versions that can be discussed regularly with end users (patients, clinicians).<sup>34</sup> Following this formula, implementation/behavioral/computer science fusions should facilitate user-friendly, contextually-targeted eHealth components ready to be embedded within ICMs.

Although alloSCT patients can clearly benefit from an eHealth-facilitated ICM, no such model currently exists nor has been prepared for implementation in real-world settings. Therefore, we are developing, implementing, and testing an allogeneic **Stem-cell-transplantation facilitated by eHealth Integrated Care Model (SMILe-ICM)** combining implementation- and behavioral methods with computer science methods. This article first reports on the methods used to develop the SMILe-ICM, then describes its characteristics and application in clinical practice.

### 4.3 Methods and Results

The development phase consisted of a sequence of four steps, with implementation science methods informing each (Figure 1): 1) Choose the SMILe-ICM's theoretical foundation; 2) Develop four theory-guided self-management intervention modules; and 3) Choose and develop the intervention's delivery method(s), i.e., human and/or technology. With the SMILe-ICM's three-step development complete, the fourth step is to report on those steps, along with its characteristics and its application in daily clinical practice. All four steps are described below.

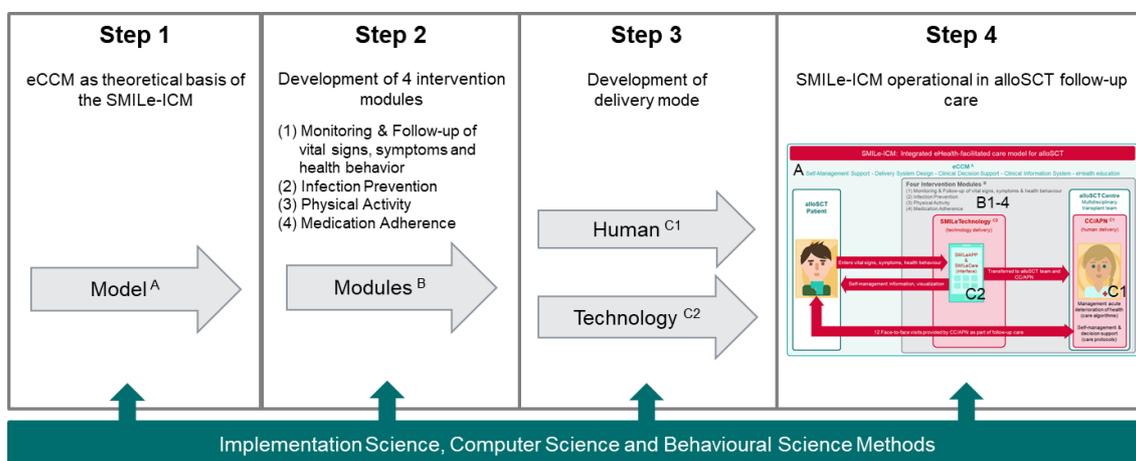
#### 4.3.1 Step 1: The SMILe-ICM's Theoretical Foundation

The SMILe-ICM is grounded in the eCCM (Figure 1 Step 1; Figure 2 A), a choice based on our contextual analysis, findings can be found in detail elsewhere.<sup>35</sup> Data from two surveys (60 patients/5 clinicians), three clinician focus groups and ten patient

## Chapter 4 – Development of the SMILe integrated model of care

interviews indicated that the existing care model is mainly acute care-driven: it focuses on diagnosing and curing patients; in- and outpatient care are separate, with limited collaboration between their clinician teams; outpatient alloSCT follow-up is primarily physician-centered, focusing mainly on medical aspects; no nurses are involved in care delivery and little attention is devoted to self-management support. Use of eCCM dimensions would quickly allow connections between in- and outpatient care teams by encouraging interdisciplinary teamwork. Further, far from replacing human contact between patients and providers, eHealth should supplement that contact, helping maintain continuity of care and self-management support.

**Fig. 1:** The three subsequent steps of the development process building up to the SMILe-ICM described in step 4

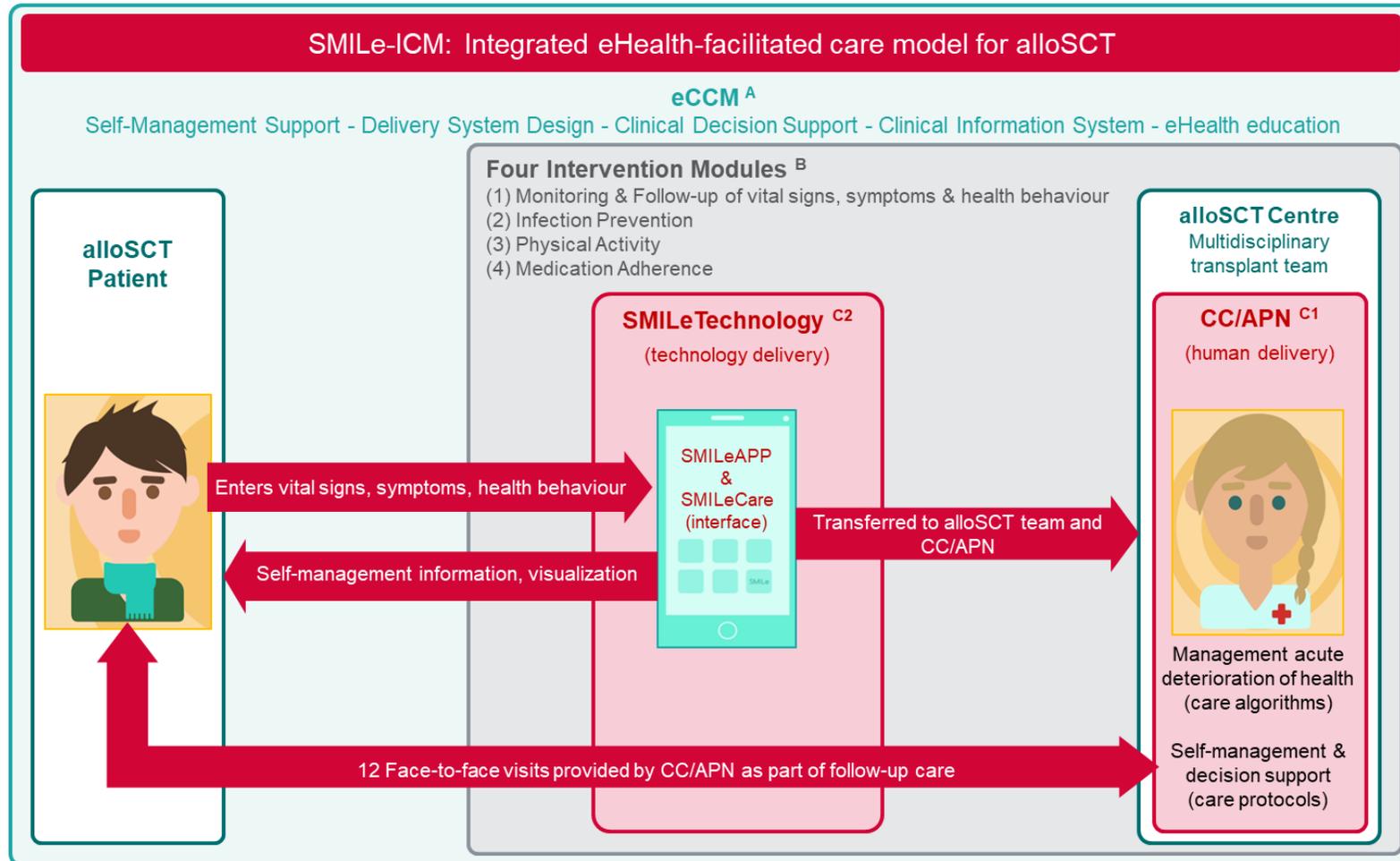


Note: A, B, C also refers to Fig.2 were the same elements can be found within the visualization of the SMILe integrated care model (ICM)

### 4.3.2 Step 2: Theory-Guided Content Development of the Intervention Modules

Our contextual analysis, empirical evidence and clinicians' and patients' endorsements led us to produce four self-management intervention modules: Monitoring and Follow-Up, Infection Prevention, Medication Adherence and Physical Activity (Figure 2; B). Content development followed the Behavior-Change Wheel (BCW). A widely used amalgamation of 19 behavior change theories<sup>36</sup>, the BCW helps its users understand, explain and change behaviors via stepwise development processes. With the Capability-Opportunity-Motivation-Behavior (COM-B) Model at its hub, the BCW meshes well with the Theoretical Domains Framework (TDF)<sup>36</sup>, which includes 14 domains, synthesizing key theoretical constructs used in behavioral theories such as knowledge, skills, goals or beliefs relating to the COM-B component.

Fig. 2: The SMILe integrated care model



**Note:** A= Five dimensions of the eHealth enhanced Chronic Care Model, B = Four intervention modules delivered partly via human (alloSCT Transplant Team and CC=C1) and partly via technology components (=C2); CC= Care Coordinator; APN= Advanced Practice Nurse

For developing our intervention modules' content, we established an interdisciplinary team with expertise in implementation and behavioral science methods (nursing scientists, psychologist). Pairs of researchers conducted a literature search to identify empirical evidence regarding a specific self-management issue, its determinants and possible target behaviors. Determinants were derived from empirical evidence, the contextual analysis<sup>35</sup> and clinical expertise of the team into the COM-B taxonomy, then discussed by the entire group. Where teams found multiple behaviors, the group chose which to target.

After choosing intervention functions for all targets, we selected appropriate TDF domains, behavioral change techniques (BCTs) and applied APEASE criteria (affordability, practicability, effectiveness, acceptability, safety and equity) to each. Finally, the teams carefully reflected upon the mode of delivery (face-to-face and/or technology-based) and added an additional step not covered by the BCW. We wrote comprehensive protocols for the intervention segments' face-to-face visits and full descriptions of the functionalities to be digitized as user stories.<sup>37</sup>

User stories are commonly formulated in a role-feature-reason format.<sup>38</sup> Each software functionality is presented as a sentence specifying the target *user/role*, the desired *feature* and a *reason/expected outcome*, e.g., “As a *patient/clinician*, I want to *monitor my pain intensity* so that I can *keep track of my pain trajectory*.” By supporting the translation of BCTs into software features, user stories inform the iterative software development process. Once the stories were articulated they were transferred to the software development team, starting the digitalization process.<sup>39</sup>

### *Description of the four Intervention Modules*

To underpin our intervention modules' content, seven intervention functions reflecting all TDF domains and 42 different BCTs from Michie's taxonomy were chosen.<sup>36</sup> These informed 39 user stories. The following paragraphs describe the intervention modules (Figure 2, B). Additional details for all modules regarding the target behaviors, behavioral issues, intervention components, user stories, behavior change techniques, intervention functions, TDF domains and COM-B dimensions are presented in Supplementary Table 1.

**Monitoring and Follow-up:** This module targets alloSCT patients' insecurity regarding recognizing and reacting to new symptoms.<sup>35</sup> Our literature review and feedback cycles indicated that remote monitoring of patient-reported data effectively allows both accurate symptom recognition and timely reactions.<sup>18</sup> To support this behavior, we composed an initial set of 17 parameters for daily monitoring.

Parameter relevance was decided via an online survey of 12 German-speaking alloSCT experts. Using 6-point Likert-type scales (0 = not at all relevant – 5 = extremely

relevant), these experts were asked to rate the importance of symptoms covered by the PROVIVO alloSCT patient-reported outcome questionnaire.<sup>40</sup> Inclusion of those with median ratings  $\geq 4$  led to a selection of 12 from the original PROVIVO questionnaire, plus one more recommended by the group: signs of bleeding. The experts also added temperature, blood pressure, weight and general wellbeing, resulting in 17 items to be monitored for this module. To support appropriate reactions, we collaborated closely with physicians involved in alloSCT care to define meaningful cut-off levels and feedback algorithms for each parameter (e.g., temperature  $>38.5$ : contact the center immediately).

**Infection Prevention:** This module targets patients' challenges regarding infection prevention measures, often leading to the significant burden of infection-related re-hospitalization—most common in the first two years post-alloSCT.<sup>2, 35</sup> Three target behaviors are covered: 1) adequate hand hygiene; 2) airborne pathogen-related risk reduction; and 3) safe food handling, preparation and consumption. This module's content required adaptivity, depending on participants' time since transplantation and immunity status. Patients' severely immuno-compromised or presenting signs of graft-versus-host disease need stricter recommendations; for those with more stable immune systems, they can be loosened. This module also adds one monitoring parameter: *adherence to infection prevention measures*.

**Medication Adherence:** This module responds to patients' calls for immunosuppressant intake support.<sup>35</sup> More than 50% of alloSCT patients reported immunosuppressant non-adherence in view of errors in correct taking and timing.<sup>3-5</sup> Medication nonadherence in alloSCT has been linked to poor clinical outcomes including graft-versus-host disease.<sup>3, 4</sup> Therefore, the Medication Adherence module targets the implementation dimension of medication adherence (taking and timing behavior). This module also adds one monitoring parameter: medication intake. A detailed description of this module's development process has been published elsewhere<sup>37</sup> and is a blueprint for how other modules were developed.

**Physical Activity:** This module targets alloSCT patients' commonly reduced physical capability due to pre-transplant treatment or post-transplant complications. In addition to lowering patients' quality of life these can shorten survival.<sup>41</sup> Conversely, improved physical condition is linked to improved health outcomes.<sup>41</sup> Our contextual analysis indicated a need for support of physical activity before, during and post-alloSCT.<sup>35</sup>

However, review of all available evidence indicated that improving physical activity would be overly ambitious as a target behavior: patients are too weak in the first month's post-alloSCT. Therefore, we reformulated the target behavior to 'reducing sedentary bouts,' increasing patients' physical activity alongside their energy levels. While we

chose *daily step count* as an indirect measure of inactivity, this obviously also indicates physical activity. All patients receive step counters and training on how and when to wear them. This module adds *daily step count* as a monitoring parameter.

### 4.3.3 Step 3: Choice and Development of Intervention Delivery Methods

Both patients and clinicians preferred a combined face-to-face and eHealth-enhanced intervention.<sup>35</sup> We operationalized all four eCCM dimensions (Table 1), and determined the most effective delivery methods (human/technology).

#### *The Human-Delivered Components*

The SMILe-ICM's human-delivered components are 12 face-to-face sessions with an Advanced Practice Nurse (APN)/Care-Coordinator (CC, Delivery System Design; Self-Management Support). Embedded in the alloSCT team, in addition to coordinating patient care and delivering information and training, the CC provides the desired human factor. Additionally, working closely with the in- and outpatient teams, the CC can strengthen the links between the two.

Patients are monitored closely during their inpatient stay, but need to build post-discharge health self-management skills. Immediately post-discharge, they return 4–8 times per month as necessary for follow-up. As their conditions stabilize, follow-up intervals gradually increase to once yearly. As the patients' first point of contact, the CC delivers all required self-management interventions within (Self-Management Support, Delivery System Design). All face-to-face sessions will follow a detailed intervention protocol, which guides the intervention delivery and support fidelity among the CCs while delivering the intervention modules. In addition to face-to-face contacts, the CC will also be connected with the patients via the SMILe technology enabling rapid responses to early signs of health deterioration.

#### *The Technology Components*

The SMILe technology includes the SMILeApp for the patient and the browser-based SMILeCare monitoring component for the care team (Delivery System Design; Clinical Information Systems). Via the SMILeApp, patients are encouraged to daily enter data for 20 monitoring parameters. These include ratings of general well-being, temperature, weight, and blood pressure measurements, 13 symptom-related parameters (pain; signs of bleeding; nausea; emesis; diarrhea; skin rash; mouth or throat sores; shortness of breath; cough; pain or burning at urination; fatigue, tiredness, or lack of energy; difficulty swallowing; decreased appetite) and three behavioral measures (adherence to infection prevention measures and medication intake, number of steps). According to the data patients enter, they receive automated feedback from the SMILeApp concerning self-management or necessary actions (Self-Management

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Support; Decision Support). If one or more parameters exceed pre-defined cut-offs, they receive instructions to contact the transplant center within the next two days, as soon as convenient, immediately, or even to call an ambulance immediately.

**Table 1** : The eCCM dimensions and described operationalization of the SMILe-ICM

eCCM	eHealth	CC	Operationalization
SM-S		x	The CC provides patients with self-management support interventions beginning 2 weeks before until 1-year post-alloSCT, delivering 12 face-to-face sessions covering four modules.
	x		Patients receive algorithm powered feedback based on entered parameters via the SMILeApp.
	x	x	SMILeCare allows to detect complications early and allows to provide tailored additional face-to-face session.
		x	In case of highly burdened patients CC provides additional support and/or case-management.
DSD	x		The use of information technology (SMILeApp & SMILeCare) is a new element and allows to adapt care-processes with the goal of optimizing both resource use and clinical outcomes.
		x	Advanced practice oncology nurses need to be in place to work in the new role of a CC.
		x	The introduction of the CC is a new element in alloSCT follow-up. Accordingly, care processes need to be adapted by the alloSCT centre and weekly interdisciplinary discussion rounds should be implemented.
	x	x	The SMILeApp contains and CC uses developed educational materials for each module.
CDS	x		If serious symptoms are entered patients receive algorithm-based feedback how fast they should contact the transplant centre.
		x	The CC's work is guided by protocols that build on the alloSCT centres' clinical practice pattern guidelines and have been approved by the centres' physicians.
		x	The CC can discuss treatment decisions/changes pro-actively with attending physicians when necessary based on the monitoring.
CIS	x		Vital signs, symptoms and health behaviours of home dwelling alloSCT patients are captured by the SMILeApp and transferred to the hospital where the CC can overview them.
	x	x	The CC can access the patient data if agreed to by the patient and share it with the attending physician if needed.
eHed		x	The patients and the CC are trained to work respectively with the SMILeApp and SMILeCare applications.

**Note:** eCCM=eHealth enhanced Chronic Care Model, CC=Care-Coordinator; SM-S= self-management support; DSD=Delivery System Design; CDS=Clinical Decision Support; CIS=Clinical Information System, eHed=eHealth education

Further, patients have access to self-management and behavioral support information via a lexicon of complications and parameters assessed by the SMILeApp (Self-Management Support). With the patient's consent, the data entered are transferred to the university hospital data center, where the CC reviews incoming values and visualizations of their development via the SMILeCare monitoring software (Clinical Information system). For alarming values, the CC reacts following the SMILe risk-

adjusted care protocol (Decision Support, Clinical Information Systems, Delivery System Design). Based on the same algorithms that guide the CC, other alloSCT team members will be involved as appropriate. Both patients and CCs receive special SMILe technology training (eHealth Education).

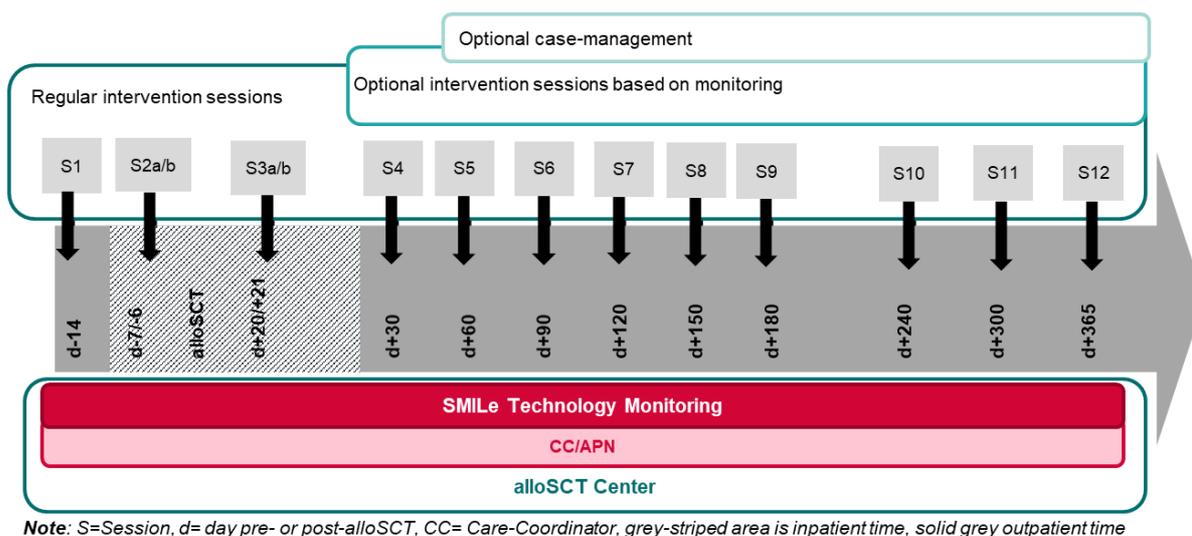
### **4.3.4 Step 4: SMILe Intervention Characteristics and Application in Daily Clinical Practice**

The three above-described steps resulted in the operational SMILe-ICM's intervention characteristics ready for roll-out in clinical practice (Figure 2). The following section describes the intervention's application in daily clinical practice.

To recruit patients, the CC contacts patients as soon as they are listed for transplantation (1 to 5 weeks pre-admission), to schedule their first face-to-face session. Patients support needs are highest in the first 6 months post-discharge. Therefore, the CC delivers most interventions between days -10 pre- and +180 post-alloSCT in close collaboration with the alloSCT team. Patient contact begins before the inpatient stay and continues via scheduled outpatient clinic appointments as part of usual follow-up care. The CC delivers the highest-frequency intervention dosage over the first two months. This usually drops in months 3-6, with the lowest dosage occurring in month's 7-12 post-alloSCT (Figure 3). The CC uses the face-to-face sessions to deliver/reiterate oral instructions and/or tailored self-management and behavioral support. Already in the first session pre-alloSCT, patients receive a step counter and the SMILeApp, either installed on their smartphone or on a hospital-provided tablet computer. After teaching them to use the step counter, the CC trains them to enter symptoms (e.g., skin rash) to the app, how to interpret the app's feedback, and how to react if no feedback is received. While hospitalized, they receive as many SMILeApp training sessions as necessary to use it confidently. Before discharge, to develop the habit of entering their daily data, patients also practice this until proficient.

Depending on the patient's condition, the intervention protocol allows stepping up of intervention dosage. I.e., for those reporting parameters above cut-off levels or requiring additional support, the CC will immediately contact the responsible clinical team (e.g. treating physician) in the in- or outpatient setting based on predefined protocols. Where patients have two or more uncontrolled symptoms, the CC also provides case management (Figure 3).

**Figure 3:** Intervention timing and dosage within the SMILe integrated care model



### 4.4 Discussion

This is the first paper to report on the theory-driven, evidence-based development of an eHealth-facilitated alloSCT ICM combining implementation, behavioral and computer science methods. This includes, respectively, a contextual analysis, the Behavior Change Wheel and user-centered design informing the agile software development. It provides not only information on this complex intervention’s content, but also step-by-step guidance on how to develop a similar care model for any context and real-world implementation.

Traditional models of care in alloSCT settings are predominantly acute care-driven, with limited focus on self-management. Based on prevailing evidence and insights from our contextual analysis, a re-engineering of alloSCT care towards an integrated chronic illness approach is urgently needed. In terms of care coordination and self-management requirements, the first months post-alloSCT are the most complex, involving high re-hospitalization risks due to various complications.<sup>2, 6</sup> EHealth-facilitated ICMs offer promising methods of improving outcomes across a variety of chronic illnesses. However, few have been applied in alloSCT settings, and none have focused on inpatients’ transitions to home—a moment when continuity of care is challenged and complications frequently arise.<sup>42</sup> Such findings are consistent with those of our contextual analysis, which indicated that patients’ greatest support needs occur during the first year post-alloSCT.<sup>35</sup>

Numerous commercial eHealth applications are available for cancer settings, some of which are connected to the patients care teams. However, while a small number are either embedded within an ICM approach or are theory-based<sup>18, 28</sup>, to our knowledge, these applications have not been developed based on an implementation science approach to ease the adaption, implementation and sustainability in real world settings.

Consequently, these interventions frequently function as black boxes regarding development, symptoms monitored or mechanisms underpinning their target behavioral changes. For example, a critical review of 23 eHealth apps for patients with cancer found that no theoretical basis was generally present: only six of the 23 even referred theories or behavior change models.<sup>28</sup> Of the other available offerings, fewer than 20% refer to empirical studies or background source information; only 11.3% are evidence-based; and just under 10.3% involve clinicians in their development processes.<sup>43-45</sup> And while many report user-centered design approaches, few support such claims with insights into end-user involvement or context-specific adaptations. This might result from a strong focus on technology development, with less attention to theoretical underpinnings: such an approach may appear to shorten the path to implementation. In addition, while many applications pay some attention to context-specific requirements, the broader perspective—re-engineering entire care teams and processes—is missing entirely. Overall, alongside the general lack of theoretical underpinnings or context-specific adaptations, the non-use or non-transparent use of user-centered design methodology preclude the uptake and sustained clinical use of virtually any off-the-rack eHealth application in real-world settings.

Furthermore, both Zhao et al. (2016) and Hamel et al. (2019) argue, that improving the effectiveness of eHealth design demands the ongoing involvement of all relevant stakeholders to produce a thorough understanding of end-user needs and preferences, with the most effective applications supplying real-time feedback, individualizable elements, and evidence-based medical information.<sup>28, 45</sup> This reflects the findings of our contextual analysis, which revealed that our target patients and clinicians are not interested in a stand-alone eHealth solution, but in a purpose-designed combination of human- and technology-delivered components best reflected by an eHealth-facilitated ICM.<sup>35</sup> It also buttresses the argument that embedding eHealth components in integrated care models facilitates much-needed continuity of care and self-management support between outpatient clinic visits.<sup>42</sup>

Our development process included certain notable limitations. As it requires an interdisciplinary team conversant with three methodologies, it is resource-intensive. Its incremental and iterative development processes, including user tests and feedback rounds, is time- and cost-intensive. Limitations of our human and time resources prevented our completion of the digitalization process as originally planned. A serious regulatory barrier was the main reason for this: The European Medical Device Regulation (MDR; EU2017/745) defines the originally-planned SMILeApp as a class 2b medical device, necessitating, e.g., tightly-regulated development, certification and ongoing quality management. Unable to meet these requirements, our academic project team

was forced to cut back the planned level of digitization. While the monitoring and follow-up module is now digitalized with intermitted automated feedback and decision support, patients receive these information's as written leaflets. The other modules are still purely in a face-to-face delivering mode. However, testing the system at this stage provides insights influencing the creation of future modules; and we believe that the methods used increase the probability of sustainable implementation and acceptance in real-world clinical practice, while reducing research resource waste.

Our next step is a hybrid-1-effectiveness-implementation RCT of the first SMILe–ICM version's clinical, economic and implementation outcomes at two alloSCT centers in Germany and Switzerland. In parallel, following all regulatory requirements (MDR; EU2017/745), the digitalization process of the eHealth components facilitating the face-to-face components will continue until all module components are digitalized and compliant with class 2b medical device regulations.

### 4.5 Conclusions

We found that the alloSCT setting would benefit strongly from the re-engineering of its care teams and processes towards an eHealth-facilitated ICM. Despite high levels of activity in the eHealth sector, though, empirical evidence is scarce. Many available eHealth applications are neither embedded within an ICM nor offer information regarding their theoretical underpinnings nor explanations of how contextual factors, end-user involvement or effective behavior change techniques were integrated into their development processes. With this report, in addition to providing step-by-step guidance for development of an eHealth-facilitated ICM, we describe how the resulting model can be integrated within alloSCT patient care. We developed the SMILe–ICM via an iterative process merging implementation, behavioral and computer science methods. This combination facilitates the development and tailoring of meaningful theory- and evidence-based interventions to end users' context-specific needs and preferences, thereby giving the resulting interventions the highest possible chance of uptake and sustained use.

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4.7 Supplementary Table 1: Description of the SMILe intervention content and mechanism of change using the Behavior-Change-Wheel <sup>1</sup>

Module: Monitoring & Follow-up							
Target behavior	Problem based on context analysis and evidence	Content to tackle the problem			Mechanism of change		
		Mode of delivery Human & Technology components	User-Story (As a...I want...so that)	BCTs	Functions	COM-B	TDF
Improved recognition, evaluation and acting upon symptom	<ul style="list-style-type: none"> <li>Uncertainty about symptom assessment [2].</li> </ul>	<ul style="list-style-type: none"> <li>CC explains &amp; trains symptom assessment &amp; SMILeApp use.</li> <li>CC evaluates SMILeApp use with patients and care-givers during visits.</li> <li>SMILeApp supports symptom assessment.</li> <li>SMILeCare facilitates symptom monitoring by CC and praises patients in visits.</li> </ul>	<p>As a patient I want a system to assess symptoms so that I feel more secure.</p> <p>As a CC I want a system to monitor symptoms of patients so that I can detect complications early.</p>	9.1 Credible source 4.1 Instruction perform the behavior 5.1 Info health consequences 6.1 Demonstration of the behavior 2.2 Feedback on behavior 2.7 Feedback outcome of behavior 8.1 Behavioral practice 15.1 Verbal persuasion 2.3 Self-Monitoring of behavior 12.5 Adding objects 2.5 Monitor outcome behavior by others without feedback 10.4 Social reward	Training  Persuasion	Physical Capability	S
	<ul style="list-style-type: none"> <li>Uncertainty about symptom judgement and reporting [2].</li> <li>High cognitive dysfunction and fatigue levels in alloSCT patients [3].</li> <li>Impaired retrospective recalling of symptoms [4].</li> <li>Improved survival, quality of life and lower re-admission rate through electronic symptom monitoring with self-management support [5,6].</li> </ul>	<ul style="list-style-type: none"> <li>CC explains critical symptoms &amp; trains how to react if problems occur with patients and care-givers.</li> <li>CC discusses frequency of SMILeApp use by patients and if they managed to enter data as agreed upon.</li> <li>CC provides feedback about development of parameters and outcomes.</li> <li>SMILeApp provides feedback on severity of symptoms &amp; how to act upon.</li> <li>SMILeApp provides a lexicon with self-management instructions.</li> </ul>	<p>As a patient I want a daily reminder for using the system so that I do not forget to enter my data.</p> <p>As a patient, I want a feedback on my self-assessed vital signs and symptoms so that I have support in my self-management and decision making.</p> <p>As a patient, I want written information 24/7 available so that I can look up discussed information.</p>	9.1 Credible source 4.1 Instruction perform the behavior 5.1 Info health consequences 6.1 Demonstration of the behavior 8.1 Behavioral practice 7.1 Prompts/ cues 1.2 Problem solving 3.1 Social support 1.1 Goal setting 8.3 Habit formation 1.4 Action planning 1.5 Review goals (behavioral) 2.6 Biofeedback 2.7 Feedback outcome of behavior 5.1 Info health consequences	Education  Training  Enablement	Psychological Capability	K MAD Br

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Improved recognition, evaluation and acting upon symptoms	<ul style="list-style-type: none"> <li>Patients and clinicians would benefit from monitoring of critical symptoms,</li> <li>No system available,</li> <li>&gt;70% of patients would share their data or use a App from hospital [2].</li> <li>Remote monitoring of symptoms improves survival [6].</li> </ul>	<ul style="list-style-type: none"> <li>SMILeApp provides opportunity to monitor symptoms.</li> <li>CC encourages daily use of SMILeApp, identifies barriers to use it and set goals with patients and care-givers.</li> </ul>	As a patient I want to have the option to assess and share my entered data so that I have the certainty that someone is watching over me.	12.5 Adding objects 1.2 Problem solving 1.1 Goal setting 1.4 Action planning	Training Enablement	Physical Opportunity	Env
	<ul style="list-style-type: none"> <li>The knowledge that someone watches over your parameters gives a feeling of security,</li> <li>Value of social support by peers and family,</li> <li>Patients rate the importance of having technologies to share their data with others with a median of 8 (0-10)[2].</li> </ul>	<ul style="list-style-type: none"> <li>CC offers 12 face-to-face sessions over the first year post-alloSCT and cares for patients and families.</li> <li>SMILeCare connects patients virtually to CC and allows to overview incoming values.</li> <li>Patients observe other patients, family members using Apps for their health.</li> </ul>	As a CC, I want a system to monitor important parameters of patients at home within the hospital so that I can detect complications early.	6.1 Demonstration of the behavior 12.5 Adding objects	Modelling Enablement	Social opportunity	Si
	<ul style="list-style-type: none"> <li>Clinicians assume that patients might be more anxious when assessing symptoms at a regular basis,</li> <li>Might increase contacts to hospital,</li> <li>Patients feel secured and watched over,</li> <li>Would value a system tracking their parameters [2].</li> </ul>	<ul style="list-style-type: none"> <li>CC reviews together with patients the use of the SMILeApp in each face-to-face session.</li> <li>CC praises the use of the SMILeApp.</li> <li>CC teach patients to leave their smartphone next to their bed as a reminder to enter parameters.</li> <li>SMILeApp provides an overview about patents parameters development over time so that they can observe changes.</li> </ul>	<p>As a CC, I want an overview how frequent patients entered their data into the system so that I can give feedback.</p> <p>As a patient I want positive feedback when I use the system on a regular basis so that I keep motivated.</p> <p>As a patient I want an overview about my entered data so that I can see changes over time and feel motivated to continue.</p>	2.2 Feedback on behavior 10.4 Social reward 7.1 Prompt and cues 8.3 Habit formation	Incentivisation  Training  Enablement	Automatic Motivation	Em
	<ul style="list-style-type: none"> <li>Patients are affright to get re-hospitalized,</li> <li>Patients believe that monitoring of medical parameters is important [2,7].</li> <li>Early recognition decreases re-hospitalization, costs and prevents co-morbidities [8].</li> </ul>	<ul style="list-style-type: none"> <li>CC discusses with patients and care-givers that monitoring of symptoms can help to detect complications early and may improve long-term outcomes</li> <li>CC offers patients and care-givers to call in terms of insecurity</li> </ul>	As a patient, I want to have contact information within the system so that I know who to contact.	5.3 Info social/environmental cons 5.1 Info health consequences	Education	Reflective Motivation	B Cap O Id

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## Chapter 4 – Development of the SMILe integrated model of care

Module: Infection prevention							
Target behavior	Problem based on context analysis and evidence	Content to tackle the problem			Mechanism of change		
		Mode of delivery Human & Technology components	User-Story (As a...I want...so that)	BCTs	Functions	COM-B	TDF
Adequate Hand Hygiene	<ul style="list-style-type: none"> <li>Patients need to apply good hand hygiene at a daily basis to prevent infections as they are immune compromised [9]</li> <li>Patients feel overwhelmed by recommendations about hand hygiene [2]</li> </ul>	<ul style="list-style-type: none"> <li>CC trains patients and caregivers how to perform the correct sequence of hand disinfection and when to apply handwashing and disinfection and how to care for their skin.</li> </ul>	As a patient I want to have information about hand disinfection so that I can refresh my knowledge at any time.	4.1 Instructions perform behavior	Enablement Training	Physical Capability	S
	<ul style="list-style-type: none"> <li>Lack of knowledge and awareness in terms of risk of infections via contamination.</li> <li>Reduced awareness of impact of hand-disinfection to reduce infections [10,11]</li> <li>Memory problems in terms of opportunities [2] when to apply adequate hand hygiene.</li> </ul>	<ul style="list-style-type: none"> <li>CC provides oral, written and visual instructions about risks of infections, procedural knowledge and opportunities of hand disinfection: correct fluids, dosing of fluids, duration and coverage of hand surfaces and demonstrates the correct performance.</li> <li>CC trains hand-disinfection and gives performance feedback using UV light box with fluorescent test lotion.</li> <li>CC discusses barriers and supports to overcome them.</li> <li>Goals will be set at each visit in terms of hand-disinfection and reviewed the next time</li> <li>CC asks at each follow-up session about behavior performance and monitors for infection.</li> <li>SMILeApp provides information about hand-disinfection.</li> </ul>		4.1 Instructions perform behavior 5.1 Info health consequences 11.3 Conserving mental resources 2.2 Feedback on behavior 1.2 Problem solving 6.1 Demonstration of the behavior 8.7 Graded tasks 8.6 Generalization target behavior 1.1 Goal setting 1.4 Action planning 2.6 Biofeedback 1.5 Review behavior goals 8.1 Behavioral practice/rehearsal	Education  Modelling  Training  Enablement  Environmental restructuring	Psychological Capability	K MAD Br
	<ul style="list-style-type: none"> <li>Lack of products and inadequate supplies [10] for adequate hand hygiene.</li> </ul>	<ul style="list-style-type: none"> <li>CC provides mini dispensers of hand-disinfection fluids which they can always carry with them.</li> <li>SMILeApp sends reminders for important hand-disinfection moments.</li> </ul>	As a patient I want to be reminded to perform hand disinfection at important moments so that I do not miss it.	12.5 Adding objects 7.1 Prompts, cues	Environmental restructuring	Physical Opportunity	Env

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Adequate Hand Hygiene	<ul style="list-style-type: none"> <li>Lack of culture of personal accountability for performing hand-disinfection [10].</li> <li>Lack of awareness of own responsibility [2] of adequate hand hygiene.</li> </ul>	<ul style="list-style-type: none"> <li>CC provides oral and written information about the association of hand-disinfection and infections.</li> <li>That it is a common and supportive behavior when being immunocompromised.</li> <li>CC encourages care-givers to support patients.</li> <li>CC refers to SMILeApp where the hand-disinfection sequence can be looked up.</li> </ul>	As a CC I want to have information about hand disinfection so that I can refer to that.	5.3 Info social/environmental cons 5.1 Info health consequences 6.3 Info others approval 6.1 Demonstration of the behavior 3.1 Social support (unspecific)	Modelling Persuasion Education Enablement	Social opportunity	Si
	<ul style="list-style-type: none"> <li>High cognitive dysfunction and fatigue levels in alloSCT patients [3].</li> <li>Smell of fluids is associated with hospital and illness and might result in avoidance.</li> </ul>	<ul style="list-style-type: none"> <li>CC offers different fluids, information about hand-disinfection and praises patients when they reached their goals.</li> <li>Encourages developing habits.</li> <li>SMILeApp sends pop-up questions once weekly to ask for hand-disinfection adherence and praises if successful.</li> <li>SMILeCare displays answers in terms of adherence.</li> </ul>	As a patient, I want to record how well I managed to disinfect my hands so that I can monitor my performance.  As a patient I want to receive a feedback when I have been adherent so that I feel motivated to continue.  As a CC I want to have an alarm if the patients entered two non-adherent answers so that I can discuss this with the patients.	4.1 Instructions perform behavior 2.3 Self-monitoring of behavior 10.4 Social reward 2.5 Self-monitoring outcomes of behavior by others without feedback 8.3 Habit formation 12.5 Adding objects	Persuasion	Automatic Motivation	E
	<ul style="list-style-type: none"> <li>Belief that there is insufficient evidence that hand-disinfection adherence reduces infection [10].</li> <li>Belief that it is needed in hospital but not at home [2].</li> </ul>	<ul style="list-style-type: none"> <li>CC supports the gain-framing toward a shared responsibility in caring for their family's well-being (rather than a cleansing act).</li> <li>Patients and care-givers reflect and compare reasons for wanting and not wanting to disinfect their hands.</li> <li>CC prompts with patient a concrete planning of a self-reward for staying committed until the next session.</li> <li>CC praises patient and caregiver for their performance and assertion that they can and will succeed in preventing infections effectively via hand disinfection.</li> </ul>		13.2 Framing/Reframing 9.2 Pros an cons 10.9 Self-reward 15.1 Verbal persuasion capability	Enablement Persuasion	Reflective Motivation	B Con B Ca Int

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Module: Infection prevention							
Target behavior	Problem based on context analysis and evidence	Content to tackle the problem			Mechanism of change		
		Mode of delivery Human & Technology components	User-Story (As a...I want...so that)	BCTs	Functions	COM-B	TDF
Reducing exposure risk to airborne pathogens	<ul style="list-style-type: none"> <li>Lack of skills how to wear a FFP2 mask correctly.</li> </ul>	<ul style="list-style-type: none"> <li>CC instructs patients and caregivers when and how to wear FFP2 masks.</li> <li>Demonstrates the correct handling and let patients practice.</li> </ul>	As a CC I want to have information about airborne pathogens and mask wearing so that I can refer to this if I think patients lack the knowledge.	4.1 Instructions perform behavior 6.1 Demonstration of the behavior 8.1 Behavioral practice/rehearsal	Enablement  Training	Physical Capability	S
	<ul style="list-style-type: none"> <li>Lack of knowledge about respiratory infections and how to reduce exposure risk [12].</li> <li>Limited ability to retain information due to cognitive impairments and fatigue [2].</li> </ul>	<ul style="list-style-type: none"> <li>CC provides oral, written and visual instructions about exposure risks of airborne pathogens and correct mask wearing.</li> <li>SMILeApp asks once weekly if patients managed to apply the exposure risk reduction for airborne pathogens e.g. mask wearing, avoiding crowds of people.</li> <li>SMILeCare displays answers in terms of adherence so that CC can give feedback at each visit.</li> </ul>	As a patient, I want to record how well I managed to wear my mask so that I can monitor my performance.  As a patient I want to receive a feedback when I have been adherent so that I feel motivated to continue.  As a CC I want to have an alarm if the patients entered two non-adherent answers so that I can discuss this with the patients.	5.1 Info health consequences 2.2 Feedback on behavior 11.3 Conserving mental resources 2.3 Self-monitoring of behavior	Education  Enablement	Psychological Capability	K MAD
	<ul style="list-style-type: none"> <li>FFP2 masks are not always available in the outpatient setting.</li> <li>Lack of knowledge in terms of exposed situations and how to avoid them.</li> </ul>	<ul style="list-style-type: none"> <li>CC provides a set of 3 masks and advice where to buy new ones.</li> <li>CC explains how to change physical environment in order to reduce risk exposure.</li> <li>Infoms that infection prevention as a socio-cultural norm is not that established as it is in other countries.</li> </ul>		12.1 Restructuring environment 5.3 Info social/environmental cons 12.5 Adding objects	Environmental Restructuring  Enablement  Training	Physical Opportunity	Env
	<ul style="list-style-type: none"> <li>Wearing masks in exposed situations is not common in European countries [13].</li> <li>Lack of social acceptance and role models [13].</li> <li>Low clinician support due to reduced belief in effectiveness of masks [13].</li> </ul>	<ul style="list-style-type: none"> <li>CC provides social support to follow recommendations and advises to exchanges with other patients.</li> <li>CC informs caregivers how to support the patient following recommendations reducing exposure risk.</li> <li>CC discusses pros and cons of recommendations.</li> </ul>		3.1 Social support (unspecified) 6.2 Social comparison 9.2 Pros and cons	Modelling  Environmental restructuring  Enablement	Social Opportunity	Si

## Chapter 4 – Development of the SMILe integrated model of care

Reducing exposure risk to airborne pathogens	<ul style="list-style-type: none"> <li>• Fear of stigmatization.</li> <li>• Negative emotions as fear, anxiety or feelings of constriction when wearing the mask.</li> <li>• No established habits to avoid exposes situations.</li> </ul>	<ul style="list-style-type: none"> <li>• CC encourages to reward self in future with valued objects if patient has adhered to recommendations reducing exposure risk.</li> <li>• CC praises patient if he stays free of respiratory infections and/or managed to adhere to recommended behavior.</li> <li>• CC assesses patient's emotions after performing exposure risk reduction (e.g. wearing a mask).</li> </ul>		10.9 Self-reward 10.4 Social reward 11.2 Reduce negative emotions 5.4 Monitoring emot. consequences	Environmental restructuring  Modelling  Enablement	Automatic Motivation	Em
	<ul style="list-style-type: none"> <li>• Patients have false beliefs about consequences and capabilities [2].</li> </ul>	<ul style="list-style-type: none"> <li>• CC reviews the set goals at each follow-up visit.</li> <li>• CC discusses discrepancies of goals and current behavior.</li> <li>• Patients identifies barriers and discuss strategies how to overcome barriers.</li> <li>• CC prompts the mask wearing for the most critical situations as e.g. sitting in outpatient waiting rooms, using public traffic.</li> <li>• Patients affirm when and where to wear a mask or to follow other recommendations reducing exposure risk.</li> <li>• CC points out that he/she believes in patients' ability to successfully reduce exposure risk to airborne pathogens in daily life.</li> </ul>		1.3 Goal setting 1.5 review behavior goals 1.6 Discrepancy behavior and goal 1.2 Problem solving 1.4 Action planning 1.9 Commitment 15.1 Verbal persuasion capability 9.1 Credible source	Education  Persuasion	Reflective Motivation	Int

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Module: Infection prevention							
Target behavior	Problem based on context analysis and evidence	Content to tackle the problem			Mechanism of change		
		Mode of delivery Human & Technology components	User-Story (As a...I want...so that)	BCTs	Functions	COM-B	TDF
Safe handling, preparation and consumption of food	<ul style="list-style-type: none"> <li>Long-term impaired cognitive function, fatigue or nausea and emesis hampering the correct selection, preparation and handing of food at home [3].</li> </ul>	<ul style="list-style-type: none"> <li>CC provides oral, written and visual information about which food to avoid, and what to pay attention to when buying/selecting food.</li> <li>CC informs that these rules change depending on the immune status.</li> <li>CC checks knowledge on which food is safe to eat and shows patients and caregivers where to look up information in the SMILeApp.</li> <li>At each follow-up visit goals will be reviewed.</li> </ul>	As a patient I want to have information about which food to avoid and how to adapt rules so that I feel secure when buying food.	4.1 Instructions perform behavior 12.5 Adding objects 1.2 Problem solving 1.5 Review behavior goals 11.3 Conserving mental resources	Enablement	Physical Capability	S
	<ul style="list-style-type: none"> <li>Problems in understanding why safe food selection and handling is important, and apply it to his/her own situation [14].</li> <li>Patient have low cognitive capacity to be able to process and remember all the instructions [2].</li> </ul>	<ul style="list-style-type: none"> <li>CC provides information on risk and consequences of foodborne/waterborne &amp; fecal-oral pathogen infections.</li> <li>CC mentions that she is very pleased to see that no infections occurred.</li> <li>Patients get encouraged to watch the videos at the SMILeApp about how to clean used kitchen utensils after usage.</li> <li>CC discusses an agreed goal</li> <li>CC asks patient to repeat the recommended food and explain how he/she would buy, store, handle food and clean kitchen utensils.</li> </ul>	As a patient I want to have instructions how to clean kitchen utensils after usage so that I'm more confident in preparing and handling food.	5.1 Info health consequences 2.7 Feedback outcomes behavior 6.3 Info others approval 10.4 Social reward 6.1 Demonstration of the behavior 1.1 Goal setting 8.1 Behavioral practice/rehearsal	Education  Enablement	Psychological Capability	K MAD
	<ul style="list-style-type: none"> <li>Lack of awareness how and where to buy safe food and where to get household help [15].</li> <li>Frequently inadequate equipment to safely store and prepare food [15].</li> </ul>	<ul style="list-style-type: none"> <li>CC instructs how to buy (e.g. which food/which condition), store (e.g. stored in boxes in a fridge with 6 °C) and handle food when cooking (e.g. which cutting boards).</li> <li>Discusses strategies if patients are not able e.g. organizing household help.</li> <li>CC and SMILeApp demonstrates how to handle kitchen utensils after use e.g. cutting boards</li> </ul>	As a patient I want to have instructions how to store and handle food so that I'm more confident in preparing and handling food.	12.5 Adding objects 12.1 Restructuring environment 3.1 Social support (unspecific) 1.2 Problem solving 6.1 Demonstration of the behavior 4.1 Instructions perform behavior	Environmental Restructuring  Enablement  Training	Physical Opportunity	Env

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Safe handling, preparation and consumption of food	<ul style="list-style-type: none"> <li>The patient's environment understands why safe food selection and handling is important.</li> <li>Patients' needs people they can rely on to do the shopping when not feeling well or when not being capable to go shopping themselves</li> <li>If others prepare meals, they need to follow the same rules regarding safe food handling, storage and preparation.</li> </ul>	<ul style="list-style-type: none"> <li>CC provides oral, written and visual information for care-givers or other supporting people about which food to avoid, and what to pay attention to when buying/selecting food.</li> <li>A bullet point sheet or visual aid will be given to the patient, to keep in his/her purse; the purse of support people, or to hang on the fridge or in the kitchen as visual aids.</li> </ul>		5.1 Info health consequences 7.1 Prompts, cues 3.2 Social support (practical)	Modelling  Environmental restructuring  Enablement  Education	Social Opportunity	Si
	<ul style="list-style-type: none"> <li>Patients need to form a habit in always carefully reflecting on whether certain food is safe to buy and to eat and form a habit in safely storing, handling and preparing food.</li> <li>Patients might feel overwhelmed or depressed when learning about all these instructions</li> <li>Eating safe food does not evoke negative emotions (e.g. it reminds of not being healthy; missing favorite foods (e.g. raw meat).</li> </ul>	<ul style="list-style-type: none"> <li>CC explains that she/he will monitor how well the patient succeeds in following rules, by asking 4 questions on a weekly basis via the SMILeApp so that feedback can be given.</li> <li>CC asks patients to memorize the list, arranges for another meeting and informs that patient can ask questions in case some info is not clear.</li> <li>CC explores how the patient can reward himself/herself regularly at home for following the rules.</li> </ul>	As a CC I want to see how well patients managed following the rules so that I can act upon that.	2.2 Feedback on behavior 8.1 Behavioral practice/rehearsal 8.3 Habit formation 10.9 Self-reward	Enablement	Automatic Motivation	Em
	<ul style="list-style-type: none"> <li>Patients need to understand/ believe that these strict rules are important for his/her health so that infections can be avoided.</li> <li>Patients need to believe in one's capability Patient needs to be optimistic that desired goal (i.e. avoidance of infections) will be attained if the rules are followed strictly.</li> <li>Patients need to express the intention to always trying to apply the rules on safe food selection, handling and preparation.</li> </ul>	<ul style="list-style-type: none"> <li>CC stresses that it is normal that this is a lot of information, but that patient will be capable of following these and that CC is there to answer questions.</li> <li>CC acknowledges that this might sound overwhelming, but she/he trusts the patient will be successful and believes the patient has the capacity to do a great job.</li> <li>CC identifies together with patient barriers for not following the rules and discuss strategies how to overcome barriers.</li> </ul>		3.3 Social Support (emotional) 9.1 Credible source 15.1 Verbal persuasion capability 1.2 Problem solving	Education	Reflective Motivation	B cons  Id

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Module: Medication Adherence							
Target behavior	Problem based on context analysis and evidence	Content to tackle the problem			Mechanism of change		
		Mode of delivery Human & Technology components	User-Story (As a...I want...so that)	BCTs	Functions	COM-B	TDF
Correct taking and timing of immunosuppressive medication	<ul style="list-style-type: none"> <li>High symptom burden of nausea and emesis, decreased cognitive functioning after alloSCT [3,16].</li> <li>Poor physical condition post transplantation [17,2].</li> </ul>	<ul style="list-style-type: none"> <li>Patients will be encouraged to prepare a plan how to deal with barriers and practice how to react at home (e.g. taking antiemetics before other medication).</li> <li>CC demonstrates how to prepare medication and when to take e.g. antiemetic's.</li> </ul>	As a patient I want to have reliable information how to plan my expected actions (e.g. taking medication while having nausea) so that I do not forget the necessary preparations.	1.4 Action planning 6.1 Demonstration of the behavior	Enablement	Physical Capability	S
	<ul style="list-style-type: none"> <li>Lack of knowledge about medication and consequences of non-adherence [18,19].</li> <li>Lack of routine and information overload [2,20]</li> <li>No sense of autonomy regarding medication intake [20]</li> <li>Forgetfulness and forgetting get a new prescription on time [17,18]</li> <li>Unable to cope with changed prescription [21].</li> </ul>	<ul style="list-style-type: none"> <li>CC provides oral, written and visual information about effects and side-effects of medication as well as consequences of non-adherence and refers to SMILeApp.</li> <li>SMILeApp asks patient to document and confirm medication intake twice daily.</li> <li>CC provides feedback about medication intake.</li> <li>CC informs about blood level of immunosuppressives, reference range and signs of acute rejection.</li> <li>CC trains and practices with the patient and caregiver how to read and prepare the medication plan.</li> <li>CC prompts patients to combine medication intake with another habit (e.g., eating breakfast).</li> <li>CC asks caregivers to support correct intake of medication by reminding, preparing or filling in the prescriptions.</li> <li>Goals will be set together with patient to take the medication correctly with a deviation &lt; 2hours in 95% of the time.</li> <li>Review of goal in terms of reach and discrepancies.</li> <li>Identification of barriers and discussion of strategies.</li> </ul>	<p>As a patient I want to find information on what my medication is for and will happen, if I do (not) take it as prescribed (incl. wrong time) so that I know the importance of doing it correctly.</p> <p>As a patient I want to get explained how to use the electronic medication plan so I can check when I have forgotten.</p> <p>As a patient I want to know how to prepare my medication so that I can do it on my own correctly.</p> <p>As a patient I want to self-monitor whether I take my medication as prescribed so that I know whether I take the drugs correctly.</p> <p>As a patient I want to get feedback whether I take my medication sufficiently as prescribed so that I can be sure that I take the medication correctly</p> <p>As a patient I want to be reminded of my set goals (which were set during visit) on a self-determined interval (e.g. daily / once a week) so that I am aware of my goal and know what to target at.</p>	5.1 Info health consequences 11.3 Conserving mental resources 2.3 Self-monitoring of behavior 2.2 Feedback on behavior 2.7 Feedback outcomes behavior 4.1 Instructions perform behavior 8.1 Behavioral practice/rehearsal 8.3 Habit formation 3.2 Social support (practical) 1.1 Goal setting 1.5 Review behavior goals 1.6 Discrepancy behavior and goal 1.2 Problem solving	Education  Enablement  Training	Psychological Capability	K MAD Br

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Correct taking and timing of immunosuppressive medication	<ul style="list-style-type: none"> <li>Not having medicines when being away from home [21,17].</li> <li>Time of intake «does not fit» to lifestyle,</li> <li>Interruptions in daily routine,</li> <li>Longer time since transplantation [17,2,22].</li> </ul>	<ul style="list-style-type: none"> <li>CC recommends to use practicable weekly pill boxes and the SMILeApp for looking up and documenting medication intake and time.</li> <li>CC instructs to store medication in clear visible places (e.g., next to the coffee machine), to prompt medication intake and to use SMILeApp for reminders.</li> <li>CC instructs patients to always have travel packs of medications prepared.</li> <li>Identification of barriers and discussion of strategies.</li> </ul>	<p>As a patient I want to have my medication plan in the system so that I can look up my medication.</p> <p>As a patient I want to be able to update the medication plan in the system when the prescription of physician changes so that I have a current medication plan.</p> <p>As a patient I want to get a reminder when I need to take my medication so that I don't forget to take it.</p>	<p>12.5 Adding objects</p> <p>7.1 Prompts, cues</p> <p>4.1 Instructions perform behavior</p>	<p>Environmental Restructuring</p> <p>Enablement</p> <p>Training</p>	Physical Opportunity	Env
	<ul style="list-style-type: none"> <li>Lack of family/social support [20,22].</li> <li>Avoiding taking medication in public / in front of friends,</li> <li>Lack of positive and negative role models [21].</li> <li>Lack of individual support (by nurses, pharmacists) [18].</li> </ul>	<ul style="list-style-type: none"> <li>CC invites caregivers to be part of the intervention sessions and to support patients in the correct intake of medication</li> <li>CC recommends to look for a self-help group / peer website to talk about strategies for medication intake if problems occur.</li> </ul>		<p>9.1 Credible source</p> <p>3.1 Social support (unspecified)</p> <p>3.2 social support (practical)</p>	<p>Training</p>	Social Opportunity	Si
	<ul style="list-style-type: none"> <li>Feeling overwhelmed [21,2].</li> <li>Burnout / treatment fatigue [18].</li> <li>Negative emotions / attitude [20].</li> <li>Desire for independence in self-management [22].</li> <li>Incompatibility of the IS,</li> <li>Side effects [22,2,20].</li> </ul>	<ul style="list-style-type: none"> <li>Patients explore difficult circumstances in which they nevertheless managed to take their medication.</li> <li>CC tells the patient that he/she can successfully perform the behavior.</li> <li>CC tells the patient that he/she can always contact her in case of difficulties.</li> <li>SMILeApp allows to document and reminds of medication intake and time.</li> </ul>	<p>As a patient I want to be able to record occasions with correct medication intake in the system so that I feel confident to be successful again.</p> <p>As a patient I want to get a motivational feedback that I can successfully perform the behavior so that I feel capable to manage the correct medication intake.</p> <p>As a patient I want to have the opportunity to call a qualified health care provider if there are unexpected barriers (which were not discussed face-to-face) so that I get support in challenging situations.</p> <p>As a patient I want to customize the system (e.g. different tones, signals, colors, pictures) so that I connect medication intake with a positive feeling</p>	<p>15.3 Focus on past success</p> <p>15.1 Verbal persuasion capability</p> <p>15.1. Written persuasion capability</p> <p>7.1 Prompts, cues</p> <p>3.3 Social Support (emotional)</p> <p>12.5 Adding objects</p> <p>1.2 Problem solving</p>	<p>Persuasion</p> <p>Environmental restructuring</p> <p>Training</p> <p>Enablement</p>	Automatic Motivation	Em Reinf

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			As a patient I want to be able to signal the CC that she/he should call back when she/he has time so that I get help without disturbing the CC in an unsuitable situation.				
	<ul style="list-style-type: none"> <li>Lack of intention to adhere [17].</li> <li>Not interested in learning about medication before transplant [21].</li> <li>Beliefs in illness, medication and side effects [17]</li> <li>No confidence in self-management [18]</li> <li>Lack of problem solving competence &amp; self-efficacy [23]</li> </ul>	<ul style="list-style-type: none"> <li>Patient list and compare the advantages and disadvantages of taking the medication correctly.</li> <li>CC point out if the recorded number / time of medication intake does not fit to the set goal.</li> <li>CC praises patient performance if the medication intake was always correct in time.</li> <li>SMILeApp provides feedback when set goals are not reached.</li> </ul>	As a patient I want to get a signal if the recorded number / time of medication intake does not fit to the goal set so that I realize that I have to change my behavior.	9.2 Pros and cons 1.6 Discrepancy behavior and goal 10.4 Social reward	Education Incentivisation	Reflective Motivation	Int B cons B cap G

Note: BCT=Behavior Change Technique; COM-B= Capability, Opportunity Motivation Behavior; TDF=Theoretical Domains Framework; domains: Knowledge=K; Skills=S; Memory attention, decision processes=MAD; Behavioral regulation=Br; Social influences=Si; Environmental context and resources= Env; Emotion=Em; Intension= Int; Beliefs about consequences= B cons; Beliefs about capabilities= B cap; Optimism= O; Goals= G; Social/professional role and identity= Id; Reinforcement=Reinf..

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Module: Physical Activity							
Target behavior	Problem based on context analysis and evidence	Content to tackle the problem			Mechanism of change		
		Mode of delivery Human & Technology components	User-Story (As a...I want...so that)	BCTs	Functions	COM-B	TDF
Reducing Sedentary Bouts	<ul style="list-style-type: none"> <li>Increased levels of fatigue and physical weakness in the first weeks after alloSCT [2].</li> <li>MET &lt; 3 decrease, MET &gt;3 increases after alloSCT [24]</li> <li>Physical inactivity 27%-85% [25]</li> </ul>	<ul style="list-style-type: none"> <li>CC provides oral and written information about breaking sedentary bouts and explains the concepts of physical activity. Shows health benefits and recommended activities and suggests intervals for breaking sedentary bouts: 3/30 min or 6/60 min.</li> <li>CC explains with examples how sedentary bouts can be reduced during in- and outpatient time (e.g., walking at the hospital ward)</li> <li>CC praises the patient if the goal was reached.</li> <li>SMILeApp collects number of daily steps and reminds once daily.</li> <li>SMILeApp shows daily steps and sends graphical feedback on behavior compared to outcome goal.</li> <li>CC encourages patients to set a higher/lower step goal of +/- 500 steps if they did not manage to reach their goal &gt; 3 days.</li> </ul>	<p>As a patient I want to document my number of daily steps so that I can see my performance.</p> <p>As a patient I want to have a visual feedback on my daily steps in comparison to my defined goal so that I can see if I was successful in reaching my goal.</p> <p>As a patient I want to have a reminder in the morning so that I can enter my number of steps performed on the previous day.</p>	5.1 Info health consequences 4.1 Instructions perform behavior 2.2 Feedback on behavior 2.6 Biofeedback 2.3 Self-monitoring of behavior 7.1 Prompts, cues 8.7 Graded tasks	Education  Training	Psychological Capability	K MAD Br S
	<ul style="list-style-type: none"> <li>Patients have the opportunity to walk.</li> <li>50% are open to use electronic devices also for counting steps and to promote health behavior [2].</li> </ul>	<ul style="list-style-type: none"> <li>Patient receives a step counter as an indirect measure of breaking sedentary bouts.</li> <li>CC encourages the patient to enter the daily steps reached into the SMILeApp.</li> <li>CC explains the step counter functions, activating step count function, check number of daily steps, setting reminder alarm. Advise to wear the tracker in a position where it also counts steps while cycling and show how to enter the steps into the app.</li> </ul>		12.5 Adding objects 6.1 Demonstration of the behavior	Environmental Restructuring  Training		Physical Opportunity

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<b>Reducing Sedentary Bouts</b>	<ul style="list-style-type: none"> <li>Patients value social support in being active [2].</li> <li>Breaking sedentary bouts in cancer patients, emphasizing this approach is promising but new [26].</li> </ul>	<ul style="list-style-type: none"> <li>CC advises caregiver how to break sedentary bouts and encourages to support the patient by joining them in being active.</li> </ul>		12.2 Restruct. social environment 3.1 Social support (unspecified) 3.2 Social Support (practical)	Enablement	<b>Social Opportunity</b>	Si
	<ul style="list-style-type: none"> <li>Patients strive for activity and have positive and negative attitudes towards eHealth,</li> <li>87% of cancer survivors are satisfied with Fitbit in intervention [27].</li> </ul>	<ul style="list-style-type: none"> <li>CC asks patient about the feasibility of performing the behavior and tells the patient that he/she can successfully perform the behavior.</li> <li>CC and SMILeApp praises patient's performance if the step goal was reached.</li> </ul>		9.1 Credible source 15.1 Verbal persuasion capability 10.4 Social reward	Persuasion  Incentivisation Environmental restructuring Modelling Enablement Education"	<b>Automatic Motivation</b>	Em Reinf
	<ul style="list-style-type: none"> <li>Patients have the intention /motivation to be active but are hampered by physical condition [2].</li> <li>Interrupting sedentary bouts with light-intensity activity helps control adiposity and postprandial glycaemia [28].</li> <li>Reducing/breaking up prolonged sedentary time decreases CV risk in general population [26].</li> <li>Exercise intervention improves QoL and fatigue in patients with hematological malignancies [29].</li> </ul>	<ul style="list-style-type: none"> <li>CC reviews the step goal and discrepancies at each visit together with patients.</li> <li>SMILeApp provides graphical feedback on behavior.</li> <li>CC asks the patient about the preference regarding intervals of breaking sedentary bouts (3/30 or 6/60) and set a step goal of daily steps until the next visit (optimal &gt;5000 outpatient/ &gt;1500 inpatient).</li> <li>Patient defines a personal goal and enters it in the SMILeApp.</li> <li>Patient identifies barriers and develops action plans to overcome barriers.</li> <li>CC emphasizes the feasibility of the recommended behavior and individual goal of steps.</li> <li>CC prompts patient to plan behavior and activities while breaking sedentary bouts.</li> <li>CC checks knowledge on the devices (step counter and App) in follow-up visit.</li> <li>SMILeApp and SMILeCare provide an overview of the daily steps and gives feedback regarding the outcome of behavior (daily steps).</li> </ul>	<p>As a patient I want to set a goal of daily steps so that I am later on able to check whether I reached them.</p> <p>As a patient I want to have a graphical overview of my actual steps in relation to my step goal so that I see my progress.</p>	1.6 Discrepancy behavior and goal 1.1 Goal setting (behavior) 1.3 Goal setting (outcome) 8.3 Habit formation 1.2 Problem solving 1.4 Action planning 1.5 Review behavior goals 1.7 Review outcome goal	Persuasion  Incentivisation	<b>Reflective Motivation</b>	Int B cons B cap G

Note: BCT=Behavior Change Technique; COM-B= Capability, Opportunity Motivation Behavior; TDF=Theoretical Domains Framework; domains: Knowledge=K; Skills=S; Memory attention, decision processes=MAD; Behavioral regulation=Br; Social influences=Si; Environmental context and resources= Env; Emotion=Em; Intension= Int; Beliefs about consequences= B cons; Beliefs about capabilities= B cap; Optimism= O; Goals= G; Social/professional role and identity= Id; Reinforcement=Reinf..

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## Chapter 5

### Implementation science meets software development to create eHealth components for an integrated care model for allogeneic Stem cell transplantation facilitated by eHealth: The SMILe Study as an example

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### 5.1 Abstract

**Purpose:** To describe a process of creating eHealth components for an integrated care model using an agile software development approach, user-centered design and, via the Behavior Change Wheel, behavior theory-guided content development. Following the principles of implementation science and using the SMILe project (Integrated care model for allogeneic **Stem** cell transplantation facilitated by **eHealth**) as an example, this study demonstrates how to narrow the research-to-practice gap often encountered in eHealth projects.

**Methods:** We followed a four-step process: 1) formation of an interdisciplinary team; 2) a contextual analysis to drive the development process via behavioral theory; 3) transfer of content to software following agile software development principles; 4) frequent stakeholder and end user involvement following user-centered design principles.

**Findings:** Our newly developed comprehensive development approach allowed us to create a running eHealth component and embed it in an integrated care model. An interdisciplinary team's collaboration at specified interaction points supported clear, timely communication and interactions between the specialists. As behavioral theory drove the content development process, we formulated user stories to define the software features, which were prioritized and iteratively developed using agile software development principles. A prototype intervention module has now been developed and received high ratings on the system-usability scale after two rounds of usability testing.

**Conclusions:** Following an agile software development process, structured collaboration between nursing scientists and software specialists allowed our interdisciplinary team to develop meaningful, theory-based eHealth components adapted to context-specific needs.

**Clinical Relevance:** The creation of high quality, accurately fitting eHealth components specifically to be embedded in integrated care models should increase the chances of uptake, adoption and sustainable implementation in clinical practice.

**Keywords:** Implementation science, User-Centered Design, Agile Software Development, eHealth, Integrated Care Model

### 5.2 Introduction

EHealth has dramatically influenced the possibilities of health care services in recent years and is soon expected to become a major driver for improvement.<sup>1</sup> Many European countries promote innovation in care delivery for chronically ill persons, whose burgeoning numbers challenge health care systems in view of their volume, the complexity of their needs and their exploding care costs.<sup>2</sup> International policy agendas commonly include calls for eHealth-facilitated care delivery.

Evidence supports eHealth's potential to fuel innovation. In particular, studies testing eHealth applications embedded within integrated care models for chronically ill persons have shown clear links to improved clinical, behavioral and economic outcomes.<sup>3-8</sup>

EHealth-facilitated integrated care models are also promising as systems to strengthen the care of allogeneic stem cell transplantation (alloSCT) recipients. With a 70-90% risk of developing complications and late effects, these patients are chronically ill and require comprehensive care.<sup>9</sup> Using eHealth solutions as part of integrated care models would allow improved support of alloSCT patients, e.g., by detecting health deterioration early, even after discharge.

However, despite increasing empirical evidence supporting eHealth integration into care delivery, sustained implementations of eHealth solutions in routine clinical practice are rare: uptake is often insufficient, adoption rates low and sustained use rates lower still.<sup>4,10-12</sup> Studies testing ready-made eHealth tools commonly report serious adoption and sustainment problems, with 44% to 67% of patients prematurely discontinuing use.<sup>13-15</sup> Also, clinicians consider a misfit with their existing clinical workflow one of the most frequent barriers for adoption to clinical practice.<sup>16</sup> Most of these failures can be traced either to a poor application fit—meaning both with end users' (patients and clinicians) needs and with the target context—or to a lack of attention to the content's theoretical foundations.<sup>13-15</sup> Indeed, of the 23 reviewed eHealth tools for patients with cancer, only six are theory-based.<sup>17</sup> Additionally, fewer than 20% refer to empirical studies or background source information, only 11.3% are evidence-based and just 10.3-50% involved clinicians in their development processes.<sup>18-20</sup> Such omissions result not only in gaps between the offered eHealth solutions and the needs and preferences of end-users, but also in ineffective content in terms of behavior change.<sup>21</sup>

Such research-to-practice gaps sometimes reflect differences between the design context and the implementation context: design decisions might not acknowledge end users' or contextual restrictions; or they might simply use too many resources.<sup>22</sup> To narrow the gaps between successful trials and long-term real-world use, various researchers have proposed combining computer science methods such as user-

centered design (UCD) with implementation science principles<sup>23,24</sup> or behavioral science.<sup>17</sup>

Each of these three fields can add to the others' strengths. By providing a firm theoretical backing for content development, behavioral science principles are essential for effective behavior change interventions. UCD is an iterative process that places end user needs at the center of the design process, with the goal of developing highly usable and accessible products.<sup>25</sup> And implementation science, as the study of methods that facilitate the uptake of research findings in clinical practice<sup>26</sup>, applies specific methodological considerations, e.g., contextual analysis and stakeholder involvement, to assure the integration of content-specific requirements in the final result.<sup>27</sup>

Considering these three methodologies' individual advantages, we believe that a mix of the three (implementation-, behavioral-, and computer science methods) can help balance context with end user needs, while guaranteeing a robust theoretical underpinning for content. If this proves true, we further expect that it will speed the resulting interventions' technology adoption while increasing their overall sustainability. To the best of our knowledge, no paper has yet been published on the combined use of the three methodologies. Even combinations of two of the three are rare, and are employed mainly in the conception phase of eHealth-facilitated care models.<sup>17, 23, 24</sup>

Besides, descriptions of eHealth tools are mostly limited to reports on their effectiveness regarding outcomes or health behaviors. The process of how associated eHealth software components are created is mentioned only marginally, if at all. In particular, questions regarding how end users have been involved, which theoretical framework guided content development or how collaboration was organized within the development team remain unanswered. This leaves developers without guidance. Even worse, the team responsible for defining content is often completely separate from that creating the software. But handing a fully defined blueprint over to a software team and waiting until it is finished bears the obvious risk that the delivered components will not look or function as intended.<sup>28</sup> In software development, employing agile software development processes can prevent just such a situation from arising.

### *But what exactly is agile software development?*

Coined in 2001, the term agile software development signifies a family of development processes that value individuals and interactions, working software, customer collaboration and responses to change over processes and tools, comprehensive documentation, contract negotiation and following a plan.<sup>29, 30</sup> As the name implies, it promotes fast and iterative development: working software increments are created, delivered and discussed regularly via collaboration between self-organizing, cross-functional teams.<sup>28</sup>

This article reports on our approach to applying UCD and agile software development principles in an implementation science project underpinned by a theory-guided content development process using the Behavior-Change Wheel.<sup>31</sup> We describe this process by detailing the development of the software components for an integrated care model (ICM) in allogeneic **Stem** cell transplantation facilitated by **e**Health (SMILe). The SMILe-ICM combines human as well as software components. First, within the outpatient transplant team, it embeds an advanced practice nurse in the role of care-coordinator (CC). Within the first year post-alloSCT, the CC delivers each patient 12 face-to-face visits to support target self-management and other health-related behaviors. Second, it includes the SMILe technology, which supports the follow-up process and complements the CC-delivered intervention content. The SMILe technology consists of a mobile app (SMILeApp) for patients, and a browser app (SMILeCare) for the CC. With the SMILeApp, patients can record notes on their daily well-being and a set of 3 medical (blood-pressure, temperature, weight), 3 behavioral (steps, medication intake, infection prevention measures) and 13 symptom-related parameters (pain; signs of bleeding; nausea; emesis; diarrhea; skin rash; mouth or throat sores; shortness of breath; pain or burning at urination; fatigue, tiredness, or lack of energy; difficulty swallowing; decreased appetite, cough). The app is also complemented by self-management information about conditions and symptoms. The entered data is transferred to the hospital's data center, where, with the patient's consent, the CC can view all incoming values, visualize their development over time in SMILeCare, and contact the patient via telephone if necessary. This remote monitoring enables the CC to provide continuous and extended follow-up care for a larger number of alloSCT patients and to detect signs of possible health deterioration early.

### 5.3 Methods and Findings

We developed the SMILe –ICMs software components via a four-part process: 1) setting up an interdisciplinary team; 2) performing a contextual analysis, the results of which would drive the content development process and allow us to define possible software functionalities based on behavioral theory; 3) transferring content to software following agile software development principles; 4) regularly involving stakeholders and end users following user-centered design principles. The following paragraphs describe each of the above-mentioned processes and the methods used to perform them.

#### 5.3.1 The Interdisciplinary Team

One primary agile software development technique is the formation of a cross-functional, interdisciplinary development team.<sup>28</sup> All competences necessary to

accomplish the project should be available within this team. Therefore, we involved experts in implementation science (nursing scientists), behavioral science (psychologists, nursing scientists) and software engineering (software developers, usability experts). While each team member preserves his/her area of expertise, all should be regarded as members of a single team rather than as independent actors sharing a common vision. Nevertheless, not everyone can be involved in every task.

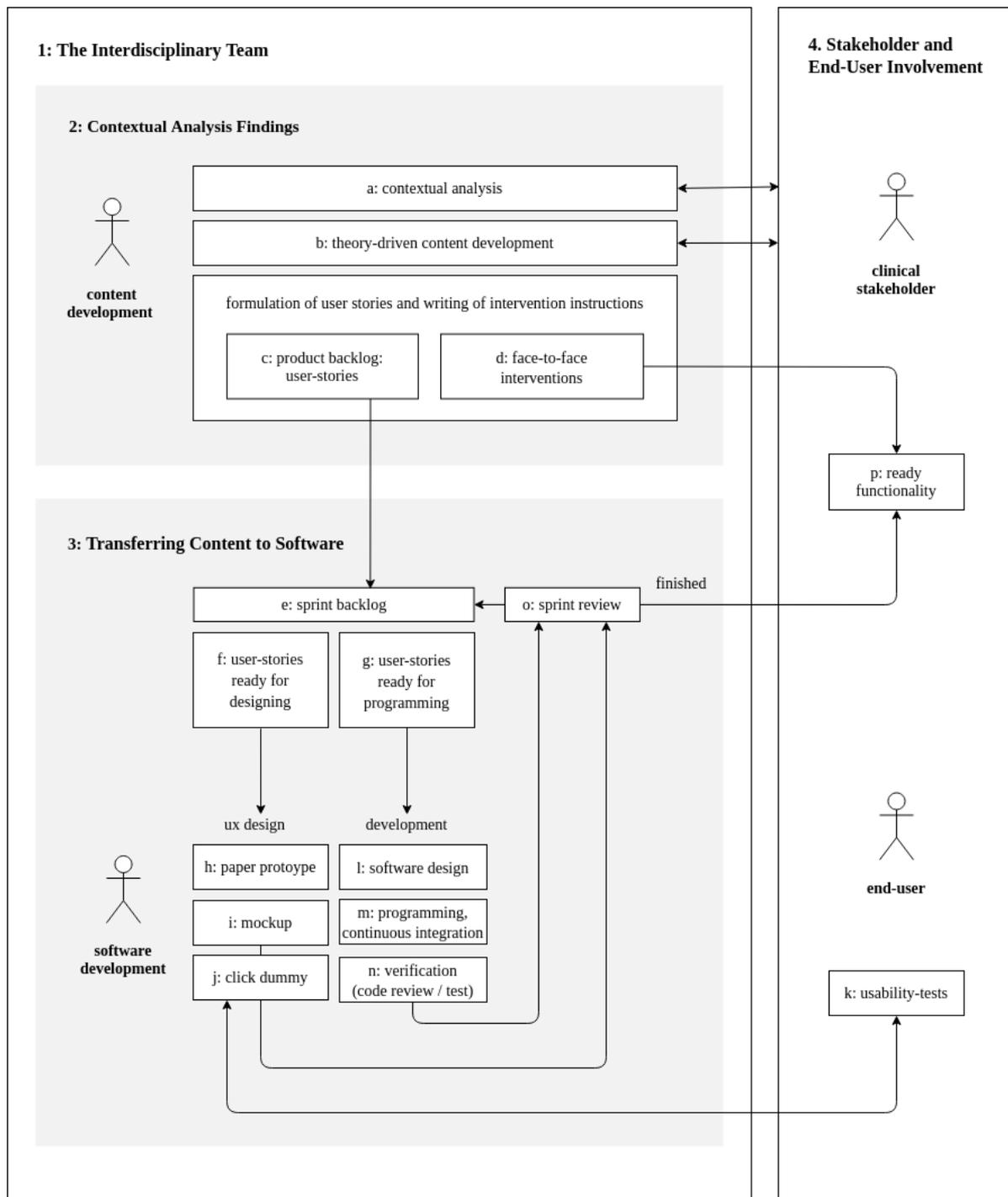
Therefore, two sub-teams were formed—one responsible for content development, the other for software development—while ensuring that representatives of each group were present at the other's meetings. Our meeting intervals and constellations are described in detail in section 3, where we describe the collaboration process.

The development team needs exchanges with two other stakeholder groups: clinicians working in the field (in our case, allogeneic stem cell transplantation: physicians, clinical nurse specialists, nurse managers) and the end users. Their involvement is described in detail in section 4.

### 5.3.2 Driving the Development Process via the Contextual Analysis Findings

After setting up the team we performed a contextual analysis (Figure 1, a) to understand any context-specific characteristics and practice patterns as well as the technology openness of the target setting's clinicians and patients. A detailed description of the used methodology and results of the contextual analysis are available elsewhere.<sup>32</sup> While the contextual analysis was mainly performed by nursing scientists, members of the software team accompanied them and observed the process to develop a shared understanding. The results indicated support needs in four areas: 1) monitoring and follow-up of symptoms to improve patients' symptom recognition and evaluation of how to react to them; 2) infection prevention measures; 3) medication adherence and 4) physical activity.<sup>32</sup> We used the Behavior Change Wheel (BCW) as our guiding behavioral theory while developing the content of each intervention module (Figure 1, b).<sup>31</sup> The BCW is a widely used behavioral theory. By combining 19 previously-developed behavior change frameworks, it effectively helps researchers understand, explain and modify behaviors. With the Capability-Opportunity-Motivation-Behavior (COM-B) Model at its hub, it supports a rigorous approach to developing effective behavior change interventions. A detailed description of how this process was applied to the medication adherence module is described elsewhere.<sup>33</sup>

Figure 1: Overview of the SMILe Software development process



### *Articulating User Stories to Inform Software Development*

As the contextual analysis also revealed that not all necessary functionalities should (or could) be delivered by technology, their modes of delivery (face-to-face and/or technology) were decided and intervention descriptions for the face-to-face sessions (Figure 1, d) formulated alongside the functionalities of the software parts. These were formulated into “user stories,” a common method of describing desired functionalities in agile software development. These typically follow the role-feature-reason format: within one sentence the role (As a...patient/clinician...), the feature (I want to...action, e.g., monitor my pain intensity) and the description of the reason (so that... expected outcome, e.g., I can keep track of my pain trajectory) are all explained.

The user stories as formulated by the content team were written down in a prioritized list, the so called “product backlog”, which then contains the main functionalities to be programmed (Figure 1, c). Each story’s priority was gauged by the content team based on the contextual analysis. According to agile philosophy, this priority can change according to the insights gained during the realization process. As the user stories only focus on desired main functionalities, those functionalities’ exact details, mechanics and appearance within the working software will be defined in collaboration with the software team immediately before creation. To guide software production, more detailed stories will be formulated.

For the SMILe-ICM, 39 user stories were formulated for the four target areas, with the nine focusing on monitoring and follow-up of symptoms assigned the highest priority. These nine (listed in Table 1) were selected for the realization of a first intervention module.

**Table 1:** Extract from the SMILe user stories as formulated by the content team

Nr.	SMILe role	SMILe feature	Expected outcome
1	As a patient,	... I want an electronic system to assess symptoms,	... so that I feel more secure.
2	As a CC,	...I want an electronic system to monitor symptoms and vital signs of patients at home within the hospital,	...so that I can detect complications early.
3	As a patient,	... I want a daily reminder for using the system ,	... so that I do not forget to enter my data.
4	As a patient,	... I want to have the option to assess and share entered data,	... so that I have the certainty that someone is watching over me.
5	As a patient,	...I want a feedback on my self-assessed vital signs and symptoms,	...so that I have support in my self-management and decision making.
6	As a CC,	...I want an overview how frequent patients entered their data into the system,	...so that I can give feedback.
7	As a patient,	... I want positive feedback when I use the SMILeApp on a regular basis,	...so that I keep motivated.
8	As a patient,	...I want an overview about my entered data,	...so that I can see changes over time and feel motivated.
9	As a patient,	...I want to have contact information within the system,	...so that I know who to contact.

*Note:* CC= Care-Coordinator

### 5.3.3 Transferring Content to Software Following Agile Software Development Principles

The following section describes the interdisciplinary team’s collaboration process, which relies heavily on agile software development techniques. One characteristic is to develop the necessary components in iterations (“sprints”) which typically last from two weeks to three months.<sup>28, 29</sup> In planning each sprint, subsets of the user stories to be realized in the next iteration are selected, based on their priority.<sup>34</sup> To decide how many of the tasks at hand can be included in each sprint, the software developers estimate the expected time and effort necessary for each and file them in a “sprint backlog” (Figure 1, e).

As user stories roughly encapsulate each desired functionality, they have to be understood fully by the software team before programming begins. This demands close collaboration between the content developers and software team’s user experience (UX) designers, who ensure that the user interface is functional, comfortable and pleasantly

designed. Factors influencing the desired functionality's definition should be explained and possible approaches discussed. After that, the user stories are ready for the visual and interaction design (Figure 1, f). Only after these processes' respective drafts are satisfactory are the user stories ready for programming (Figure 1, g). To sufficiently define each functionality's specifications, then, the UX designers always have to work at least one sprint ahead of the programmers.

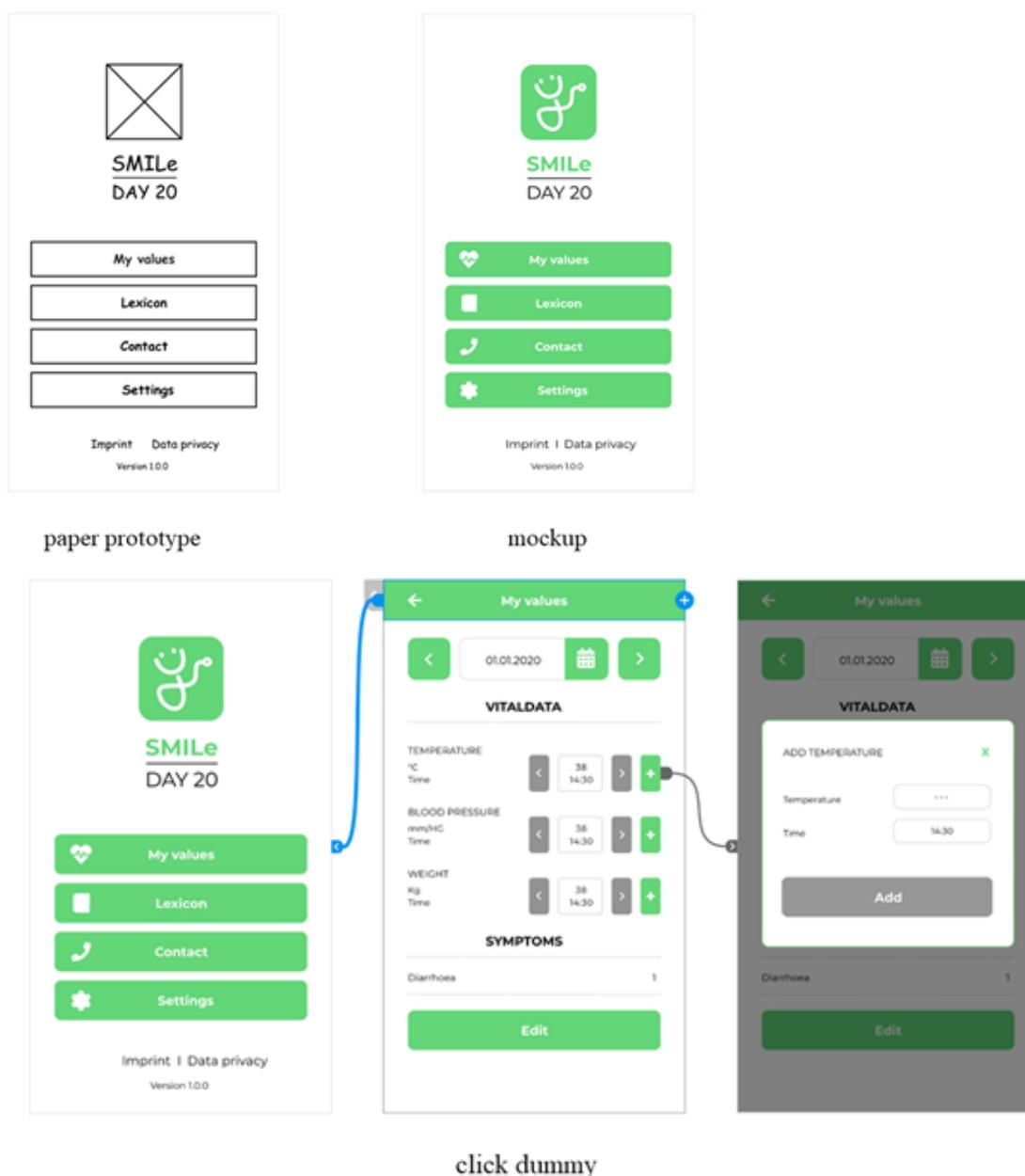
### *Moving Through the Prototyping Process*

One efficient way of communicating and discussing ideas at an early stage is “paper prototypes” (Figure 1, h; Figure 2). This category of low-fidelity prototype is determined by rather rough, analog crafted monochrome wireframes, which lay out the basic structure and target functionalities. The users move across the software (“user flow”) to use each functionality, which should already be recognizable. After the paper prototype has been discussed, the next stage is to convert it into a “mockup” (Figure 1, i). This high fidelity, static design representation of the user interface serves as a draft canvas upon which to experiment with colors, shapes, textures, spacing and fonts. Such a mockup is useful not only for communication with the content team, but also for the programming of the components. In a third step, for major functionalities, “click dummies” can be created (Figure 1, j). For these, a partially interactive demo of the user interface is constructed to simulate the tested software's functions and end-user interactions (Figure 1, k).

Once the designs are ready to give to the programming team, the technical aspects of the functionalities are further detailed (Figure 1, l) and programming starts (Figure 1, m). Regular integration of the new software into the existing code ensures that a concise software version is always available. Functional unit-level software tests and code reviews are essential to obtain high software quality (Figure 1, n). During the sprints, the software team needs at least weekly meetings with the content team in order to clarify any remaining open details, with openings for more to deal with urgent matters.

After the completion of each sprint, the designs or implemented functionalities from the current sprint are presented and discussed within an interdisciplinary team “sprint review” (Figure 1, o). All stakeholders have to decide whether the requirements of user stories have been applied correctly. With the acceptance of designs, the related user story is ready for programming and any complete programmed functionalities (Figure 1, p) can be released into the final software. Partially completed or insufficient work results are considered incomplete and have to be allocated to the next sprint.

**Figure 2:** SMILeApp UX design process



### 5.3.4 Stakeholder and End User Involvement Following User-Centered Design Principles

As stakeholders in the field and end users are not part of the interdisciplinary team, team members have to be very careful to adequately incorporate their needs, ideas and feedback.

#### *Involving Stakeholders*

All clinical stakeholders were involved by inviting them to regular meetings with the interdisciplinary team. In the project's initial stage, we also invited patient representatives. Due to their high symptom burden, patients could not attend continuously. Meetings were held at least twice yearly during the two years of

development—more frequently if decisions were urgently needed. This ensured a context-adapted development process that integrated setting-specific stakeholder needs.

### *Involving End Users*

End users were directly involved at three points. The first was very early in the process during the contextual analysis.<sup>32</sup> Later, for the click dummy usability tests and, of course, for the completed software, end users' feedback was also essential. For usability tests, end users are asked to verbalize their thoughts (think-aloud method) as they perform specific application-based tasks while UX experts observe and document their behavior. As an evaluation instrument, usability testing is designed not only to determine whether an item is adequately adapted to the target group and their needs, but also to ensure that its use entails no risks.<sup>35</sup>

One quick and widely-used means to quantitatively assess a user's satisfaction with a software system is the System Usability Score (SUS).<sup>36</sup> The SUS is a highly robust, reliable and valid 10-item questionnaire using five-point Likert-style response options (4=strongly agree; 0=strongly disagree). The five odd-numbered items are calculated by subtracting 1 from the raw score, even-numbered items by subtracting the raw score from 5. All scores are summed and multiplied by 2.5 to yield a total score between 0 and 100. SUS scores above 68 are considered above average; those above 80 belong to the top 10% of user experience.<sup>37</sup>

### *Usability Test Results*

We performed two rounds of classical user testing. For the first round we recruited a convenience sample of 5 alloSCT patients from the outpatient clinic, by asking all available patients at a certain day if they are willing to take part in the user test. For the second round, we recruited 6 alloSCT patients over one week, by applying a purposive sampling approach to guarantee that all educational level, gender and age are represented by the two user tests. Patients of both groups tested the SMILeApp interface regarding the symptom monitoring and follow-up module. According to existing guidelines, this number of patients is sufficient to identify up to 80% of usability problems.<sup>38</sup> The first test included slightly younger patients (test 1 mean age: 43.7; test 2: 48.2). Regarding gender and cohabitation status, the two groups were very similar, with 60% male and 90% living in partnerships for both; however, 90% of test group 1 patients had completed at least some post-secondary education, while 90% of those in group 2 had not. Each round included 14 practical tasks (e.g., opening the SMILeApp, entering blood-pressure) which the patients had to solve while thinking aloud. After completing the tasks, the participants filled in their SUS questionnaires, yielding mean scores of 88 points for group 1 and 79.5 points for group 2. We also elicited and

integrated feedback on SMILeCare's usability from the hospital care coordinators via regular discussion rounds.

### *Extended End User Involvement*

Besides incorporating patients in the contextual analysis and usability tests, further patient involvement was sought over the course of development. Partly to help the development team settle design questions, and partly to increase the software's acceptability, we set up an additional round of patient input, this time with a self-help group of cancer survivors (n=11) and caregivers (n=8). After presenting feature designs based on an intermediate version of the app, we asked them about their preferences, particularly concerning the frequency of data entry, different SMILeApp logos, different types of reminders, and feedback on set behavioral goals (e.g. reached step goal). As monitoring of behavior was one included behavior change technique, we were interested in how frequent patients would be willing to enter data in terms of a performed behavior. Of the eleven patients, six were willing to enter medical and symptom data daily, four every third day and one once weekly. Regarding a pro-active weekly schedule for questions monitoring positive health behaviors, 12 of 19 patients and caregivers would be willing to receive 4 questions distributed across the week, 5 no more than 2 questions and 2 just one per week (e.g., Did you remember to apply correct hand hygiene?). All 19 favored the idea of daily pop-up reminders, preferably graphical, to enter data into the app.

## 5.4 Discussion

In this paper, we describe how, within an implementation science project, agile software development principles can be applied alongside user centered design and theory-guided content development to create and embed tailored software solutions in an integrated care model. This contrasts with the more frequent approach of integrating software developed in an unrelated process or even preexisting software that basically fits the purpose. In our experience, there are typically two main approaches to eHealth software development: either software companies drive the process, seeking contact with medical teams to receive content to be implemented, or clinician teams specify a concept to be programmed by a software team. In either case, even if both groups provide their best efforts to do their jobs separately, gaps remain between content development and software production, making inaccuracies and misunderstandings virtually inevitable.

### 5.4.1 Team Effort

To minimize such shortfalls, we treated the content developers and the software developers as a single interdisciplinary team working towards a custom-fit software solution. Accordingly, we included meetings between various constellations of specialists at various intervals in our agile development process. Including software developers in the contextual analysis and nursing scientists in the software development process (e.g., at the sprint reviews and usability tests) greatly helped these groups' mutual understanding. Similarly, regular feedback from both stakeholders in the field and end users helped validate the anticipated solutions.

### 5.4.2 Theory-based Content Development

Guided by a solid contextual analysis underpinned by the BCW as behavioral theory, we were able to build meaningful theory-based user stories as a basis for software development. As this employment of user stories was newly introduced to the content team by the software team, the content developers were often tempted to incorporate design ideas into the user stories early in the process; however, design and interaction ideas should be developed at later stages, in collaboration with the UX team, as its members have greater expertise in such matters.

### 5.4.3 Application of User-Centered Design

The use of UCD techniques, especially mock-ups and user flows, increased the discussion between the content and UX teams. The early usability tests helped to identify several weaknesses affecting previous designs, leading to an improved user interface. This part of the process was rather straightforward to accomplish: as the software programming remained incomplete, the programmers were less reluctant to make changes.

In line with the UCD principles of 1) focusing on users and tasks, 2) measuring usability empirically; and 3) designing and testing usability iteratively<sup>39</sup>, usability tests offered opportunities for members of both the content team and the software team to evaluate their work. The tests were not only used summatively, i.e., to determine the SUS score, but also formatively, i.e., to help us find improvable points within the software. With a score of 88, the first test group's mean System Usability Score (SUS) was already within the top 10% of possibilities (>80).<sup>37</sup> The second group's lower mean SUS (79.5) might reflect the complexity of the functionalities tested, that group's higher mean age or their lower educational level. This indicates that the raw numbers have to be interpreted with caution. For our purposes, the qualitative results of the think-aloud methods were more beneficial.

### 5.4.4 Principles of Agile Software Development

This project's use of iterative processes reduced its overall complexity by dividing it into manageable parts. Typically, each iteration deals with several user stories, but only as many as the software team thinks can be completely finished in the time allotted. Ideally, each iteration review includes the presentation of a usable piece of software that adds value for the customer. In our setting, though, we found that this was often not possible, as the content team's stories were too long to finish in a single iteration and had to be broken down into multiple shorter ones. Also, our process, whereby the stories first have to be designed, then programmed, led to the same story stretching across several sprints. For example, after looping two or more times through the design cycle, a story could do the same with the programming cycle.

Not knowing how many iterations would be necessary made it difficult to schedule the associated functionalities' release dates. As our two-weekly sprints were rather short, the most obvious solution would be simply to lengthen the sprints to deal with each story. On the other hand, as no components were released before we agreed they were satisfactory, the quality of the resulting software components was very high. As noted above, this was reflected in the end users' test ratings.

One considerable drawback of using agile software development in a medical context is that the agile development style values working software above highly-detailed documentation. This priority conflicts with the US FDA's stipulations surrounding Software as Medical Devices (SaMDs) and with the EU's Medical Device Regulation (MDR; EU2017/745), both of which define Apps with certain functionalities as Medical Devices. Both cases entail exhaustive documentation of each detail of the production process.

For the first SMILe module, then, as the certification process was simply not feasible for our group, we chosen to realize only functionalities that fall outside the MDR classification (e.g., rather than receiving integrating algorithm-based automated feedback via smartphone messages, patients can look them up in a lexicon integrated in the app). The chosen functionality is now operational and can be used by patients as well as caregivers on the targeted devices.

In future work, we hope to tackle the remaining functionalities. This will require following a more stringent software development process—a need we can meet by defining specification and verification documents as required by the FDA or ISO62304 as sprint goals and further formalizing the development process.

In February 2020, following the agile principle of evaluating prototypes early, we initiated a randomized controlled trial (DRKS00020347) at Germany's Freiburg im Breisgau, University Hospital (FiB). As the first participating center, FiB is using only the

symptom monitoring and follow-up eHealth module. At the time of writing, the other modules are in a face-to-face only delivery mode. In parallel, the software development team is constructing software features to continue with the digitalization process.

### 5.5 Conclusions

Across countries, diseases and settings, there can be little doubt that eHealth will play a central role in the future of health care. However, successful implementation of the necessary technology into any clinical setting requires first thoroughly analyzing not only end users' needs but the entire target context, then using the results to develop effective and meaningful content. In our case, an interdisciplinary team with expert knowledge of implementation science, behavioral science and computer science methods—particularly user centered design and agile software development—facilitate the planning, design, construction and testing of eHealth components with an increased chance of uptake, adoption and long-term sustainability. Reflecting context-specific requirements, these components are tailored to end user needs and can effectively influence their behavior in ways we fully expect will lead to improved medical outcomes. In addition to providing guidance for other groups interested in developing and integrating eHealth components into care models, this report presents an innovative method of re-designing chronic illness care towards more effective and resource-efficient eHealth-facilitated clinical processes.

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## Chapter 6

### Implementation and testing of an Integrated Model of Care in Allogeneic Stem Cell Transplantation facilitated by eHealth - The SMILe project

*Protocol for a hybrid-1 effectiveness-implementation science study*

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Planned to submit to a scientific journal

### 6.1 Abstract

**Background:** Integrated care models (ICM) facilitated by eHealth have the potential to support follow-up care of allogeneic stem cell transplant (alloSCT) patients, in need of chronic illness management support. No ICM for alloSCT has yet been developed, implemented and tested. Therefore, building on a series of preliminary studies, we developed an ICM for alloSCT survivors facilitated by eHealth (SMILe-ICM) combining implementation, behavioral and computer science methods. SMILe-ICM includes four self-management modules delivered by a Care Coordinator (CC) and the SMILeApp. We aim to implement and test the SMILe-ICM regarding its effectiveness, its implementation outcomes and implementation pathway.

**Methods:** In a single-center, non-blinded hybrid-1-effectiveness-implementation randomized controlled trial, we will include 70 adult alloSCT patients from the University Hospital Freiburg im Breisgau (Germany). Approximately ten days before participants' scheduled alloSCT, a stratified randomization will assign recruited patients 1:1 to the usual-care group or the SMILe-ICM group. A logic model describes the SMILe-ICM assumed mechanism of change leading to the desired outcomes. We will test the effectiveness of SMILe-ICM in view of its total healthcare utilization costs (primary outcome); re-hospitalizations, lengths of stay, medication non-adherence, treatment burden, health-related quality of life, graft-versus-host disease episodes, re-hospitalization-free survival, and survival in the first year post-alloSCT. Further, implementation outcomes (i.e., feasibility, acceptability, appropriateness, fidelity), and the implementation pathway will be evaluated. Standardized unit costs will be applied to calculate total healthcare utilization costs. Quantitative data will be collected in a standardized way using established measures. Implementation will be evaluated using mixed-methods. Intention-to-treat and per-protocol analyses will be conducted using generalized linear models, the Kaplan-Meier method and the log-rank test. Qualitative data will be analyzed using mind-mapping techniques and thematic analysis.

**Discussion.** The SMILe-ICM implies a system innovation in the follow-up care of alloSCT patients. Our dual focus will generate evidence on effectiveness, yet also provide insights regarding the implementation pathway. Should the SMILe-ICM prove effective, this will facilitate either scaling it up for broader use or scaling it out to other settings.

**Trial registration:** The SMILe study in Freiburg is registered at the German Clinical Trial Register which is linked to the WHO register of clinical trials: DRKS00020347

### 6.2 Background and rationale

Allogeneic stem cell transplantation (alloSCT) is highly effective and often curative against a range of hematological malignant or non-malignant diseases. Ongoing improvements in related technologies have greatly increased both alloSCT recipients' survival rates and, the numbers of alloSCT survivors in follow-up has increased.<sup>1, 2</sup> The European Society of Blood and Marrow Transplantation (EBMT) have recorded continuously rising numbers of people receiving a alloSCT, with 42,901 patients across Europe in 2018.<sup>2</sup>

AlloSCT entails lifelong, generally complex care requirements<sup>3,4</sup> and re-hospitalization rates are higher compared to cancer or other chronically ill populations. Common reasons include neutropenic fever in the first 30 days post-SCT or respiratory infections, gastrointestinal symptoms skin or musculoskeletal complications in the subsequent 10 years post-alloSCT.<sup>5,6</sup> Further, as many as up to nine-tenths develop one or more chronic conditions, the most common of which include chronic graft-versus-host disease (GvHD) (50–70%), and frequently experience psychosocial issues as fatigue (9–80%) and depressive symptomatology (8–20%).<sup>7–10</sup> Recipients' secondary malignancy rates are also two to six times those of the general population.<sup>11</sup> This range of conditions—and the risk of developing further comorbidities—necessitates a complex therapeutic regimen covering medication, physical activity, infection prevention and diet. Not surprisingly, non-adherence is common<sup>12, 13</sup> further putting them at risk for more complications.<sup>14–16</sup> Survivors should be treated as a chronically ill population<sup>17, 18</sup> as their needs progress from early complications through late-effects.<sup>18, 19</sup> Integrated models of care (ICM) and treatment management plans appropriate for chronic illness groups imply promise to improve outcomes.<sup>20</sup>

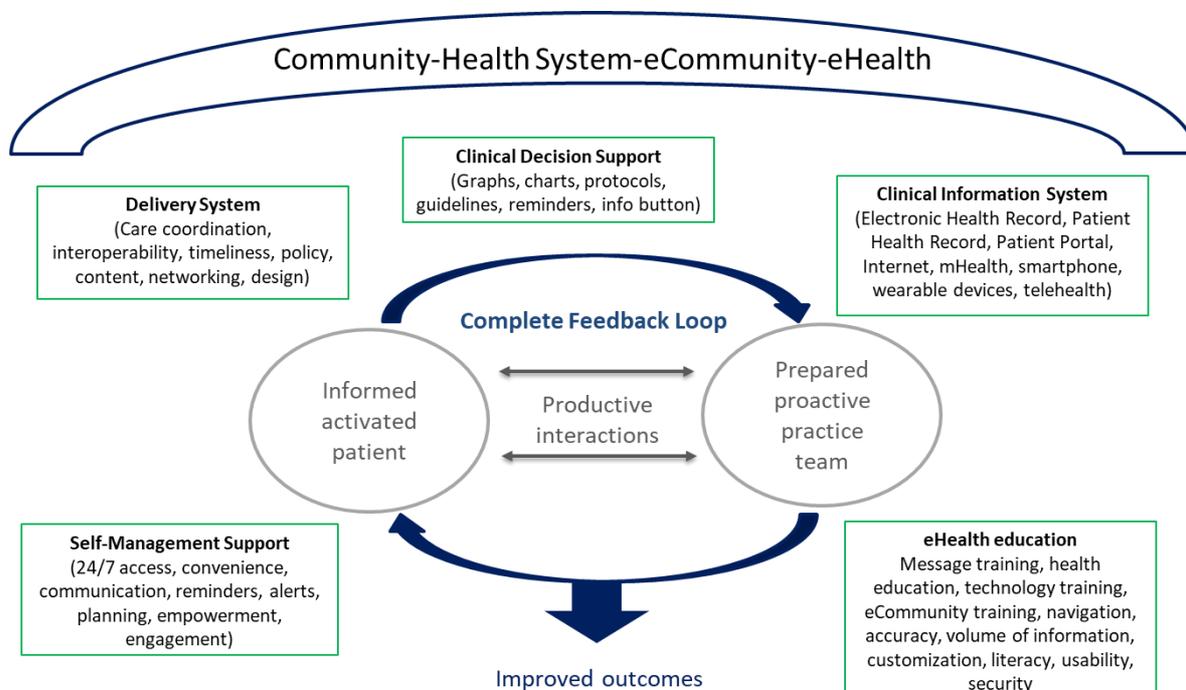
In patients with cancer or solid organ transplantation self-management strategies including vital sign monitoring and training on how to respond to alarming symptoms or health changes have proved effective at reducing readmissions and improving quality of life.<sup>21–23</sup> However, alloSCT patients and their caregivers often receive inadequate preparation for self-management, leaving them overburdened after discharge<sup>24–27</sup>, a finding confirmed by our contextual analysis.<sup>28</sup>

In order to strengthen ICMs addressing not only biomedical needs yet also behavioral and psychosocial needs of alloSCT patients, providing post-transplantation self-management support, and allowing early detection of complications, is facilitating intervention delivery by internet-capable devices — particularly smartphones. Several working groups, i.e. the US National Institutes for Health (NIH) Late Effects working groups have noted that such an approach would be useful to improve alloSCT survivor care.<sup>18, 20, 27, 29</sup> Likewise, in our contextual analysis, both patients and clinicians indicated

their openness to and a need for an ICM facilitated by eHealth to support their self-management once discharged.<sup>28</sup>

At the basis of ICM are accepted principles of chronic illness management. One excellent example is the Chronic Care Model (CCM) which is constructed from four dimensions: patient self-management support, decision support, clinical information systems and delivery system design.<sup>30</sup> In the hands of practice teams who are fully-prepared and proactive, and patients who are informed and activated, the CCM provides methods to consistently break down and address complex care needs, leading to improved patient outcomes.<sup>30, 31</sup> Regarding common chronic conditions such as asthma, heart failure and diabetes, study results indicated reduced mortality risk, improvements in health behaviors and increased quality of life (QoL).<sup>32</sup> As these, in turn, lead to lower healthcare use and reductions in health-related expenditures.<sup>33</sup> A greater number of CCM dimensions in ICM tend to result in better outcomes.<sup>34</sup> In 2015, the CCM has been expanded with a fifth dimension, eHealth education, resulting in the eHealth enhanced CCM (eCCM, see Figure 1).<sup>35</sup> In addition to speeding communication between outpatients and their clinical care teams, it accelerated improvement tremendously by enabling continuous feedback loops.

Figure 1: The eHealth Enhanced Chronic Care Model.<sup>35</sup>



Evidence from systematic reviews and meta-analyses on eHealth-facilitated ICMs in general but particularly in cancer and organ transplantation show favorable biomedical, behavioral and psychosocial outcomes.<sup>21-23, 36-42</sup> Findings on improved economic outcomes (e.g., all-cause hospitalizations, all-cause emergency department visits, hospitalization days) are also emerging.<sup>21, 22, 37, 38, 42</sup> Especially eHealth-facilitated care models incorporating at least two eCCM dimensions — e.g., *self-management support* and *delivery system redesign* — had beneficial effects on *biomedical* (e.g., cardiovascular<sup>37, 38</sup> and metabolic outcomes<sup>38</sup> and mortality<sup>36, 37</sup>). Favorable outcomes have also been shown for *behavioral outcomes*<sup>22, 42, 43</sup>; yet the evidence remains inconclusive.<sup>38, 39</sup> Regarding *psychosocial outcomes*, significant effects both on depressive symptoms and on overall QoL have been observed respectively in patient groups with chronic diseases<sup>37, 44-46</sup> and in larger chronic illness populations.<sup>22, 37, 38</sup>

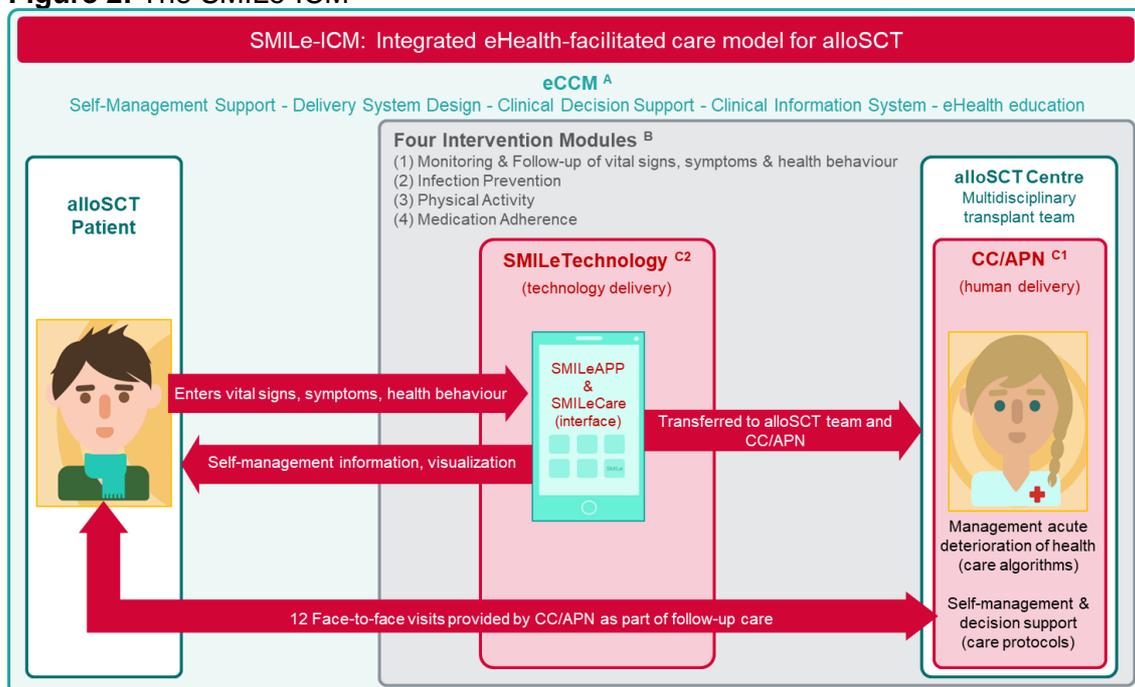
Despite emerging evidence of eHealth-facilitated ICMs' power to improve clinical<sup>22, 23, 37-39</sup> and economic outcomes in chronically ill populations<sup>21, 37, 38, 42</sup>, major barriers hinder either implementing or sustaining such models in *routine clinical practice*: of the few that are adopted, fewer remain in use two years later.<sup>37, 38, 47, 48</sup> Even published drop-out rates of 44–67%<sup>49-51</sup> only convey part of the story: in fact, only one in every ten thousand (0.01%) available eHealth applications overall is ever adopted into common use.<sup>52</sup> Two methodological shortfalls account for much of this near-perfect failure rate. The first is the lack of a theory-based intervention development<sup>53</sup> and user-centered design process during development<sup>54</sup>; the second is a failure to apply appropriate methodology to the translational process (e.g., implementation research).<sup>55</sup>

The miniscule adoption rate reflects the fact that, in terms of underlying theories, integrated intervention characteristics and the hypothesized “mechanisms of change” expected to produce the desired outcomes, most reported eHealth-facilitated interventions remain black boxes.<sup>56, 57</sup> The use of logic models, which systematize the causal processes through which interventions and implementation strategies produce effects<sup>56</sup> and specify resources/inputs, activities, outputs, outcomes and impacts of a given intervention, is essential to clarify and communicate the overall program theory. It also supports the planning, monitoring and evaluation of programs, communication of the strategies used, and the conveyance of understanding to stakeholders regarding the operative care model. Equally importantly, in cases of non-adoption, logic models support the interpretation of whether the implementation, the intervention, or both were inadequate.<sup>57, 58</sup>

While eHealth has been applied to deliver caregiver support<sup>59</sup> or individual self-management support interventions in alloSCT<sup>60, 61</sup>, no eCCM-ICM has yet been developed for alloSCT recipients. The importance of addressing alloSCT patients'

complex care needs, combined with the need to remold the prevailing acute care-oriented alloSCT follow-up system towards one driven by chronic illness management also emerged from our contextual analysis.<sup>28</sup> Therefore, building on a series of preliminary studies, by combining implementation, behavioral and computer science methods, we developed the SMILe-ICM (allogeneic **St**em cell transplantation faciLitated by **e**Health **I**ntegrated **C**are **M**odel).<sup>28, 62</sup> Building on the eCCM, the SMILe-ICM (Figure 2; A) consist of four self-management modules (Figure 2; B), with intervention components delivered via human and/or technology components (Figure 2; C1/C2). First, an Advanced Practice Nurse in the role of care-coordinator (CC) delivers 12 face-to-face visits fostering patients’ self-management in terms of symptom recognition, infection prevention, medication adherence, and physical activity. Second, the SMILe Technology connects the patients via the SMILeApp to the CC in the center helping to collect and document on import medical, behavioral and symptom-related data which they need to follow-up after alloSCT. The goal is the promotion of patients’ self-management and empowerment. Each module addresses another aspect of self-management or important health behaviors important during and post-alloSCT care. The SMILe-ICM intervention development and its characteristics are described in detail in a separate publication.<sup>63</sup>

**Figure 2: The SMILe-ICM**



**Legend:** A= Five dimensions of the eHealth enhanced Chronic Care Model, B= Four intervention modules delivered partly via human (alloSCT Transplant Team and CC=C1) and technology components (=C2); CC= Care Coordinator; APN= Advanced Practice Nurse

### 6.3 Objectives

Several factors determined this study's foci: 1) a call by the NIH<sup>64</sup> and the; 2) the growing body of evidence supporting eHealth-facilitated ICMs' efficacy<sup>21-23, 37-39, 42</sup>; 3) the major issues surrounding eHealth-facilitated interventions' adoption, implementation and sustainability in real-world clinical settings<sup>37, 38, 47-52</sup>; 4) the increasingly clear importance of theory-based interventions<sup>53</sup>, the use of a user-centered design<sup>54, 65</sup> and implementation science<sup>55</sup> regarding complex intervention development and real-world clinical implementation; and 5) our preliminary work.<sup>28, 62</sup> From these emerged two aims and one central hypothesis:

1. To test the effectiveness of the SMILe-ICM in view of total healthcare utilization costs (primary outcome), re-hospitalization rate, re-hospitalization lengths, medication non-adherence, treatment burden, health-related quality of life, incidence and grade of acute and chronic GvHD episodes, re-hospitalization-free survival and overall survival rate (secondary outcomes) in the first year post-alloSCT.

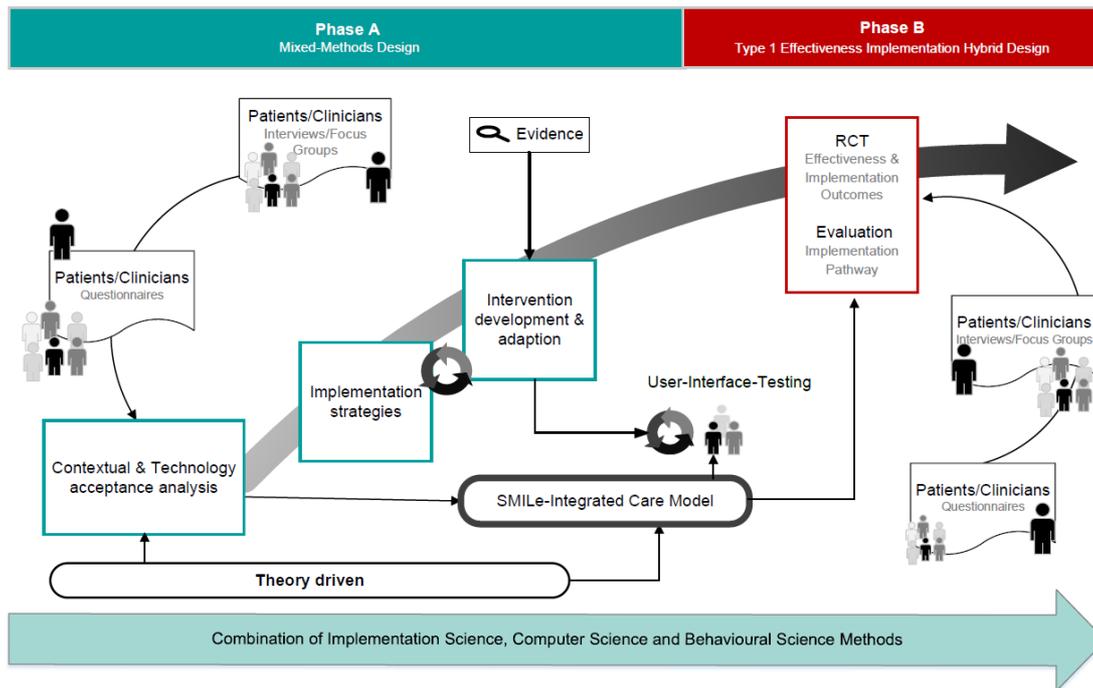
**Hypothesis:** We hypothesize that patients in the SMILe-ICM will have lower total healthcare utilization costs, fewer re-hospitalizations, shorter re-hospitalization lengths, less medication non-adherence and treatment burden, equal HRQL and equal medical outcomes (acute and chronic GvHD, re-hospitalization-free survival, overall survival) compared to the usual care group.

2. To evaluate the *implementation* of the SMILe-ICM regarding its feasibility, acceptability, appropriateness and fidelity and its implementation pathway.

### 6.4 Methods

The SMILe project is a multiphase implementation science project consisting of two major parts (Figure 3): The already completed *Phase A* focused on contextual analysis<sup>28, 62</sup>, including an analysis of technology acceptance to develop and adapt the SMILe-ICM, which fused implementation, behavioral and computer science methods.<sup>63</sup> Phase A's methods and findings have been reported elsewhere.<sup>28, 62</sup> *Phase B* includes the implementation and evaluation of the SMILe-ICM. The methods employed for phase B are the focus of this study protocol and are reported in accordance to the SPIRIT 2013 guidance.<sup>66</sup>

**Figure 3:** Overview of the SMILe project with its two phases



### 6.4.1 Study design

To evaluate both the SMILe-ICM's *effectiveness* and its *implementation outcomes*, we plan to conduct a single-center, non-blinded, randomized controlled hybrid-1-effectiveness-implementation study-(Figure 4).<sup>67</sup>

### 6.4.2 Study setting and sample

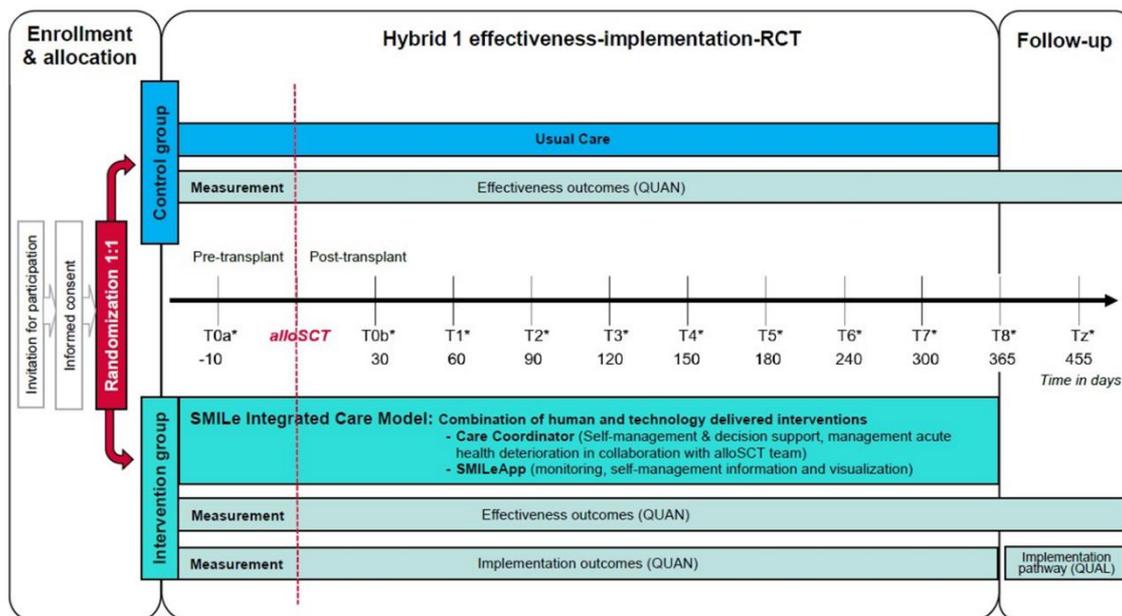
Adult alloSCT patients will be recruited from the University Hospitals Freiburg im Breisgau; Germany (FiB). The FiB University Hospital is one of the largest academic hospitals in southwest Germany with a catchment area of about 100 km<sup>2</sup> and performs around 100 adult alloSCTs annually. Information on setting specific perceived care needs, relevant practice patterns, stakeholders' technology openness, our basis for developing the SMILe-ICM and our choice of implementation strategies are reported elsewhere.<sup>28, 62</sup>

### 6.4.3 Eligibility criteria and recruitment

The project leader will screen potentially eligible patients. After reviewing their medical records, patients, who meet the study's inclusion criteria will be invited to participate about 10-14 days before their scheduled alloSCT. Inclusion criteria include: 1) transplanted and 2) followed-up at the FiB University Hospital, 3) basic German language proficiency; 4) access to internet at home (WLAN or mobile data transfer) and 5) provide written informed consent. Patients will be excluded if they have physical or

mental conditions precluding the use of the relevant technology or self-management activities. Patients with an ECOG (Eastern Co-operative of Oncology Group) Index  $\geq 4$  are assumed not being able performing self-management tasks independently. Written informed consent will be obtained from all participants before enrolment followed by randomization.

**Figure 4:** The SMILe study flow diagram



#### 6.4.4 Interventions

*Usual care.* Usual care at the FiB University Hospital is standardized, according to clinical practice guidelines, focusing on medical aspects of treatment. The inpatient and the outpatient setting is working with an electronic medical record (MEONA ©), which also includes a follow-up care plan. During the first 3 months following alloSCT, depending on health status, patients return for follow-up one to three times per week. On recovery, follow-up appointments are extended to weekly, monthly or quarterly appointments during the first year post- alloSCT.

As our contextual analysis indicated, the practice patterns at the FiB alloSCT center reflects an acute care driven system. This is mirrored by their outpatient programs, where self-management support for alloSCT patients is severely limited, the majority being provided to inpatients (e.g., medication management). And regarding modes of delivering that support, the teams working in- and outpatient clearly prefer patient education over behavioral change interventions.<sup>68</sup> While there is an Advanced Practice Nurse only for specific aspects of alloSCT care in the inpatient care, there is no multidisciplinary in the outpatient care. All patients receive a pre-transplant educational visit informing about transplant procedures.

*SMILe-ICM.* Participants in the intervention group (IG) will receive the SMILe-ICM as described above and published in detail separately.<sup>63</sup>

Between admission and transplantation, each patient will meet the CC twice; post-alloSCT, two more visits will be planned: one before discharge and one shortly after. The remaining eight visits will take place in months 3, 4, 5, 6, 9 and 12 post-transplant. These will follow the defined care protocol. During their first visit, CCs will teach patients to enter data in their SMILeApp. CCs' feedback on entered data, as well as their collaboration with the alloSCT team, will follow predefined algorithms and care protocols.

*The SMILe-ICM Logic Model.* Figure 5 shows the SMILe-ICM Logic model, summarizing the intervention's guiding program theory. Building on the SMILe-ICM's intervention development and technology development, as well as on theoretical and empirical evidence<sup>35, 68</sup>, this specifies its *RESOURCES/INPUTS*, *ACTIVITIES*, *OUTPUTS*, *OUTCOMES* and *IMPACT* and summarizes all *intervention components'* and *implementation strategies'* hypothesized *MECHANISMS OF ACTION*.<sup>28, 56-58</sup> Reading from left to right, four categories of *INPUTS* are specified for the model: Relevant *multi-level context-related variables* were factored into choices regarding both implementation strategies and intervention development.<sup>28</sup> The SMILe-ICM's *ACTIVITIES* include nine contextually adapted *implementation strategies*<sup>28, 69</sup> to support specific tasks. We used specific taxonomies<sup>70, 71</sup> to describe these strategies. Other activities include the various *intervention components*.

At the SMILe-ICM's organizational and patient levels, the hypothesized *MECHANISMS OF ACTION* are the used intervention functions and behavioral constructs informing the behavioral change techniques (BCTs), practice-related and care-organizing interventions chosen to achieve the target outcomes. Seven human organizational and three technology-related categories are expected to change and impact outcomes. On the patient/family level, each module's BCTs are expected to impact patients' capability, opportunity and motivation, thereby facilitating the target behavior. *OUTPUTS* describe countable actions which will result from the intervention's application and which will influence the *SHORT- AND LONG-TERM OUTCOMES*.

For example, at the patient level the CC delivers 19 BCTs to effectively support patients medication adherence towards immunosuppressive medication (activity-mechanism of action). Including strong techniques such as monitoring of behavior, goal setting or action planning it's very likely that this will result in a greater number of patients being adherent (output). Evidence shows that improved medication adherence towards immunosuppressant's impacts the incidence and severity of GvHD episodes (short-term outcome), which in turn might impact the number and length of re-hospitalizations

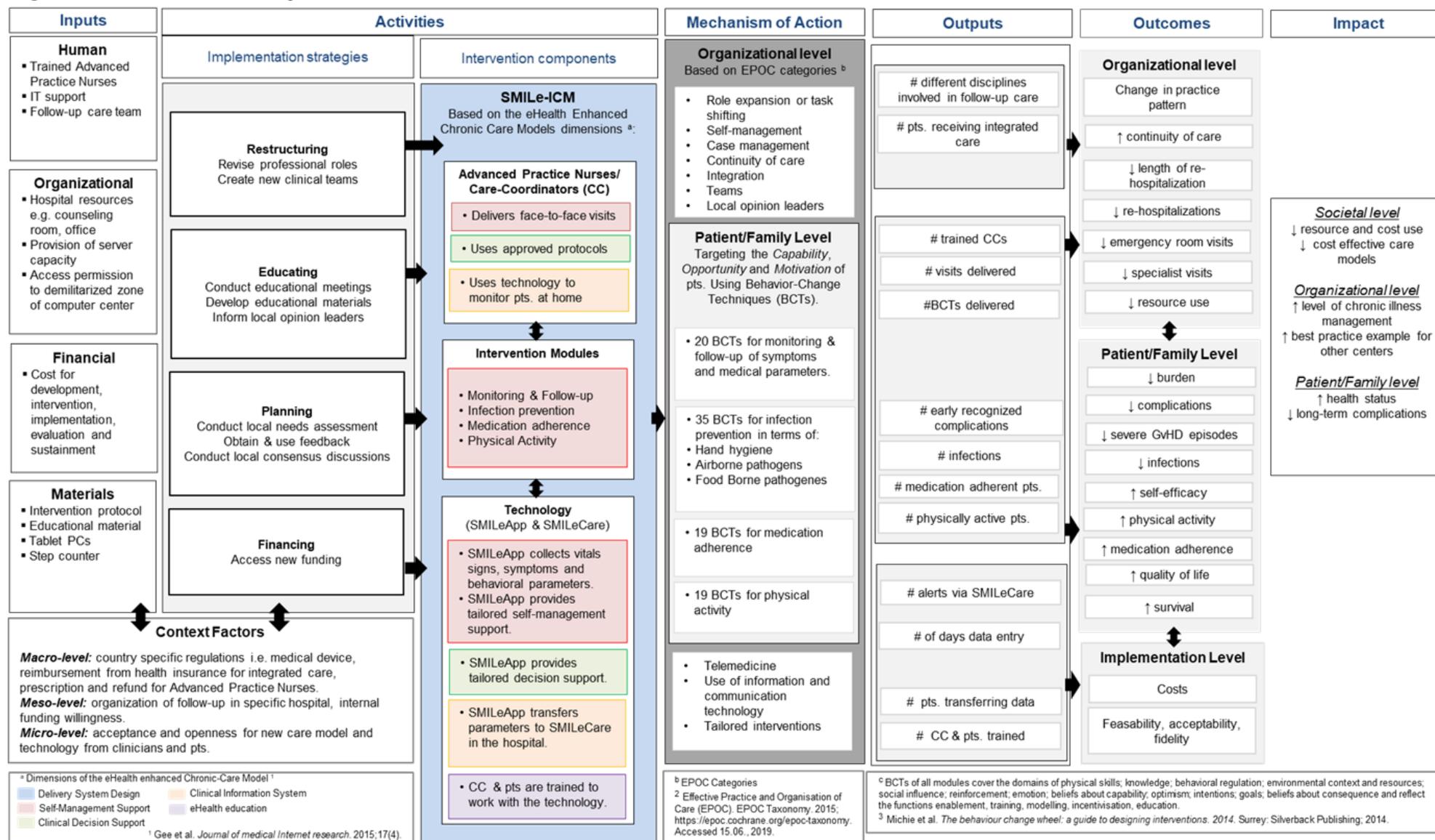
## Chapter 6 – The SMILe study protocol

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needed in the first years post-alloSCT (long-term outcome), leading to improved health status years later (impact).

At the organizational level, we assume that for example the restructuring of care delivery (activity) will lead to multidisciplinary teams in follow-up care (mechanism of action) resulting in a greater number of patients receiving integrated care (outputs) leading to a change in practice pattern (outcome) and improved chronic illness management in the long-run (impact). We expect *OUTCOMES* on the organizational, patient/family and implementation level, The most pronounced impact, which is expected to occur after 7-10 years, will be at the societal level, with long-term decreases in resource use and costs. Related improvements are expected at all levels. For example, we expect to see rising levels of chronic illness management, hopefully making the FiB University Hospital as a best practice example among transplant centers.

Figure 5: The SMILe-ICM Logic



### 6.4.5 Outcomes and measurement

Information on variables and measurements is summarized in Table 1.

*Primary effectiveness outcome.* The primary outcome will be total first year post-alloSCT healthcare utilization costs. Healthcare utilization data will be collected from medical records and validated via an adapted version of the generic self-reporting FIMA<sup>®</sup> questionnaire and analyzed quarterly, with calculations made from a payers' perspective.<sup>72</sup> While the original 28-item FIMA<sup>®</sup> instrument was designed to measure health care utilization in elderly persons, we have adapted and shortened it to seven items gathering retrospective data regarding all major types of health care utilization (e.g., primary care appointments), plus a single item of the respondent's medical insurance. The resulting data will be analyzed based on standardized unit costs across the five categories: number of hospitalization days (initial and re-hospitalization), number of rehabilitation days, number of ambulatory healthcare visits, number of ambulatory stays in hospital, nursing and home care services.<sup>73, 74</sup>

*Secondary effectiveness outcomes.* As a secondary effectiveness outcome, the first year post-alloSCT re-hospitalization rate includes total all-reason hospital readmissions between initial post-alloSCT discharge and the study's end. Length of re-hospitalization in the first year after alloSCT is the total number of days hospitalized for any reason over the same period. To gather data on both of these variables, we will review all available medical reports and the adapted FIMA<sup>®</sup> questionnaires<sup>72</sup>; in both cases, the last possible usable data will be from 372 days post-transplant.

Medication non-adherence (implementation & persistence dimension)<sup>75</sup> will be assessed via self-report using the 5-item Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS<sup>®</sup><sup>76, 77</sup>). The 5-item BAASIS<sup>®</sup> instrument is a validated self-report measure that assesses adherence implementation and persistence via yes/no questions. Non-adherence is indicated by a YES response to any item.<sup>76, 77</sup> Additionally, blood levels of immunosuppressive drugs will be retrieved from medical records. Medication adherence to immunosuppressive drugs will be assessed between day +30 ±7 (according to the usual start of the oral immunosuppressant drug intake) until discontinuing of the immunosuppressive medication or end of study.

Treatment burden will be measured via the German version of the PETS<sup>®</sup> self-reporting questionnaire<sup>78</sup>. Its 46 items are distributed across nine multi-item scales, each of which measures a separate domain of chronic illness treatment burden. All items use 4- or 5-point Likert-type response scales and a recall time frame of 4 weeks. Generating an assessment involves converting individual domain scores to percentages, then summing these. Higher scores indicate greater treatment burden.

HRQoL will be measured using the EQ-5D-5L<sup>®</sup>, a validated 6-item questionnaire.<sup>79</sup> It covers five dimensions measured on a 0-to5 Likert scale (0 = no problems, 5 = extreme problems): mobility, self-care, usual activities, pain/discomfort and anxiety/depression. It also includes the EQ-Visual-Analogue Scale (VAS), on which individuals rate their overall perceived health state (scale of 0 to 100).<sup>79</sup>

Incidence and grade of chronic and acute GvHD episodes, re-hospitalization free survival and overall survival rate will be retrieved from medical records. For chronic GvHD scoring, clinicians use 2014 NIH consensus criteria<sup>80</sup>; for acute GvHD scoring they use the modified Glucksberg criteria. Patients' GvHD maximum grades will be extracted from their medical records. Demographic and clinical variables will also be retrieved from the medical records.

*Evaluation of the implementation outcomes and implementation pathway.* Using quantitative methods at the patient and CC level, we will assess *acceptability, appropriateness, feasibility and fidelity* (implementation outcomes). We will measure *acceptability*, generally regarded as a reliable barometer of end user satisfaction, via the 4-item *Acceptability of Intervention Measure* (AIM).<sup>81</sup> To measure *appropriateness*, i.e., the intervention's perceived suitability to address the target problems within its setting<sup>81</sup>, we will use the 4-item *Intervention Appropriateness Measure* (IAM). To assess *feasibility*—the intervention's perceived suitability for everyday use—we will use the *Feasibility of Intervention Measure* (FIM).<sup>81</sup> Further, to measure *technology acceptability* i.e., the ratio of days with data entry to the number of technical problems, using data gathered via the SMILeApp. And to gauge *intervention fidelity*, i.e., a measure of how fully the intervention delivery methods adhere to the overall plan, we will following methods. Considered the gold standard of intervention delivery<sup>82</sup> we will randomly testing 5% intervention sessions for fidelity to the protocol. As a further step regarding intervention patients, the CC will note their attendance as scheduled to face-to-face visits T0 – T8 (fully, partly or not at all). All deviations either from the number, length, and frequency of contacts, or from the delivered content (in relation to the protocol's specifications) will be noted. Qualitative methods will also be used to evaluate the implementation pathway. Via focus group interviews with all involved clinicians, we will identify and explore potential barriers and facilitators of the implementation process and problems experienced during the intervention's delivery. After completion of the study 10 individual interviews will be conducted with intervention patients. All interviews—both with focus groups and with individuals—will be audio-recorded, pseudonymized during transcription, and their qualitative data analyzed using mind-mapping techniques and thematic analyses. After the study's end, all recordings will be deleted.

**Table 1:** Outcomes and measurement instruments and time-points

Variables	Measurements	T0 a	T0b	T1	T2	T3	T4	T5	T6	T7	T8	Tz
<b>Effectiveness outcomes</b>												
<b>Primary outcome</b>												
Healthcare utilization costs	Medical records & FIMA® (10 Items) Standardized unit costs			x x								
<b>Secondary outcomes</b>												
Re-hospitalization rate	Medical records & FIMA® (10 Items)			x x								
Length of re-hospitalizations	Medical Records & FIMA®			x	x	x	x	x	x	x	x	x
Medication non-adherence	BAASIS® (5 items)		x	x	x	x	x	x	x	x	x	x
Treatment burden	PETS® (60 items)	x			x			x			x	
Health-related Quality of Life	EQ5D® (5 items)	x	x	x	x	x	x	x	x	x	x	
Incidence/grade chronic and acute GvHD	Medical record		x	x	x	x	x	x	x	x	x	
Overall survival rate	Medical record		x	x	x	x	x	x	x	x	x	x
<b>Demographics</b>												
Age	Medical Record	x										
Sex	Medical Record	x										
Education	Questionnaire (4 items)	x										
Living alone	Questionnaire (1 item)	x										
Disease	Medical record	x										
Conditioning regimen	Medical record	x										
If death: Date and cause of death	Medical record		x	x	x	x	x	x	x	x	x	x
If relapse: Date of relapse	Medical record		x	x	x	x	x	x	x	x	x	x
<b>Implementation outcome (IG / CCs)</b>												
<b>Patients</b>	Acceptability	AIM (4 items)	x	x	x	x	x	x	x	x	x	x
	Appropriateness	IAM (4 Items)	x	x	x	x	x	x	x	x	x	x
	Feasibility	FIM (4 items)	x	x	x	x	x	x	x	x	x	x
	Technology feasibility	N (days with data entry), N (technical problems)										
	Intervention fidelity	N (visits), Minutes (visits), N (BCTs) compared to protocol										
<b>CC</b>	Acceptability	AIM (4 items)	x	x	x	x	x	x	x	x	x	x
	Appropriateness	IAM (4 Items)	x	x	x	x	x	x	x	x	x	x
	Feasibility	FIM (4 items)	x	x	x	x	x	x	x	x	x	x
	Intervention fidelity	5% of intervention sessions randomly chosen will be audiotaped and checked for protocol congruence										

**Note.** T0= baseline (T0a = day ±10, T0b = day 30 ±7), T1= day 60 ±7, T2= day 90 ±7, T3=day 120 ±7, T4=day 150 ±7, T5=day 180 ±7, T6 = day 240 ±7, T7= day 300 ±7, T8=day 365 ±7; Tz=day 455 ±7)

### 6.4.6 Sample size calculation and recruitment

Drawing on our experience in renal transplantation, we calculated our minimum sample size based on an  $\alpha$  level of 0.05, a power of 80% revealed an estimated number of required at least  $n=35$  patients per group ( $N=70$ ). With approximately 100 alloSCTs/year and anticipating 10% not fulfilling the inclusion criteria, 10% of patients declining to participate and considering a 15% drop-out rate we estimate that the recruitment of our target sample size will take approximately 12 months.

### 6.4.7 Allocation and blinding

Eligible participants will be randomly assigned 1:1 to either IG or the CG (Figure 4). Randomization will be stratified by age <65 and >65 years, gender and living alone. The concealed randomization procedure will be done using secuTrial®, a web-based clinical data management system. To avoid predictable alternation of treatment allocation, patients will be allocated with a probability of 80 percent to the treatment group that would minimize the imbalance between the two treatment groups within each study site. While the randomization and allocation procedure will be concealed from all clinicians, blinding the participating patients and the members of the alloSCT care team to group allocation is not guaranteed.

### 6.4.8 Data collection and management

Throughout the study, all data collection processes will be standardized. Standard follow-up measurements will be conducted at 3, 6, 9 and 12 months post-intervention, with an additional 15 month follow-up scheduled to test the intervention weaning effect (Figure 4).

Data collection will take place from 02/2020 until 06/2023 at pre-defined time points (Table 1). Electronic data will be collected continuously via the SMILeApp and stored at the hospital server.

Questionnaire data will be collected paper-based and entered to the online clinical data management system secuTrial®, creating an electronic case Report Form (eCRF) per patient. All entered data will be double checked by a study nurse. Original questionnaires and interview data will be stored and locked in a cabinet within the hospital or a password protected database.

### 6.4.9 Statistical methods

Statistical analyses will use the Stata, SPSS or R software packages, with missing data handled via multiple imputations. Data will be systematically screened for out of range values and inconsistencies. As appropriate, descriptive statistics will be

applied to all variables. Using standardized unit costs for Germany, which will yield total costs per group, we will conduct Intention-to-treat and per-protocol analyses. Costs will be compared via generalized linear models with two-sided significance set at 0.05. Cost development over time will be calculated. Together, these analyses will help test our hypothesis that the SMILe-eICM care model will lead to reduced health care utilization costs.<sup>73, 74, 83</sup> For the secondary outcomes, we will consider statistical analyses descriptive, meaning no adjustments will be necessary for multiple testing. To analyze the development of the target outcomes, we will construct generalized linear models. And to account for the availability of multiple estimates for each patient, these will include computation of cluster-robust standard errors. We will use the Kaplan-Meier method and the log-rank test to test overall survival. Implementation outcomes will be measured in intervention group.

### 6.4.10 Data monitoring

The project leader and a designated independent study monitor will conduct one site initiation visits and two routine monitoring visits. The monitor will approve and confirm that the study is being conducted according to the protocol and data are being collected accurately and completely within the eCRF. There are no interim analysis planned.

### 6.4.11 Ethics and dissemination

The study protocol has been approved by the Ethics committee of the FiB University Hospital (EK 309/19) and will be conducted according to the Declaration of Helsinki. All participants will be assured that they can withdraw from study participation at any time without consequences.

The study is registered on DRKS and the WHO study register and will be published in an open access journal. All belonging publications will be prepared according to the International Committee of Medical Journal Editors' recommendations. The results will also be published in lay language for patients and at conferences.

## 6.5 Discussion

While many countries promote innovation in chronic illness care delivery, such as that for alloSTC recipients, none have yet developed a model of care both based on principles of chronic illness management and facilitated by eHealth. While evidence from RCTs of such models is promising, translating innovative solutions into real-life-settings remains a challenge.<sup>84, 85</sup> This paper describes the methodology of the SMILe project, an implementation science project aiming to implement and evaluate the SMILe-ICM, an eHealth-facilitated ICM for alloSCT, in a first alloSTC center. Beginning with and based on an in-depth contextual analysis, its development fused implementation, behavioral

and computer science methods to guarantee a thoroughly developed, theory-based, contextually adapted care model.<sup>28, 62</sup> This included implementation strategies to facilitate its implementation in a first European alloSCT center. A hybrid 1 effectiveness-implementation design is proposed.

Despite their obvious benefits, eHealth-facilitated ICMs should also be reflected from a critical perspective in terms of ethical and social dimensions. Most studies reporting on eHealth-facilitated ICM primarily purely focus at effectiveness and pay little attention to possible negative effects for patients such as equality of access and availability, autonomy, anxiety caused by monitoring or an overextension of clinicians by the amount of data or possible workarounds.<sup>86, 87</sup> Using technology in care delivery requires access for patients to devices as smartphones, putting patients at risk not to benefit if they cannot afford or access it. There is already evidence that certain populations experience this boundary, as for example patients with lower health literacy, socio economic status and higher age are less likely to use eHealth applications or owning a smartphone.<sup>88,89</sup> Also giving patients the possibility to control their physiological data can increase patient empowerment and autonomy in terms of self-management.<sup>87</sup> But besides the shifting towards a more active participation and potential improvement of the autonomy and own health this can also lead to the contrary, an increased dependency or anxiety by the enlarged responsibility of their own health-management.<sup>87</sup>

The increased use of eHealth in clinical care may also influence the patient-clinician communication or may change normative notions. Clinicians might focus purely on data rather than on the patient as a person which can become overburdened depending on the amount of data and the readability.<sup>86</sup> This may hinder being aware of the patient as a person with expectation of everyday life and existential needs leading to a loss of trust in the own body, in clinicians and a weakening of the relationships. Given these ethical and social challenges related to eHealth-facilitated ICMs ethical reflections should be part of the development process. Therefore, besides our approach of testing the effectiveness and implementation outcomes we initiated a sub-project (**DARE**-new **DA**ta new **RE**sponsibilities) reflecting on these ethical and social issues. This project will provide important insights into the ethical and social implications of eHealth solutions and thus add a crucial dimension for potential future digitalization process and scaling-up of the SMILe-ICM.

In addition to expanding our understanding of The SMILe-ICMs effectiveness outcomes, then, this project offers a rare opportunity to explore both its implementation outcomes and its implementation pathway and linked to the its sub-project insight into ethical and social implications. Indeed, should implementation of the SMILe-ICM should be successful and the new care model prove effective, it is designed for upscaling or

outscaling to other alloSCT settings. Given the pressure alloSCT centers are currently facing to gain accreditation, and that 1-year post-transplant survival is a major benchmark for that process, many of those transplant and follow-up facilities might recognize SMILe-ICM as a well-engineered systemic approach to optimizing their outcomes.<sup>90</sup> With strong results in alloSCT, it would be natural to expand and adapt the principles of SMILe-ICM first to closely-related patient populations such as autologous or solid organ transplant recipients, then to people living with cancer, then, eventually, to any population in need of a solidly founded, chronic illness management-based integrated care approach.

### 6.6 Conclusion

The SMILe-ICM adds a systemic innovation to alloSCT follow-up care. Representing the fusion of implementation, behavioral and computer science to guarantee a solidly scientific, fully adaptable basis for the intervention, it also offers a comfortable fit for end users. The logic model shows the intervention's inputs, outputs and outcomes, while highlighting both its underlying principles and its implementation strategies. And when the SMILe-ICM is evaluated, this dual focus on effectiveness and implementation outcomes will not only allow it to hit its targets, it will also help tremendously regarding its acceptance and adoption—first in its initial context, then, with its built-in scaling-up or –out options, to wherever it is needed.

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# Chapter 7

## Synthesis, Discussion and Perspectives



Within this section, the key findings will be synthesized, discussed and reflected upon in light of available evidence, likely future perspectives, limitations and implications for clinical practice, research or policy. This chapter's content is guided by the SELFIE framework.<sup>1</sup>

### 7.1 Synthesis of key findings

Despite advances in transplant-related treatments and supportive care regimens, alloSCT survivors commonly experience short and long-term complications.<sup>2</sup> As well as contributing to a significant decrease in their quality of life<sup>3</sup> and higher rates of hospital re-admission<sup>4</sup>, these complications influence morbidity and long-term mortality rates: in the 15–20 years following alloSCT, this group's mortality rate is 4–9 times higher than the general population's.<sup>5,6</sup> To date, to improve long-term outcomes, most researchers have focused on the pathophysiological mechanisms underpinning these complications explored potential treatments, or tried to prevent these complications by optimizing transplant-related procedures.<sup>5</sup> However, following alloSCT, prevailing care models observe only medical factors, and rarely offer regular long-term interdisciplinary follow-up care. Ideally, this would incorporate psychosocial and health-focused behavioral interventions alongside medical follow-up, i.e., an integrated care approach.

Although alloSCT patients would benefit from re-engineering towards an integrated care model (ICM), no such model has yet been developed, implemented and tested within clinical settings. And as eHealth has the potential to increase alloSCT patients' engagement in at-home self-management tasks and can delay or reduce complications and late effects, it is increasingly put forward to facilitate such a model.<sup>7-9</sup> Therefore this dissertation's aim was to develop and test an ICM for allogeneic **Stem** cell transplantation facilitated by eHealth—the SMILe-ICM—spanning from immediately pre-transplant to one year post-alloSCT. AlloSCT survivorship begins with a 5–6 week intensive in-patient acute care period, then transitions to the a tight follow-up schedule of outpatient visits in the first months post-transplantation leading to the long-term survivorship phase beyond the first year post-alloSCT. Given patients' frequent clinic visits, this first years is ideal to support their self-management skills and to promote beneficial long-term health behaviors.

Successful, sustainable implementation of complex interventions such as eHealth-facilitated ICMs into clinical practice is often limited by three deficiencies: a lack of adaptation/adaptability to context-specific conditions; the absence of theoretical frameworks to structure their content or guide eHealth integration into existing care models; and, perhaps most importantly, their developers' failure to embrace a user-centered design approach throughout the development process.<sup>10-12</sup> To overcome these shortcomings, we combined methods from implementation science, behavioral science and computer science for the first time to describe the context-driven, theory-guided and user-centered development of an

eHealth-facilitated ICM and its implementation and testing within a first clinical setting.

At University Hospital Freiburg, the first results of our current hybrid 1 RCT of the newly developed SMILe-ICM's effectiveness and implementation seem to affirm this decision. Thus far, we observe smooth implementation with no drop-outs due to adoption or acceptance problems. The final results, which will be available at the end of 2022, will enable the first effectiveness and economic analysis of an eHealth-facilitated ICM in alloSCT. Hopefully, this will foster future scaling-out or scaling-up of this and other ICMs.

Thus, this dissertation provides the first description of how implementation science, behavioral science and computer science methods can be embedded in the process of intervention production from the initial contextual analysis to the phases of development and user testing. As evidence is limited regarding how to conduct a contextual analysis<sup>13</sup>, SMILe will also serve as a methodological blueprint for others. **Chapter 3** includes detailed guidance first on how to conduct a thorough contextual analysis, then on choices regarding further implementation strategies and their application.<sup>14</sup>

For the contextual analysis, we merged two implementation science-related frameworks, i.e., we embedded the eCCM within the CICI framework. This helped us to understand setting- and context-related practice patterns, organizational structures and clinicians' and alloSCT patients' technology openness—vital prerequisites to the development and implementation of an ICM for this group. The results showed low levels of chronic illness management and interdisciplinarity, with gaps in important areas of self-management and health behavior support (i.e., recognizing, evaluating and acting upon new symptoms, infection prevention, medication adherence, physical activity). For patient support, eHealth was seen as a complementary tool, not a replacement for human contact.

The results also informed our selection of eight of the 73 possible ERIC implementation strategies to facilitate implementation in the Freiburg alloSCT outpatient clinic.<sup>15</sup> For instance, the center's low level of chronic illness management and lack of interdisciplinary care called for the formation of new clinical teams (e.g., integration of advanced practice nursing roles within the existing follow-up care team) plus revision of some existing roles to provide the needed self-management and behavioral support. This in turn demanded access to the necessary funding.

**Chapters 4 and 5** give guidance on developing the evidence-based, theory-driven and contextually-adapted intervention following principles of user-centered design and agile software development. The SMILe-ICM development process is described regarding content (**Chapter 4**) and transferring content towards technology components (**Chapter 5**).<sup>16, 17</sup> Both these chapters build upon the findings of the contextual analysis and demonstrate implementation strategies such as obtaining and using patients'/consumers' and family members' feedback (e.g., usability tests), conducting local consensus discussions (e.g.,

## Chapter 7 – Synthesis, discussion and perspectives

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defining feedback algorithms) and developing educational material (e.g., regarding intervention component content). With the intervention components' content tailored to contextual findings and available evidence, the Behavior Change Wheel (BCW) served as our guiding behavioral theory (**Chapter 4**). Embedded within the principles of agile software development, user-centered design informed our decisions on how this content could best be transposed to software features (**Chapter 5**). Also based on user-centered design principles, frequent stakeholder involvement and usability tests led to the creation of the SMILe-ICM's first running eHealth component.

The merging of computer science and implementation science is occasionally described in the literature.<sup>11, 18, 19</sup> However, to our knowledge, our three methodologies (i.e., from implementation science, behavioral science and computer science) have not previously been applied together to eHealth-facilitated ICMs. This development approach has the potential to inspire future academic projects in this field and may, alongside effectiveness testing, contribute to complex interventions' sustainable implementation.

**Chapter 6** presents the study protocol for a hybrid 1 effectiveness-implementation randomized controlled trial at the first participating center, University Hospital Freiburg. It also includes a first draft of a logic model describing how we expect the SMILe-ICM mechanism of change to lead to the desired outcomes.

### 7.2 Re-engineering acute care towards principles of chronic care

Based on our contextual findings and recent evidence, we chose the eCCM to guide our construction and operationalization of the SMILe-ICM. Building directly on the widely used and effective Chronic-Care Model, the eCCM re-engineers chronic illness care towards an integrated care approach.<sup>20-22</sup> Admittedly, while the eCCM focusses strongly on developing and organizing care at the micro- and meso-levels, that focus softens somewhat at the macro level.<sup>22, 23</sup>

### 7.3 The SELFIE framework

A recently conducted systematic review of theoretical frameworks for care coordination and integrated care found the **S**ustainable **i**ntegrated chronic care **m**odels for multi-morbidity: **d**elivery, **F**inancing, and **p**erformance (**SELFIE**) the most comprehensive currently available.<sup>24</sup> First published in 2018, the SELFIE framework reflects on the micro-, meso- and macro-level perspectives relevant to care integration for multi-morbid patients. It is presented in Figure 8.<sup>1</sup>

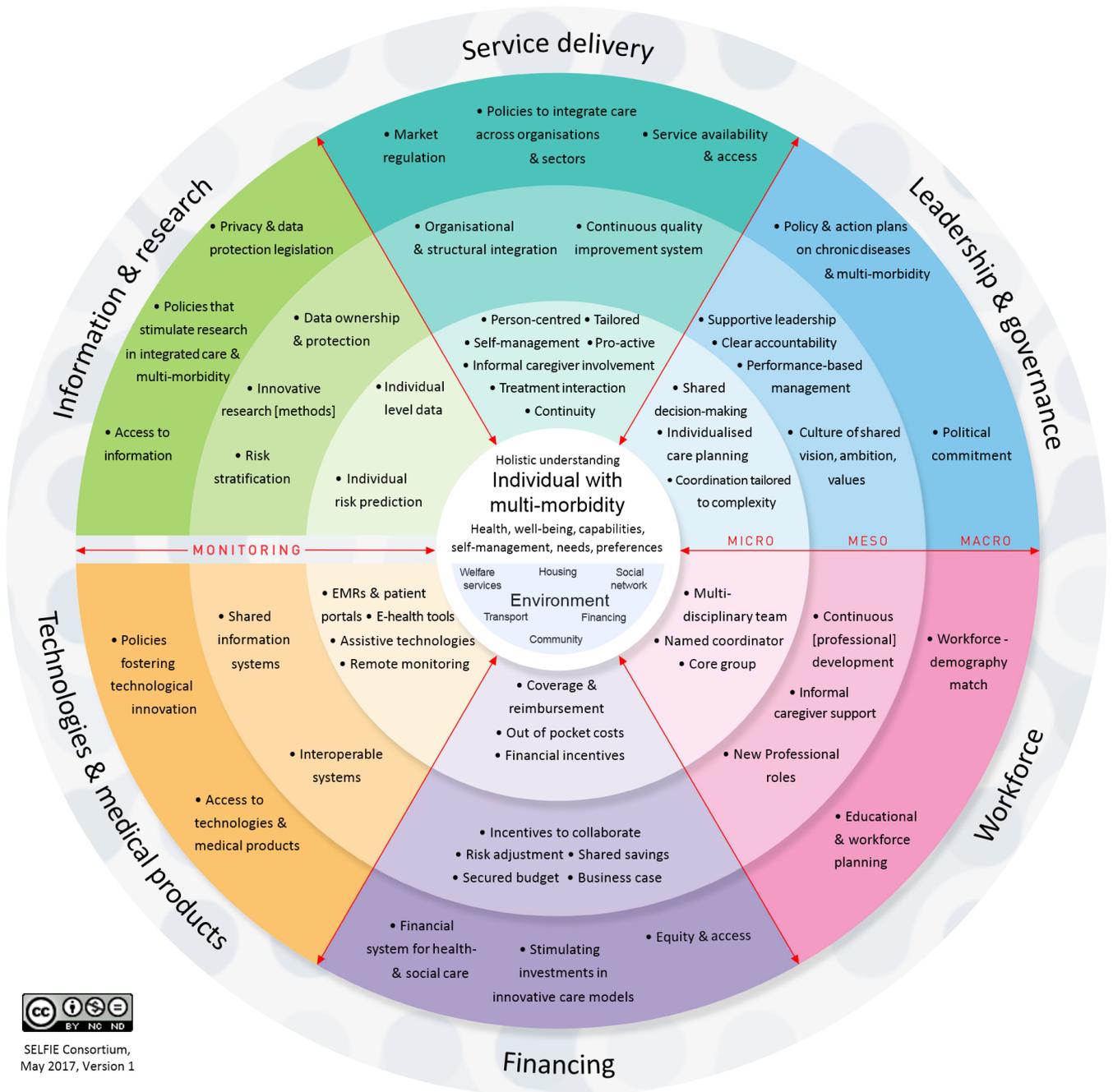
With the patient at its core, the SELFIE framework facilitates the use and coordination of the six WHO integration elements (i.e., service delivery, leadership/governance, workforce, financing, technologies/medical products, and information/research).<sup>25</sup> It also provides

## Chapter 7 – Synthesis, discussion and perspectives

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guidance both on how these six elements interact with the micro, meso, and macro levels of care and on how integrated care models can be monitored in terms of their triple aim, i.e. improving population health, improving patient experience and reducing/preventing increases in costs.<sup>26</sup> When we planned and started our contextual analysis and even during the model's development, the SELFIE framework was not yet available. Now, having seen its comprehensiveness, we suspect that it reflects the current state of science and is more suitable and attractive as a guiding framework for future ICM development processes than our composite of the eCCM and CICI frameworks. Therefore, in the following paragraphs we use the SELFIE framework to reflect on our work, potential limitations or adaptations of the SMILe-ICM, areas for future research and implications for clinical practice or policy.<sup>1</sup> Each sub-chapter first provides a short description of the relating SELFIE element before reflecting this element in light of our work.

Figure 8: The SELFIE framework for Integrated Care for Multi-Morbidity <sup>1</sup>



### 7.2.2 The individual with multi-morbidity

The SELFIE framework is constructed around a holistic understanding of the multi-morbidity-affected individual in his or her environment. Multi-morbidity is hereby defined as the presence of more than one chronic condition in the same person. Alongside the patient's capacity and ability to self-manage, attention should also be paid his or her well-being, needs and preferences. Despite environmental factors interacting with the individual, such as their social network, financial and housing situation, the community services available to them, including transport and welfare services, should be formally assessed.<sup>1</sup>

#### *The alloSCT recipient as multi-morbid patient*

With 50% of alloSCT survivors reporting at least two chronic health conditions and 35% reporting three or more, the majority fit the definition of multi-morbidity.<sup>27</sup> Hence, alloSCT patients need lifelong systematic follow-up, focusing not solely on surveillance for disease recurrence and late complications but also on screening for secondary malignancies and routine health maintenance.<sup>28</sup> Additionally, the literature recognizes both that active health promotion and education, psychosocial support, rehabilitation, financial counseling and reintegration into society are necessary and that they require an interdisciplinary care approach.<sup>5, 29</sup>

While developing the SMILe-ICM, we reflected carefully upon on all the aspects that comprise the SELFIE'S core and beyond, via a thorough contextual analysis.<sup>14</sup> Our results showed that the current outpatient follow-up model was purely physician-centered, with no structured self-management or behavioral support. We identified a low level of chronic illness management and important areas of self-management support also informing the choice of necessary implementation strategies.<sup>14,17</sup> By learning about patients' and clinicians' technology openness, we were also able to choose intervention content and a mode of delivery that fit both well. And because the user-centered design approach was fed smoothly into the agile software development process, it allowed us to target the integrated eHealth components according to the target context and patient-specific needs and preferences. This further facilitated a holistic understanding of the patients' situations.

#### *Observing the context*

To developing the SMILe-ICM, we performed one contextual analysis at the beginning, which provided us with the information needed to start development. While the current SMILe-ICM does not integrate regular, standardized monitoring of the individual's most important environmental factors such as available social networks or financial and housing situation; future iterations should include them, as such factors constantly and dynamically influence care needs.<sup>1</sup> For example, in Freiburg im Breisgau, our first SMILe-

ICM test center has already implemented the Distress Thermometer<sup>30</sup> to formally assess some environmental factors regarding social, financial, emotional or practical problems as well as physical symptom integral to them as well as the psychosocial distress they cause. Other relevant factors could easily be included in its monitoring targets. Also, as patient-related environmental factors can interact with interventions, monitoring those might be a worthwhile option.

Changing the perspective from an acute towards a patient-centered, holistic and proactive care approach within a specific setting can be a complex task regarding personnel, time-related and financial resources. In some cases, it might be necessary to assess factors known to influence implementation more than once, either to guide the time-point when implementation is possible or to monitor whether already-implemented adaptations are actually needed. As examples of factors that can influence an intervention's first implementation or later adaptations, the literature names i.e. the target institution's readiness<sup>31</sup> or leadership engagement.<sup>32</sup>

Scaccia and colleagues define an institution's readiness according to a) its staff's motivation to implement innovation; b) its general capacity to do so; and c) its innovation-specific capacity.<sup>31</sup> These three components are both dynamic and mutable. Therefore, while an institution might not be ready for an implementation at one point, this can change with time.<sup>31</sup> Likewise, leadership commitment to supporting an intervention's implementation and maintenance can also change.<sup>32</sup>

A thorough contextual analysis represents a considerable investment in itself. Pre-assessing key contextual factors such as institutional readiness for implementation or leadership engagement before moving to the full analysis might save resources and help adapt/implement interventions only to settings where similar changes in practice pattern are welcome and possible. Also, of course, regular observation of contextual factors might help prevent de-implementation due to changes in those contextual factors.

To date, the SMILe contextual analysis has not yet led to the selection of any centers based on their readiness or leadership engagement. Also, we have not implemented a regular monitoring of contextual changes. However, as we worked with innovators situated within the centers, we were able to assess and monitor their readiness or leadership engagement constantly. This also facilitates a fast capturing and adaptation towards organizational changes e.g. change of nursing leadership. Therefore, and because of the strong academic research partnership between the University Hospital Freiburg and the University of Basel, the three components of readiness, i.e., motivation, general and innovation-specific capacity and leadership engagement and compatibility all appear to be firmly in place: to date, the implementation phase is going smoothly.

### *Implications for future research and practice*

To the SMILe-ICM's core elements, future researchers should consider adding a structured, systematic assessment to regularly monitor each patient's most relevant environmental factors. By facilitating an understanding of the individual's dynamic situation, this will inform service delivery. Further, when considering scaling the SMILe-ICM up to another center, before investing in a full contextual analysis, future researchers might first consider assessing the staff's readiness to change their care perspectives and practice patterns. Also, the development of a methodology and instruments to regularly monitor contextual changes—which may necessitate adaptations to an intervention— or to define the compilation of the essential contextual factors which should be assessed within a contextual analysis might be areas of research useful for future projects.

### **7.2.3 Service delivery**

At the micro level, service delivery refers to holistically-informed, patient-centered, proactive, individualized care provision, with attention to all relevant individual dynamics. The meso level requires linkages between its actors—health, social and community services—as well as a continuous quality improvement system. And on the macro level, supported by market regulations and legislation, policies to stimulate integrated care across organizations and sectors are necessary.<sup>1</sup>

Within integrated care models, micro-level service delivery mostly includes self-management support. This includes behavioral/lifestyle changes<sup>33</sup>, facilitation of coping strategies<sup>34</sup>, care-coordination and navigation<sup>35</sup>, communication skills, prioritizing, and care planning.<sup>22, 35</sup>

Within the SMILe-ICM, we integrated an APN as the alloSCT team's care coordinator. In addition to supporting patients' self-management and fostering care-coordination, this person will provide case management as needed. Plus, using the SMILe technology to monitor patients' health, service delivery is tailored to a holistic understanding of each patient's needs, supporting the ability of each to confidently self-manage his or her health after discharge.

Elements at the meso-level are also in place at the Freiburg alloSCT center, where collaborations are already in place with other involved healthcare and social work stakeholders. Weekly interdisciplinary rounds bring together physicians, social workers, psychologists, nutrition experts, palliative care workers, physiotherapists, community service representatives and chaplains. However, as practice patterns and organizational structures vary widely, this might not be the case at other alloSCT centers; therefore, fully unlocking the

potential of an integrated care approach may require implementation of such interdisciplinary rounds involving a broad range of disciplines.<sup>36</sup>

### *Variability in service delivery across centers*

Indeed, at University Hospital Freiburg im Breisgau (FiB), Germany being the first site where we have performed and reported a contextual analysis<sup>14</sup>, we continued by conducting a similar analysis at a second (University Hospital Basel) and a third alloSCT center (University Hospital Zürich). Our aim was to try the process of adapting the developed SMILE-ICM to other settings. Although these analyses are not yet complete and are beyond the scope of this dissertation, initial results suggest considerable differences in practice patterns and organizational structures, while patients' perspectives are predominantly similar.

Such variability in alloSCT centers practice patterns is also described in the literature.<sup>37, 38</sup> For example, the longitudinal, observational multicenter studies by the US Center for International Blood and Marrow Transplant Research (CIBMTR), described that variations are particularly common regarding patient selection, transplantation regimens, supportive care practices, and the management of post-transplant complications.<sup>37, 39</sup> In addition, infrastructure and care delivery models, which have been shown to influence one-year survival, differ substantially between centers. For example, high-volume STC centers ( $\geq 40$  alloSCTs/year) had an 8% higher 1-year survival compared to lower-volume centers. Additionally, the attendance of physicians answering after-hours calls and a higher physician-per-patient ratio<sup>38</sup>, or an implemented interdisciplinary survivorship program dedicated to alloSCT recipients has been found to positively impact 1-year survival across US centers.<sup>37</sup> I.e., the delivery of optimal care leads to improved clinical outcomes.<sup>37, 38</sup> Or, put differently, patient outcomes have improved in line with how effectively centers manage their follow-up care.

However, most alloSCT centers still organize follow-up care reactively—acting only when patients arrive at their clinics with complications. Considering the high cost of acute treatment versus those of on-going preventive measures such as e.g. supporting patients in recognizing health deterioration early and acting accordingly<sup>40</sup>, there is a clear need to re-engineer care processes towards proactive chronic illness management. This principle was recently confirmed when a US matched comparison study found that costs declined by \$781.29 per quarter and patient (estimated \$19 million savings per year in the participating hospitals) after an integrated care model was implemented for geriatric cancer patients. This ICM's aim was to identify patients' needs early, coordinate and connect their service delivery and support them to take a more active role in their own health care.<sup>41</sup>

### *Implications for future research, practice and policy*

Within the meso-level service delivery element, we advise future intervention researchers and developers when planning to conduct a contextual analysis to carefully

define which contextual factors are essential and should be assessed. As our results indicates that patient preferences differ much less between centers than context-related practice patterns. Assuming this is so, future contextual analyses might be performed much more quickly by focusing at the most essential factors.

Further, researchers might consider incorporating interdisciplinary collaboration across health- and social care sectors as a core element of any new ICM. Reflecting on macro-level conditions, the existing evidence and our findings highlight the need to pool alloSCT competencies at high-volume centers while re-engineering follow-up care towards interdisciplinary approaches at the national level. To date, no policies either regulate alloSCT centers' minimal volume requirements or specify standards regarding the implementation of dedicated interdisciplinary survivorship programs. In addition to hindering broader service delivery at a national level, this regulatory gap impedes the use of such programs, as no reimbursement systems have yet been implemented and market regulations are not easily understandable (see also the *financing* and *technologies & medical products* section).<sup>42</sup>

Therefore, we encourage politicians to reflect on payment systems that do not put providers at risk for treating multi-morbid individuals. For organizations to commit sustainably to integrated care provision, they require a basic level of financial security. This will also depend on the evidence base provided by projects, such as our SMILe project, providing a health economics evaluation which will influence future policy decisions.

### 7.2.4 Leadership and governance

At the micro level, prioritization and individual care planning should occur throughout the process of shared decision making between care providers, patient and their caregivers. At the organizational (meso) level, in cases where the institutional culture includes a shared vision and values, leadership support can help tremendously to ensure ICMs' adoption. This should also be reflected at the political (macro) level, where committed officials can both promote and fund interdisciplinary inter-organizational and collaborative care.<sup>1</sup>

For multi-morbid patients, various problems frequently occur simultaneously; therefore prioritization and individual care planning is very important. While the SMILe-ICM offers comprehensive support in prioritization and individual care planning during the first year post-alloSCT, some patients will need ongoing support beyond this time. As transplant center follow-up appointments become less frequent and care is incrementally transferred to local non-transplant physicians, these patients require particular consideration.

#### *Continuity of care beyond transplant centers*

Although published guidelines and recommendations for alloSCT follow-up care exist, clinicians not familiar with transplantation procedures are likely to be unfamiliar with these

recommendations or simply to lack confidence in treating such complex patients.<sup>28, 43</sup> As these patients transition from alloSCT center specialist care to that of non-transplant physicians, communication and collaboration are needed to minimize uncertainties and prevent care gaps.

To realize individual long-term care planning for alloSCT patients, one useful strategy is to set up tailored survivorship plans.<sup>28</sup> To determine the preferred content, timing and format of such plans, Morken and colleagues (2019) surveyed 18 US alloSCT clinicians and 29 patients.<sup>44</sup> They found that more than 85% of clinicians and patients would prefer them to include information on received treatments, along with recommendations regarding follow-up and health maintenance, i.e., vaccinations and screening, survivor and clinician resources, GvHD and other late and/or chronic health conditions.<sup>44</sup> While 93% of the patients preferred to receive a printed version either immediately after the acute treatment phase (70%) or within the first few months post-alloSCT (67%), clinicians favored a digital solution linked to their center's electronic health record system (89%). Majorities of both patients (82%) and clinicians (61%) welcomed the idea of a survivorship care plan available on an electronic patient portal. Patients considered it suitable to regularly discuss the plan with their treating physician, and almost all (93%) would also be comfortable reviewing it with an APN.<sup>44</sup>

The current SMILe-ICM includes neither written nor electronic survivorship plans for the long-term phase beyond the first year; however, its content already reflects many elements of such plans (e.g., support for symptom management, promotion of healthy living). A full survivorship care plan, which could be provided by the end of the first year post-alloSCT (when patients' close monitoring phase ends) as part of SMILe, could be implemented in future iterations of the intervention. However, developing an additional intervention component as complex as a long-term survivorship care plan might require further contextual analysis to clearly define its content, timing and mode of delivery (paper and/or electronic) for the Swiss or German setting.

### *Comparing effective care delivery across European centers*

At the meso and macro levels, ICMs can be facilitated by supportive leadership, transparency and collaborations to realize a shared vision and commitment among an organization's physicians and nurses. Still, while international transplant experts are committed to ICMs for alloSCT recipients<sup>28, 45</sup>, this commitment is not yet reflected at the political level. Also, performance-based management is currently only benchmarked regarding 1-year survival data across alloSCT centers accredited at the Joint Accreditation Committee of the ISCT and EBMT (JACIE).<sup>46</sup> Across European centers, economic evaluations and other relevant variables such as current practice patterns are not yet monitored and compared in relation to patient outcomes.<sup>46</sup> However, centers that have implemented integrated care models and can show clear clinical and economic benefits might

be able to justify such models' existence. Hopefully, the SMILe-ICM's economic evaluation—the first alloSCT-related model to provide a solid economic case—will also help to foster a national-level system change.

### *Implications for future research and practice*

Future researchers might explore the possibility of developing and implementing survivorship care plans. Alongside supporting alloSCT recipients independently of the alloCT center after their first year-post-alloSCT, these can foster communication and collaboration with non-transplant physicians. Depending on center-specific resources, where electronic patient platforms are already available, these provide an excellent place to share and discuss such plans. Still, for others reaching out to non-transplant physicians, complete written plans might be most useful. To assess context-related preferences a new contextual analysis might be needed. For a contextual analysis to define care plans' content, timing and mode(s) of delivery, we recommend following our Basel Approach for Contextual Analysis (BANANA).<sup>47</sup> Developed based on our SMILe contextual analysis and on previous work by Stange and colleagues,<sup>48</sup> a contextual analysis should always consist of following steps (1) choice of a theoretical framework underpinning analysis of context and a setting specific theory for increased granularity; (2) use of available empirical evidence on relevant contextual information; (3) involvement of multilevel stakeholders; (4) collection and analysis of data by applying mixed methods; (5) determine contextual and setting factors' relevance for implementation strategies, outcomes and intervention co-design; (6) publication of findings of contextual analysis by using appropriate guidelines.<sup>47</sup>

To facilitate a consensus on what constitutes effective post-alloSCT care among meso- and macro-level international transplant policymakers, societies such as the EBMT could also consider benchmarking additional variables such as re-hospitalizations, costs or practice patterns. Multi-center studies on ICMs' impacts in alloSCT recipients are also needed, both to increase the current evidence base and to support policies promoting such models for this and comparable populations.

### **7.2.5 Workforce**

At the micro level, integrated care calls for teamwork across health sectors: an interdisciplinary core team embedded within a diverse network of professionals. As well as providing continuous professional education regarding self-management support techniques and communication, macro-level actors will need to adapt their organizations' workforce planning accordingly. And at the macro level, workforce development should fit societally-defined needs.<sup>1</sup>

At the level of care delivery, ICMs require interdisciplinary teams drawn not only from across departments, but from separate organizations and even health and technological sectors. Within each such team's core is a central coordinating person who serves as the patients' first point of contact.<sup>1</sup> At the meso level, this might entail the implementation of new professional roles such as those fulfilled by APNs.<sup>1</sup> This requirement was also highlighted by our contextual analysis, which showed a clear need for an integrated care approach and therefore informed the application of two implementation strategies, i.e., creating new clinical teams and revising professional roles. Within the FiB context, the APN role was already present but was oriented towards other tasks. Now re-embedded within the transplant team, the APN now connects directly to the alloSCT in- and outpatient setting, serves as the patients first point of contact, and provides continuous self-management support and care coordination.<sup>17</sup>

### *Preparing the necessary workforce*

Caring for chronically ill or multi-morbid patients requires a whole set of competencies.<sup>49</sup> Besides organizing the care around the patient, communication and collaboration skills are needed to work across services. Additionally, the quality of care needs constantly evaluated and the teams should be able monitoring their patients across time using available technology.<sup>49</sup> To fulfill these competencies highly trained nurses such as APNs are needed. In general, the pool of nurses trained and specialized to levels comparable to APNs' is still low in Germany.<sup>50</sup> Keeping pace with the rising need for health professionals who can scale complex interventions out and up while guaranteeing high-quality care will require more APN educational programs similar to that available at the Institute of Nursing Science in Basel, Switzerland.

Our analysis of the FiB context indicated that the most common strategies to support patients' self-management or to promote target health behaviors were educational/cognitive interventions.<sup>14</sup> As SMILe integrates a combination of cognitive, psychological and behavioral elements, we are aware that few of the clinicians involved have the training to effectively apply such methods.<sup>51</sup> Therefore, the implementation, along with any necessary scaling-out and -up, of the SMILe-ICM would require not only strongly-focused workforce planning (to support systemic changes while moving from a reactive to a proactive system), but also considerable political and organizational assistance to develop and offer educational programs for alloSCT survivorship care. This could be done as part of a nursing science program to prepare the APN taskforce or to develop educational programs i.e. online programs to also prepare highly trained oncology nurses working in the role of care-coordinators, where the APN workforce is still not sufficient. Hopefully, the results of the hybrid I implementation effectiveness RCT currently testing and evaluating the SMILe-ICM

will also deliver strong arguments as to why highly trained nurses are required and how delivering optimal integrated care can impact patient outcomes.

### *Implications for future practice and policy*

Ensuring the availability of highly trained and specialized nurses at the micro/workforce level will demand solid workforce planning at the organizational and national levels. Organizations interested in implementing ICMs should first take stock of their workforce resources. Early investments in the identification and promotion of engaged, interested nurses to develop their competencies will later pay off as those nurses not only implement innovative care models but deliver top-quality care. Further, it is critical to develop educational programs that prepare the APN and oncology nursing workforce to deliver integrated care that goes beyond purely medical considerations.

### **7.2.6 Financing**

Along with macro-level policies regarding coverage of and institutional reimbursement for integrated care, meso-level payment systems will need to ensure fair compensation to all involved professionals and reward interdisciplinary care.<sup>1</sup>

For interventions embedded within an ICM, coverage and reimbursement policies need to ensure equity in terms of both patient access and the involved professionals' time.<sup>1</sup> One major barrier to the sustained implementation of interventions such as the SMILe-ICM is their lack of cost-coding and reimbursement either for care coordination or for delivery of components that promote self-management or target healthy behaviors. Both Germany and Switzerland have mandatory health insurance systems; however, these only cover costs for physician-led follow-up consultations and medication<sup>52, 53</sup>, i.e., both are geared towards acute physician-led care. In Germany, financial coverage of outpatient services are currently defined by the German Uniform Evaluation Standard (EBM). The EBM is based on a mixed calculation and consecutive quarterly pays a fixed sum which potentially leads to a significant underfinancing in the alloSCT follow-up care, as recently shown in a cost analysis of two German transplant centers.<sup>54</sup> So far, less complex patients finance more complex patients, but there is no mechanism to pay nurses for providing outpatient self-management and health behavior support interventions. In order to pay for nurse-led services in outpatient settings—and, even more importantly, to support the successful transformation of care towards a proactive chronic care approach—changes to the existing reimbursement regulations are urgently needed. For example, by facilitating the sustained implementation of the SMILe—ICM, a functional remuneration system would allow the intervention team to focus on life-long

outpatient follow-up need such as survivorship care planning, self-management and behavioral support, and detection and prevention of health deterioration.

### *Facing the challenge in eHealth-facilitated ICM development*

When developing and preparing eHealth-facilitated ICMs' human/technological components for implementation, intervention designers also face major financial challenges. First it can be challenging even to classify eHealth components, as the boundaries are often blurred between creating software-based medical devices versus applications classable as wellness-promoting technology. When developing the SMILe-ICM, for example, we could not find a clear rule or guideline on how to classify our eHealth components. Consequently, we developed a fully functional eHealth components that fit our target patients' needs and preferences. When we applied for ethics approval, though, the ethics committee informed us that they would classify our eHealth components as class 1 medical device software. At this point we learned that, as soon as eHealth components combine electronic symptom monitoring with algorithm-based feedback, or use visual decision support (i.e., color-coding for the care coordinators to recognize critical changes) they would fall under the Medical Device Regulation (MDR).

This is because automatized feedback and color-coding can be interpreted as diagnostic or therapeutic tools, i.e., software classifiable as a medical device.<sup>55</sup> Additionally the MDR's authors wanted to implement new rules in May 2020. Although this update have been postponed to May 2021 due to the corona crisis, when it is enacted, it will shift former class 1 software to class 2 medical device status. In doing so, in addition to tightening its already strict requirements, the MDR will impose significant financial challenges on applicable applications' development on top of its strict regulation requirements side.<sup>56</sup> More specifically, the MDR already necessitates substantial investments of money, time and effort for developers trying to comply with all the regulatory norms—even before knowing that the components in question will achieve their hypothesized effects. When our SMILe research group faced these challenges, we decided to continue with eHealth components not classified as medical devices (i.e., no automated feedback for decision support, no color-coding for the care-coordinator). Not only did this force changes to the original intervention design, it also hindered responses to the problems, needs and preferences found in the contextual analysis.<sup>14, 17</sup>

We suspect that these limitations are extremely problematic for small academic research teams, while favoring corporate producers. However, while the MDR appears to protect patient safety, it has no apparent bearing on quality or usability. As discussed above, commercially developed eHealth components or stand-alone apps frequently lack theoretical bases: 80% are neither founded on evidence or a behavioral theory (74%) nor are co-designed alongside end users (89.7%).<sup>7, 10, 57</sup> The resulting misfits between functionalities

and users' needs and preferences lead to issues first with effectiveness, then with sustainable implementation. The most common final product might be resource and research waste.<sup>12</sup> Hence, the development of partnerships among academic research groups and private companies both, interested in effective and sustainable solutions might be needed to finance and fully unfold the potential of eHealth-facilitated ICMs (e.g. with included algorithm-based feedback).

### *Implication for policy and funders*

In the cases of Switzerland and Germany, the public health systems' above-noted lack of compensation for integrated care provided by nursing professionals hinders the adoption of innovations that both improve care outcomes and save money. However, the problems named here are by no means limited to these two countries. Every healthcare system that does not already reimburse ICM-embedded nurse-led services needs to do so.

For similar reasons, resources are urgently needed to increase not only the feasibility but the overall attractiveness of developing evidence-based, user-centered eHealth components—where the most common alternative is industrially-produced applications that bear little relation to individual patients' needs or perspectives, or that fail to incorporate effective behavioral change techniques.

Extremely useful EU-wide funding research programs do exist. For example, the Horizon 2020 program, which focuses on personalizing health and care by supporting and empowering patients, includes the use of eHealth technologies. However, the sustainable implementation of any solution, eHealth or otherwise, is a local matter. As such, it requires country-based reimbursement structures.

### **7.2.7 Technologies & medical products**

The technology and medical product element is closely linked to the information and research element. However, its adoption and sustainability depend heavily upon the development of supportive user-friendly technologies. At the micro level, examples include electronic health records, patient portals or eHealth components that monitor or support patients at home; at the meso and macro levels, they include policies promoting the development and shared use of such technologies. In addition to fostering innovative eHealth solutions, national policies should ensure equity regarding access to eHealth-facilitated ICMs (e.g., via rural internet provision).<sup>1</sup>

eHealth can act as a key facilitator for integrated care programs. For example, electronic information systems can ensure timely access to care and advisory services and facilitate shared understanding of data significant at levels ranging from individual patients to entire populations.<sup>20</sup> Electronic Medical records allow exchanges between professionals and

can be linked to patient portals. Likewise, the integration of electronic patient reporting of medical, symptom-related or behavioral outcomes (i.e., ePROs) can reveal valuable information to understand treatments' consequences, support needs, safety or effectiveness. They also provide a fuller view of patients' experience and well-being outside of formal care environments. This is especially true regarding symptoms, which clinicians frequently underestimate, leading to inadequate support and avoidable distress.<sup>58, 59</sup>

With the development of the SMILe-ICM, we were the first to create an evidence-based, theory-guided and user-friendly integrated model of care using eHealth as one mode of delivery to support the needs of alloSCT patients. By offering the option of remote monitoring and evaluation of important ePROs as part of the SMILe-ICM, this fosters early identification of health deterioration and tailored self-management support. For the moment, however, the SMILe technology is not connected to the local electronic medical record systems, as the care coordinator needs to use the SMILeCare web-application to view incoming patient data. To fully realize ePROs' potential, the addition of a digital interface that “communicates” with existing medical record systems would be a logical development. Although we initially planned to integrate the SMILe technology into the electronic medical record, this proved unfeasible: fulfilling this plan's regulatory requirements would have delayed the implementation considerably while adding a heavy financial burden for a tool whose effectiveness has not yet been tested (see also financing).

### *EHealth as part of integrated care models*

Nevertheless, the SMILe-ICM is far more than an eHealth solution: its technological component facilitates integrated care but is not meant to replace clinician-patient encounters. In fact, one common shortcoming of recent studies on eHealth-facilitated ICMs is that their authors tend to focus closely on their e-components' development processes, then give nebulous accounts of their integration into care processes or the re-structuring of care they necessitate.

The current literature includes reports on two basic classes of eHealth component: those developed by academic development teams interested in research, and those developed commercially. Both tend to focus on eHealth solutions' effectiveness within clinical trials, which is a poor predictor of uptake, adoption or use in real-world conditions.

Further, the concept of conception-to-implementation reporting is quite new. For example, one major eHealth landmark is the electronic Symptom Management using Advanced Symptom Management System Remote Technology (eSMART) project, a massive academic-led project that developed and tested the Advanced Symptom Management System (ASyMS) in patients with breast, colorectal, lung, or hematological cancers receiving chemotherapy.<sup>60-65</sup> While several publications dealt with the ASyMS technology's evaluation and adaption<sup>61, 62, 65, 66</sup>, we could find nothing on content

development, how the system was integrated into care processes, its underlying behavioral theory or its end users' involvement during development.

The ASyMS was implemented and tested within 13 centers across Europe.<sup>67</sup> While the authors described a number of context-specific adaptations (e.g., language, technical infrastructure) and updated their self-care information based on a systematic review of the latest evidence base.<sup>68</sup> Its first feasibility study, involving 64 patients from 11 centers, showed promising results in terms of technology acceptance and adoption from the patients' point of view. However, the original sample had included 13 centers. The remaining two could not implement the intervention due to resource shortages and misfits with their workflow.<sup>67</sup> While no final publications are yet available regarding the ASyMS's long-term results, we suspect that few, if any, of the centers that implemented the system will continue using it after the study's completion.

This misgiving has no bearing on the project's research, which was exemplary. Instead, recent implementation science research findings<sup>12</sup> suggest that, while the eSMART research team devoted copious resources to ASyMS's eHealth components, the chances of sustainable implementation are greatly improved by context-adapted re-engineering of care processes. If any centers do retain it, its success will rely largely on their ability to adapt it to their individual contexts. In our opinion, only a contextually-adapted approach can fully unfold the potential of an eHealth-facilitated ICM.

Commercially developed eHealth components for patients with cancer such as KAIKU©, NOONA© or CANKADO ©, also frequently report on their effectiveness testing only, but give neither information on the evidence-base of the content, the development process nor the theory behind or how these applications will be embedded within care models.<sup>7, 69, 70</sup> Consequently, so far most existing eHealth solutions, either stand alone or embedded interventions frequently function as black-boxes regarding development, content or mechanisms underpinning their target behavioral changes.

This has also been described in the literature, where a critical review of 23 eHealth applications for patients with cancer found that in general no theoretical basis was present: only six of the 23 studies mentioned the use of theories or behavior change models<sup>10</sup>. Of the other available applications, fewer than 20% referred to empirical studies or background source information; only 11.3% are evidence-based; and just under 10.3% involved clinicians in their development processes.<sup>57, 71, 72</sup> While many report user-centered design approaches, few support such claims with insights into end-user involvement or context-specific adaptations. This might result from a strong focus on technology development, with less attention to theoretical underpinnings, although the latter could shorten the path to implementation. In addition, while many applications pay some attention to context-specific requirements, the broader perspective—i.e. re-engineering entire care teams and

processes—is missing entirely. We believe the sum of the arguments hold a high risk for implementation failure and resource/research waste.

### *Implications for future research, practice and policy*

We believe that the combined use of implementation science, behavioral science and computer science methods as we applied to develop the SMILe-ICM, is crucial to sustainably implement eHealth-facilitated interventions when moving from the trial to real-world settings. So far, there are no policy regulation on how eHealth should be embedded within integrated care models or how eHealth components should be developed (i.e. context-adapted, theory-guided, user-centered). Thus, international guidelines and nationwide policies are needed that foster eHealth integration into ICMs giving clear guidance on how development processes should be done. We hope that our used methodologies within the SMILe project can serve as a road map for future researchers to develop such guidelines for the research community and also for policy regulations in terms of technologies and medical product development.

### **7.2.8 Information & research**

Within the micro level, individual level data can effectively be used in care processes for e.g. risk prediction or stratification. Innovative research methods are needed to show potential benefits of such methods. This should be embedded within solid data protection agreements across involved professionals and organizations. The macro level should give clear guidance in terms of privacy and data protection regulations and should not challenge research in this field with lacking transparency.<sup>1</sup>

At the micro-level, information and research refers to the effective use of the created individual data.<sup>1</sup> Besides facilitating a shared understanding of symptom experience or other complications, the ePROs collected via the SMILe technology help to detect and manage health deterioration early, and promote patient self-management and empowerment of individuals in this regards. The SMILeApp collects a daily set of important medical, symptom-related and behavioral parameters at the patients' home and transfers them to the transplant centers. A system such as the SMILe technology can therefore help to 'triage' patients. Indeed, while some patient develop very few complications, others experience multiple symptoms and complications that are severe and distressing. Hence, the SMILe technology helps to identify patients with more severe symptoms, complications or problematic behaviors allowing to align resources to patients needing it the most.

Any data collected can also be used for future purposes that will benefit clinical care and research—by increasing clinicians' understanding of symptom trajectories or clusters, for instance, or by supporting machine learning techniques towards individual risk

prediction.<sup>73</sup> These, in turn, will help implement pro-active symptom management, thereby helping to prevent severe complications.<sup>74</sup>

Moreover, innovative research methods could rapidly build on the evidence base regarding eHealth-facilitated ICMs. Via an implementation science study design, we have already applied at least one such method:<sup>75</sup> combined with a randomized trial design, however, its use might also compromise weaknesses, as using a control group that is not exposed to changes in care content, patterns or processes can be challenging in real-world trials.

As an example, within the SMILe-ICM, the APN's interactions with the treating physicians and other team members will trigger a change in care perspectives. Close collaboration would certainly promote physicians' awareness of existing behavioral problems, persisting symptom burden and its' psychosocial aspects. This, in turn, might result in subtle but significant changes of treatment also within the control group. In such a case, despite the lack of direct exposure to the SMILe-ICM, the results could be compromised. On the one hand, this might reduce the apparent effectiveness of the program; on the other it might also help to smoothen the implementation process. Applying other designs, e.g., pre-posttest or stepped wedge that include multiple centers might help to prevent such "contaminating" effects. Our research group lacked the resources to run a multi-center stepped-wedge study. However, a pre-posttest design would have been a comparable alternative.

Regarding data protection regulations, we had very few guidance regarding the implementation and setting-up of the server infrastructure to run the eHealth components within a hospital setting. While the General Data Protection Regulation (GDPR) as the toughest privacy and security law in the world became active during the SMILe development (May 2018), gave us guidance in terms of e.g. privacy by design principles (e.g. end-to-end encryption), it does not give guidance how to implement certain aspects within clinical infrastructures (e.g. standards for server setup).

### *Implications for future research, practice and policy*

Regarding the SMILe-ICM's information and research element, we see a strong potential for innovative research methods handling big data, e.g., the machine learning approaches noted above regarding symptom management. Further, we recommend further increasing the evidence on ICMs' effectiveness, with or without eHealth facilitation, via large multicenter studies employing, e.g., stepped wedge hybrid implementation designs. And, as we discovered, the development and implementation of data protection guidelines in terms of practical implementation within health care settings might be valuable support.

### 7.2.9 Monitoring

Monitoring refers to the monitoring of the three aims of integrated care and can occur at all three levels. At the core and micro-level it refers to the monitoring of e.g. self-management tasks. At the meso-level this refers to an ongoing quality improvement system leading the optimization of processes. At the highest level it can be used to monitor the workforce-demography match.<sup>1</sup>

As illustrated in Figure 8, the last major element, which relates to all six overarching elements (see red arrow crossing the micro/meso and macro levels in figure 8) and is particularly important to inform information and research, is the monitoring of the three ICM aims: 1) improving the health of a given population; 2) improving patient experience, and 3) reducing costs.<sup>76</sup> Monitoring can occur at all three system levels. At the core and micro level it can apply to self-management tasks or changing preferences. At the meso level, one example is an ongoing quality improvement system to optimize processes. And at the macro level, based on regional or national data on the prevalence and incidence of multi-morbidity, it can help researchers focus on how well the available workforce matches relevant demographic needs.<sup>1</sup>

SMILe currently only incorporates monitoring elements at the core, micro and the meso level. As within SMILe the effectiveness implementation process is being assessed in terms of the three aims of integrated care. Furthermore, our draft logic model could potentially serve to monitor the ICM itself, while helping detect gaps in theory.<sup>77, 78</sup> More specifically, Rohwer and colleagues stated that logic models can help conceptualize and manage complexity in three ways: 1) describing the core characteristics of the intervention(s) and its/their relationships/connections with outcomes; 2) illuminating underlying theories of change, while providing information about influential contextual factors; and 3) presenting assumptions about causal pathways relevant to the intervention's potential impacts on outcomes.<sup>79</sup> In situations such as this, logic models facilitate clear, transparent, and potentially comprehensive communication between the research team and potential stakeholders regarding intervention effects. According to Fielden and colleagues, logic model development should be iterative and flexible, with regular review and revision based on first insights of an intervention's interactions and effects.<sup>80</sup> Thus, logic modelling changes through the project planning, implementation and evaluation phases. A final model can only be constructed after completion of the evaluation phase.<sup>81</sup>

During the SMILe-ICM's planning phase, the research team developed a first draft of a logic model, which we will review after the completion of the first implementation and testing phase at the first participating center (FiB). However, in light of the great variety of contextual factors potentially influencing the intervention and the implementation processes, we must acknowledge that the logic model's linearity might present over-simplification both of the

operative change mechanisms and of the intervention characteristics' interactions with outcomes. It is a well-known limitation of logic models is their assumption that elements only interact with each other linearly—especially as most systems are dynamic and have complex interrelationships.<sup>82</sup> Therefore, methods grounded in systems, such as causal loop diagrams, might be more adequate to plan, implement, monitor and evaluate complex interventions such as the SMILe-ICM. Such methods will be considered during the first logic-model revision.<sup>82</sup>

However, at the macro level, the idea of a workforce-demography match seems promising; however, choices may be limited, as European countries are already facing serious shortages of healthcare professionals. In addition, combined with the absence of regulations on an optimal nurse-to-patient ratio in oncology, the lack of instruments to determine the workforce needed will make this a challenging element to fulfill.

### 7.4 Conclusion

Incorporating eHealth into an ICM has numerous potential benefits; still, ensuring uptake and sustained use will require innovative approaches. The construction of a theory-grounded ICM using both behavioral-guided content and iterative, user-centered software development demand accurate information regarding all relevant contextual characteristics. As demonstrated with the SMILe-ICM project's combination of behavioral and computer science principles, implementation methods are indispensable to drive, inform and coordinate these methodologies. While this requires an additional time investment at the beginning of a project, that investment will pay off later, in the smooth fitting of purpose-engineered, contextually-tailored intervention components to re-designed care models.

While pre-packaged eHealth solutions can be added to existing care processes, their users commonly experience implementation issues, i.e., successful adoption and sustainability are rare. In truth, for the issues involved, there are no simple solutions. To make the necessary changes, future project teams will need to reflect both on how to re-design their entire care models and on where it is possible to use eHealth as a mode of delivery. And as every context is unique, each project needs to start with a thorough contextual analysis. However, the current evidence indicates that patient preferences differ much less between centers than context-related practice patterns. Assuming this is so, future contextual analyses might be performed much more quickly, conserving more resources to adapt the intervention to the target context.

Using guiding frameworks as the recently developed SELFIE can help to operationalize and structure ICMs and provide a more comprehensive understanding of relevant elements of integrated care for multi-morbid patient populations such as alloSCT. While using the eCCM as guiding model to build the SMILe-ICM, we already developed a

rather comprehensive ICM but with a weaker focus at the macro level perspective. By reflecting in light of the SELFIE framework we showed that SMILe already integrates the most important elements. Main areas for future implications at the research, clinical, and policy dimension can be found at the macro level. Especially the elements leadership & governance, workforce and financing could profit from future reflections in terms of i.e. pooling and regulating alloSCT centers' minimal volume requirements, specifying standards regarding dedicated interdisciplinary survivorship programs; the importance of the workforce preparation; and lastly, maybe most importantly, the implementation of reimbursement systems for delivering integrated care. In terms of eHealth component development, market regulations and standards are needed how to develop evidence-based, theory-guided and user-centered components, incorporating effective behavioral change techniques. Finally, to further increase the evidence on ICMs' effectiveness, with or without eHealth facilitation, large multicenter studies are needed.

Therefore, this dissertation's scientific contribution is both clinical and methodological. That is, the SMILe-ICM is expected to improve alloSCT patients' biopsychosocial outcomes while providing guidance on the used methodologies. Implementation science methods—in this case, the use of a contextual analysis to inform the co-development of behavioral theory-based content, combined with the use of computer science methods—can be used as blueprints for other projects to develop, scale up or scale out eHealth-facilitated-ICMs.

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