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by

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DIGITAL HEALTH TO ENHANCE ADJUVANT ENDOCRINE THERAPY ADHERENCE IN BREAST CANCER

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Abstract

Introduction

Despite the availability of many effective adjuvant endocrine therapies (AET), which reduce the risk of breast cancer (BC) recurrence during the post-acute treatment phase, non-adherence is continuously reported (31%-73%). Most effective medication adherence-enhancing interventions (MAEI) did not lead to large improvements in adherence or clinical outcomes as they fail to identify the dynamic behaviour of medication adherence. Often MAEIs were created without the end-user's involvement and/ or theory-based frameworks. Using Patient-provider involvement and interprofessional concepts to manage medication adherence is key in research and implementation of MAEI into the healthcare setting. Therefore, the overall aim of the present thesis was to use a patient-provider involvement approach and a theory-based framework to develop a digital MAEI for AET in BCS and test its feasibility.

Method

The presented research used a scoping review to identify current MAEI and to synthesize their effectiveness. After, a contextual analysis of AET use in BC survivors was conducted to analyse current digital health usability patterns and level of acceptance towards a digital MAEI supporting AET in BCS and HCP. A theory-driven framework (Behaviour change wheel) then defined the problem of AET adherence in behavioural terms, identified intervention options and determined content and implementation options. Finally, a digital MAEI was constructed based on the previous studies' results a digital MAEI and its feasibility was explored.

Results

BC survivors claimed increased support from healthcare professionals. MAEIs' components change over time depending on the adherence phase of the adjuvant endocrine therapy. MAEI during initiation should envisage AET beliefs and habit creation. During implementation, MAEI intervention should focus on side-effect coping strategies and patient-healthcare provider

interaction. BC survivors and healthcare providers would accept to use of a digital MAEI for AET. Preferences were multifaceted digital MAEI; AET management (e.g. adherence and side-effects), medical information, social support network, and interaction with a healthcare provider. Specific behaviour change techniques tackling these needs are Prompts/cues, pharmacological and social support, instructions, goal setting feedback and habit formation. Thus using the contextual analysis and the behaviour change wheel constituted to the development of a real-time digital MAEI for BCS taking AET.

Discussion/Conclusion

Digital interventions may be a game changer for medication adherence as they offer new ways of measuring adherence, collecting patient-reported outcomes and experiences, and providing intervention directly in the patient ecosystem, thus limiting patient burden. Another beneficial aspect of digital medication adherence technology is the 'timing'. Digital medication adherence technologies have the potential to intervene in the moment of need providing the intervention of need. Future MAEI research projects need to follow implementation research principles and involve the system level. Luxembourg specifically needs to raise medication adherence awareness across all levels, implement accessible medication adherence assessment databases, restructure the follow-up care for BC survivors and encourage an interprofessional healthcare ecosystem.

Acknowledgement

First, I would like to express sincere thanks to my PhD supervisors, Dr Guy Fagherazzi, Prof Laetitia Huiart and Dr Bernard Vrijens for their valuable guidance and support during the previous four years. Their dedication to medication adherence and digital research is inspiring and I am very grateful to have been mentored by you. Thank you Prof Iris Behrmann for having been a constructive CET member.

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Abbreviations

AET - Adjuvant endocrine therapy

BC - Breast cancer

BCN - Breast cancer nurse

BCS - Breast cancer survivors

BCT - Behaviour change techniques

BMQ - Beliefs of medicines questionnaire

CHEM - Centre Hospitalier Emile Mayrisch

CHL - Centre Hospitalier du Luxembourg

CI - Confidence intervals

CRN - Clinical research nurse

GP - General practitioner

HCP - Healthcare providers

ICF - Informed consent form

MA - Medication adherence

MAEI - Medication-adherence enhancing interventions

MATech - Medication adherence technology

MEMS - Medication Event Monitoring System

MNA - Medication non-adherence

MPR - Medication Possession Ratio

OAC - Oral agents in cancer

OR - Odds ratio

PDC- Proportion of days covered

RCT - Randomized controlled trial

SD - Standard deviation

SE - Side-effects

uMARS -User mobile application rating scale

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Chapter 1

Introduction to oral medication adherence

1.1 Medication adherence to long-term treatments

Patients with chronic conditions such as cancer, diabetes, cardiovascular diseases or respiratory diseases, are living longer than ever (United Nations, 2015). The rise of chronic diseases requires a multidisciplinary response, which often involves lifestyle changes and lifetime medication use.

Despite the availability of many effective drugs, the literature shows that 30 to 50% of patients do not take their medications as prescribed (van Dulmen et al., 2007; World Health Organization, 2003). In a systematic review, by Walsh et al medication non-adherence was associated with a higher risk of all-cause hospitalization and mortality (Walsh et al., 2019). For instance, they demonstrated that medication non-adherence has a significant negative association with a range of health outcomes (e.g. mortality and hospitalization).

Despite extensive efforts in pharmacology research and pharmacovigilance based on patient-focused drug development, long-term treatment, on the one hand, encounters various challenges related to adhering to medication/drugs (e.g. personal, cognitive, psychological, organizational, social, economical and cultural factors, more information in section 1.1.2) (Kardas et al., 2013; Sabaté, 2003). On the other hand, long-term treatment has a significant impact on the monetary healthcare system resources. In the European Union, medication non-adherence is associated with €80-125 billion of potentially preventable direct (e.g. hospitalizations, waste of medication) and indirect (e.g. work productivity losses) costs (European Commission/Medi-Voice, 2011). Khan et al highlight that increased morbidity, mortality and healthcare costs due to medication non-adherence are preventable (Khan & Socha-Dietrich, 2018). Therefore, preventing non-adherence as well as understanding patients' perspectives, beliefs and reasons for not adhering to treatment are crucial in the development of interventions to enhance medication adherence at the healthcare system level, the healthcare provider level and the patient level.

Even though the literature raised the striking non-adherence problem worldwide, medication adherence remains a major overlooked public health problem urgently in need of multidisciplinary action (Zullig et al., 2018). Thus, understanding the complex and dynamic behaviour of medication

adherence, promoting effective self-management and offering medication adherence-enhancing interventions (MAEI) will improve clinical outcomes, patient autonomy and quality of life.

Before diving further into how medication adherence is a public health burden to chronic diseases worldwide, let's elaborate on what medication adherence is (history, terminology and guidelines), what its determinants are and how we can measure it.

1.1.1 History, terminology and guidelines

The history of medication adherence dates back to 400 BC when Hippocrates was the first to recognize that patients did not take their medication as recommended (Vrijens et al., 2012a). In 1882, Robert Koch specified that patients not complying with their medication are "careless consumptives, and/or irresponsible" (Lerner, 1997). Medication nonadherence awareness was raised in 1985 by US Surgeon General C. Everett Koop stating "Drugs don't work in patients who don't take them" (Osterberg & Blaschke, 2005). Hence, medication non-adherence is a long-recognized public health concern with increased interest in the last four decades (Dunbar-Jacob & Mortimer-Stephens, 2001; van Boven et al., 2021).

'Compliance', 'concordance' and 'adherence' are terms used in relation to the complex behaviour of medicine-taking. These words have frequently been used interchangeably, generating confusion (De las Cuevas, 2011a; Horne et al., 2005). Nevertheless, each term has a different meaning and highlights different patient-physician relationships (De las Cuevas, 2011b; Vrijens et al., 2012a).

During the early years of medication adherence research, the role of the patient's view on the topic was ignored. 'Compliance', has been identified as the extent to which patients follow doctors' treatment prescriptions (Hayne 1979), leaving a negative undertone that patients are subservient to their doctors (Hughes, 2004; Vrijens et al., 2012a). 'Concordance' on the contrary refers to the support given in decision-making partnerships and the medicine-taking process but has been misused as a synonym for 'compliance' (De las Cuevas, 2011b) (Vrijens et al., 2012a). In 2003, the World Health Organization defined 'adherence' as *"the extent to which a person's behaviour (taking medicine) corresponds with agreed recommendations from a healthcare provider" (World*

Health Organization, 2003). To date ‘adherence’ is preferentially used as it promotes patient-prescriber partnership (Nieuwlaat et al., 2014; “Terminology Used in Medication Adherence Research Must Reflect Current Models of Health Care,” 2009; Vrijens et al., 2012b). Hence, the present thesis will use, hereafter, the term ‘medication adherence’ to describe medication-taking behaviour.

Even though ’adherence’ is the preferred term, literature raised uncertainty as to what it entailed. Following this unclarity, 40 international experts in medication adherence got together as part of the Ascertaining Barriers to Compliance (ABC), to develop a consistent, transparent and common taxonomy to describe ‘adherence’ (Vrijens et al., 2012c). The taxonomy describes on the one hand the process of medication adherence and on the other hand the process of medication management (Figure 1.1).

Medication adherence, as described by the ABC taxonomy, is ‘the process by which the patient takes their medication as prescribed’. Furthermore, this process is divided into three phases of medication adherence: initiation, implementation and discontinuation. After the first prescription of treatment, the process starts with initiation, where the patient takes the first dose of treatment. Next, the dosing regimen is implemented, and the patient's actual dosing matches the prescribed dosing regimen from the first to the last dose. In case of discontinuation of therapy, the patient stops taking the prescribed medication. Therefore persistence is defined as the length of time between initiation and discontinuation of therapy.

The process of medication management is applicable in all three phases of medication adherence and relies on monitoring/measurement and support/intervention. Several stakeholders together with the patient himself can take part in this process, such as the healthcare systems, healthcare providers and the patient's social environment/network.

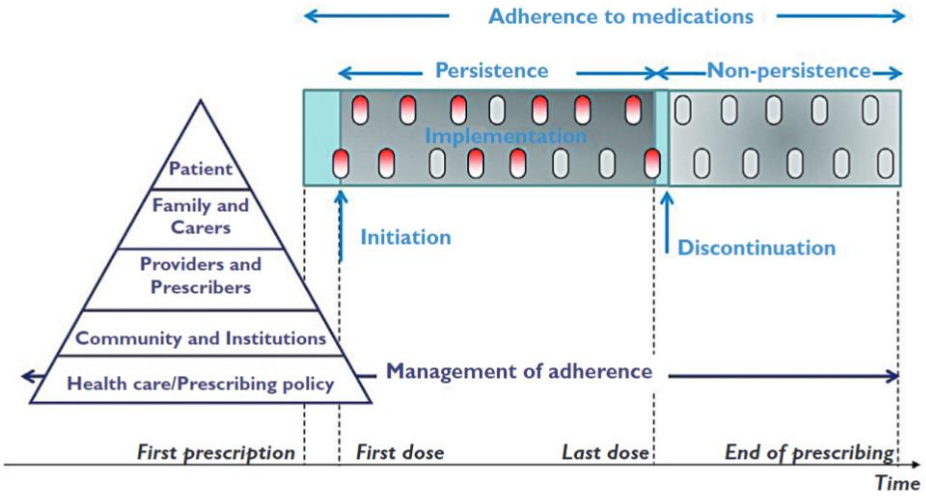

Figure 1.1: ABC taxonomy: the process of adherence to medication (light blue) and the process of management (dark blue). Source: (Vrijens et al., 2012a, 2016)

Even though the ABC taxonomy marked an important step in the standardization and development of both clinical research and medical practice, huge variability in methodology use and incomplete reporting of medication adherence research (e.g. inconsistent definitions, inadequate measurement of adherence outcomes) remained. Thus the ESPACOMP Medication Adherence Reporting Guideline (EMERGE) were developed to improve transparency and detail of medication adherence reporting by synthesising findings across studies (De Geest et al., 2018). EMERGE includes four minimum reporting criteria: (1) phases of medication adherence; (2) operational definition for each phase(s); (2) measurement of each phase(s); (3) results for each phase.

Lately, the Timelines-Events-Objectives-Sources (TEOS) framework was released, providing a methodological consideration on estimating medication adherence from various assessment tools (e.g self-report, electronic monitoring, electronic healthcare databases) (Dima et al., 2022).

Thus using the above-mentioned medication adherence guidelines will improve the quality, reproducibility and comparability of the medication adherence study methodology hence the results.

1.1.2 Medication adherence determinants

The literature shows limited evidence of effective medication adherence behaviour change and improvement of its related outcomes. This observation is due to a limited understanding of medication adherence determinants and their interplay. The notion that patients are completely responsible for taking their treatment regimens is misleading and frequently stems from an ignorance of the various factors that influence people's behaviour and ability to follow their treatment regimens (Sabaté, 2003). It is crucial to understand the dynamic and complex nature of medication-taking behaviour and its influence by determinants, which may evolve over time and across pathologies.

The World Health Organization (WHO) recommends classifying the multifaceted determinants of medication adherence into five multi-levelled dimensions: patient-related factors, condition-related factors, therapy-related factors, healthcare team/system-related factors and socio-economic factors (Sabaté, 2003). In 2013, Kardas et al. identified over 700 determinants (Kardas et al., 2013). Figure 1.2 illustrates the five dimensions of adherence, and examples of specific determinants found for each dimension (Some determinants can be classified within two dimensions (e.g. patients & treatment, treatment & healthcare system)). Figure 1.2 is adapted from both sources the WHO and Kardas et al.

Some determinants are disease-specific (e.g shame and stigma in human immunodeficiency virus) while most are present across diseases. Hence certain intervention components such as support have a positive impact across diseases whereas other components only work in specific diseases (e.g incentives in developing countries) or settings (e.g access to care).

In addition, determinants can be either barriers (e.g. side-effects) or facilitators (e.g accessibility) to medication intake and adherence. Besides, a large number of determinants can be modified (e.g. patient's beliefs) whereas some others are unmodifiable and represent risk factors (e.g. age). Moreover, patient-level determinants can be classified as intentional or unintentional (Wroe, 2002). The former describes a patient who deliberately decides not to take the treatment whereas

unintentional non-adherence assumes that the patient is forgetful. For the majority of patients, both coexist and the boundary between the two categories is porous (Gadkari & McHorney, 2012).

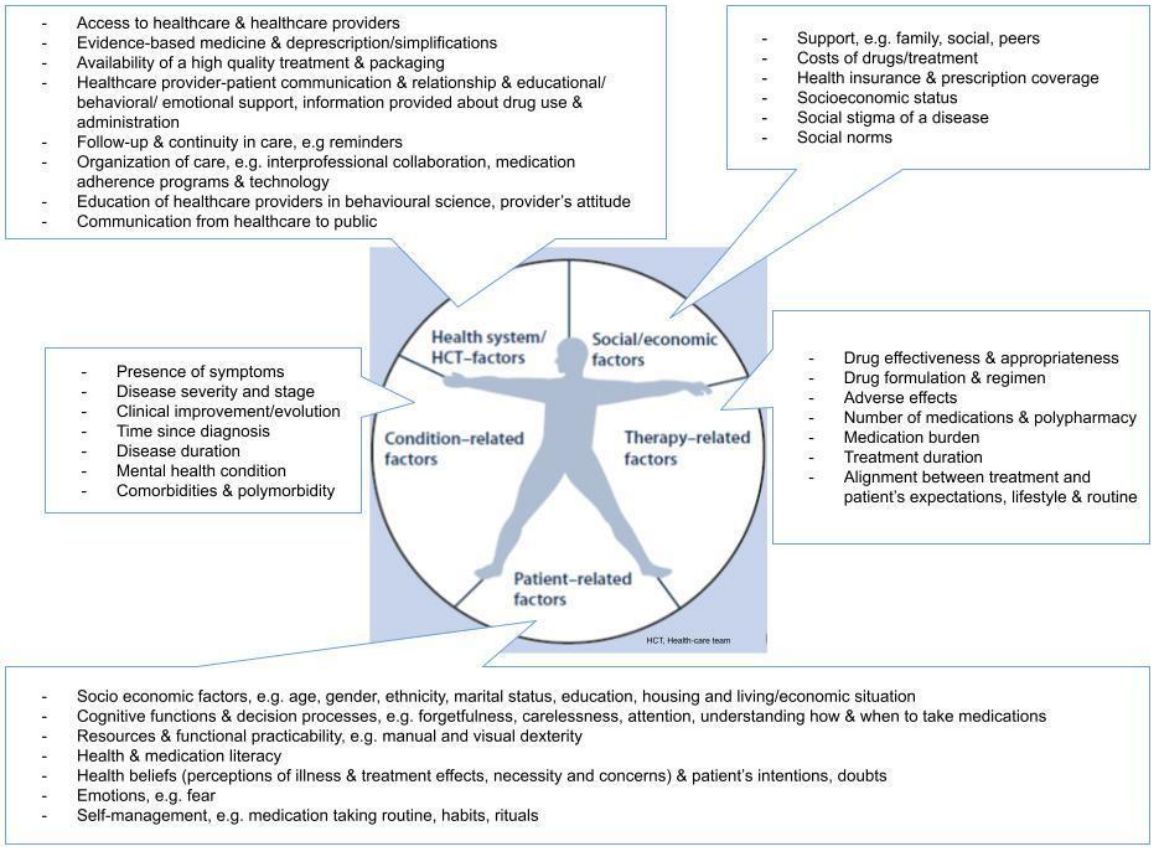

Figure 1.2: Five dimensions of adherence and its determinants (non-exhaustive list) adapted from (Kardas et al., 2013; World Health Organization, 2003). Source: Goetzinger, Schneider 2023; Drug Utilization Research - Chapter 3.5.5 Interventions to improve medication adherence

In the past, non-adherence was perceived as the sole responsibility of the patient, neglecting the role of the healthcare providers and healthcare systems. Thus patient-, condition- and therapy-related factors are the most acknowledged and commonly studied determinants compared to socioeconomic and healthcare system factors, which are less studied. However, evidence shows that healthcare systems have an influential effect on determinants impacting medication intake

hence adherence. For example, poor access to healthcare and medicines, frequent changes in prescriptions, unclear information about drug administration and side-effects, as well as poor follow-up, and poor provider-patient communication and relationship may negatively influence patients' medication intake and adherence.

Lastly, the determinants for non-adherence differ among the three stages of medication adherence (initiation, implementation, and discontinuation) (Vrijens et al., 2012c). Medication non-adherence comprises non-initiation of treatment, suboptimal implementation of the regimen, and/or early discontinuation of treatment. Therefore it is crucial to understand which determinants influence the initiation, implementation and/or persistence. In their review, Kardas et al. highlighted that most of the adherence determinants they retrieved were linked to the phase of implementation followed by persistence and a few were associated with the initiation phase (Kardas et al., 2013).

Future research should consider the three different phases (initiation, implementation and long-term persistence) when studying which determinants are relevant to improve medication adherence. As shown above, non-adherence is hard to predict among patients and thus needs to be measured.

1.1.3 Measuring medication adherence

A systematic review by Walsh et al. has established a significant association between medication non-adherence and adverse health outcomes (Walsh et al., 2019). Thus measuring medication non-adherence for optimal health outcomes is crucial, but its assessment remains challenging (Whalley Buono et al., 2017). Figure 1.3 illustrates the journey of a patient taking a treatment during a defined period of time. Non-adherence to medications can include late initiation or non-initiation of the prescribed treatment, suboptimal execution of the dosing regimen, early discontinuation of the treatment, or a combination of those three elements (Blaschke et al., 2012; Vrijens & Heidbuchel, 2015). Assessing medication adherence can be approached through objective/direct and or subjective/indirect means (Osterberg & Blaschke, 2005; Whalley Buono et al., 2017; Wroe,

2002). The former entails measuring drug concentration in the body fluid (e.g. blood, urine) whereas the latter incorporates self-reported questionnaires for instance.

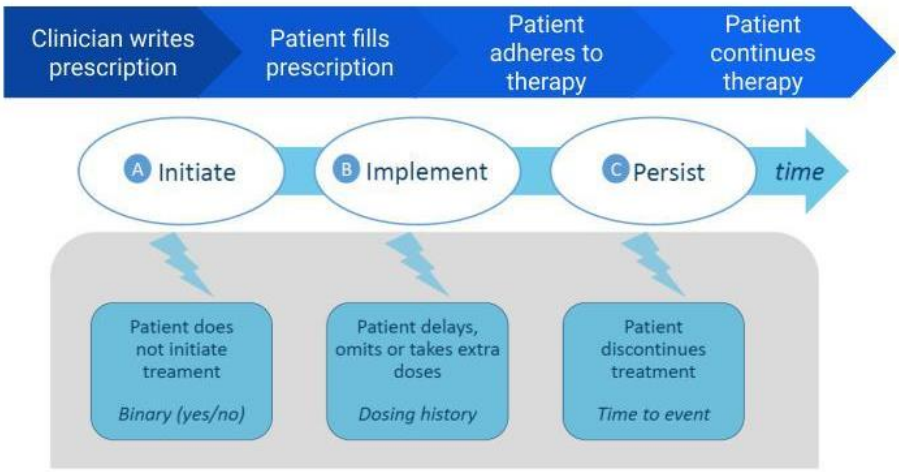

Figure 1.3: How to measure adherence using the ABC taxonomy adapted by (Vrijens et al., 2012c)

Table 1.1 shows a list of different medication adherence assessment tools and their source of bias. Direct measures might be the most objective assessment tools but these methods can burden the patient's quality of life, are time-consuming and very costly (Osterberg & Blaschke, 2005; Williams et al., 2013). All the other medication assessment tools highlighted in table 1.1 are indirect measures and subject to assumptions that need to be drawn (Elseviers & Vrijens, 2016; Garfield et al., 2011; Grégoire & Moisan, 2016; Horne et al., 2005).

Administrative data, incorporating prescription and dispensing data, are retrieved from available longitudinal databases such as medical records, pharmacy claims data or health programs (Grégoire & Moisan, 2016; Ogdie et al., 2012). Assumptions must be made using prescription data (the prescription is filled the same day it is issued, patients fill all prescribed renewals, and the drug is taken according to the prescribed dosage regimen) and dispensing data (drugs in a patient's possession will be taken, that such drugs are still being prescribed, the patient is still on treatment with all the drugs). Furthermore, dispensing data is sensible to reimbursement rules, as those that are not reimbursed may not appear in the database. Thus both prescription and dispensing data

have their advantages (objective and easy to obtain), but they do not represent the actual ingestion of medication. In addition, they require a closed pharmacy system (Osterberg & Blaschke, 2005).

Self-reported questionnaires are the most popular assessment tools as they are cost-effective and easy to administer. To date, a large number (up to 58) of self-reported questionnaires exist (Dobbels et al., 2010; Garfield et al., 2011; Nguyen et al., 2014). Estimates on medication adherence resulting from such self-reported questionnaires need to be considered cautiously as they are susceptible to error and recall bias (Garfield et al., 2011; Glintborg et al., 2007; Osterberg & Blaschke, 2005; S. R. Smith et al., 2007). Most of these are used to assess implementation, followed by discontinuation and rarely initiation. Dichotomous answers or Likert scales are used in these self-reported questionnaires.

Pill count counts were one of the first methods used to assess medication adherence by counting the remaining pills after a period of suspected medication intake (Grégoire & Moisan, 2016). This assessment tool shows only aggregated consumption. Pill counts are subject to overestimation of adherence due to upward bias (Osterberg & Blaschke, 2005).

Literature reveals that electronic monitoring has the biggest potential to estimate medication adherence accurately but its use in clinical practice remains limited. Electronic monitoring or Medication event monitoring systems (MEMS) is a medication adherence assessment tool using electronics that are incorporated into packaging that records events that are proxies for medication taking (e.g. package opening) (Elseviers & Vrijens, 2016; Vrijens et al., 2012c; Whalley Buono et al., 2017). Even though electronic detection of package entry and actual medication intake is an indirect measure, it has been considered the most reliable assessment tool as it accounts for the complex nature of medication adherence behaviour (Demonceau et al., 2013; Osterberg & Blaschke, 2005; Vrijens et al., 2005, 2012c). MEMS are available for multiple drug administration routes and come in digital pill bottles, or blisters for oral medication, digital inhalers or spacers for inhaled medication and digital injection pens or needle containers for the injectable medication (Chan et al., 2022; Checchi et al., 2014). To date, electronic monitoring devices are still very expensive and lack reimbursement and implementation into clinical practice.

Table 1.1: List of different adherence assessment tools and their source of bias. Adapted from (Elseviers & Vrijens, 2016; Vrijens & Heidbuchel, 2015)

	Initiation	**Implementation**	**Persistence**
Prescription and refill databases	Gold Standard	Only aggregated summary	Gold Standard
Electronic monitoring	Gold standard (clinical trials)	Gold standard	Gold standard (clinical trials)
Direct determination in body fluid	Requires sampling after prescription	Sampling is too sparse	Subject to white coat adherence
Self-report	Desirability bias	Recall bias	Desirability bias
Pill count	Easily censored by patients	Only aggregate summary	Easily censored by patients

Next to the different data sources that can be used to assess medication adherence there are also various parameters to estimate medication adherence from those data sources. For long-time literature reported medication adherence using thresholds/cutoff points. The most used threshold is 80% (≥ 80% is good adherence and < 80% is poor adherence). As demonstrated in Figure 4, using the 80% threshold a lot of important information on medication adherence intake behaviour is missed. Even though there still is no consensus on what the gold standard is for reporting medication adherence, the proportion of days covered (PDC) and medication possession ratio

(MPR) are more accurate and reliable estimates compared to specific thresholds/cut-off points (Allemann et al., 2019).

Figure 1.4 shows how electronic monitoring tools (e.g MEMS) are capable of capturing the dynamic process of medication adherence. If the 80% threshold would be used both patients would be classified as having 80% adherence. The vertical bars represent a missed dose, while each blue point means one opening of the MEMS. When looking closer into each patient, we observe that they have very different medication adherence behaviour. There is huge variability in the timing of medication taking in the morning as well as in the evening. The grey zone for the patient on the left represents a whole week without any medication intake.

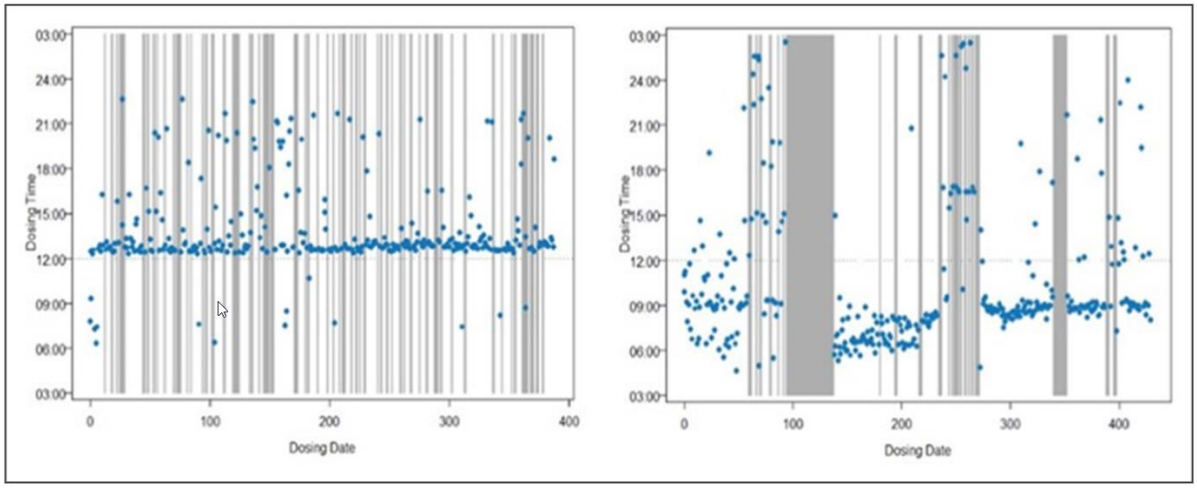

Figure 1.4: Using MEMS to assess the dynamic process of medication adherence. Adapted from (Burnier & Egan, 2019)

Dr Dima stated that 'all adherence situations are alike; every non-adherence situation has its own determinants'. This highlights the complex challenge medication non-adherence raises, urging for an accurate assessment, hence adopting effective interventions to enhance medication adherence. So far electronic monitoring devices have been shown to capture the timing of medication taking and observe its dynamic behaviour. Even though electronic monitoring is the best-validated tool in the clinical trial setting, its use in clinical practice is still limited (Dobbels et al., 2010).

1.2 Medicines use in cancer patients

Since the early 2000s oral agents for cancer (OAC) have observed a considerable increase, resulting in a paradigm shift regarding the process and outcomes in oncology care (Bedell, 2003; Colomer et al., 2010; Gralow et al., 2008; Winer et al., 2009). On the one hand, this shift reflects the chronicity of cancer treatment and on the other the adherence to these therapies, which became a major issue in the field of oncology (Ruddy et al., 2009; Tipton, 2015). OAC, compared to intravenous forms, are facilitating the logistics of treatment administration (e.g. self-administration, comfort) for both patients and physicians (Bedell, 2003).

OACs are self-administered and allow the patient to take the treatment from home, reducing hospital visits. Thus OAC therapies often remain unobserved for months or even years raising the complex issue of treatment management (e.g adherence, tolerance) (Puts et al., 2014; Spoelstra & Rittenberg, 2015). Adherence to the OAC regimes may be challenging for some patients. These regimens may be simple (e.g once-daily dosing) or complex (e.g more than once-a-day dosing, on- and off-cycling, two or more drugs) (Spoelstra & Rittenberg, 2015; Weingart et al., 2008). Therefore it is important to assess and monitor adherence to OAC.

Table 1.2 illustrates the major and manifold consequences of non-adherence to OAC underlying the major public health concern (Puts et al., 2014; Spoelstra & Rittenberg, 2015). Adherence to the OAC regimen is crucial to therapeutic success and health outcomes (Bestvina et al., 2014; Bozic et al., 2013; Davies et al., 2013; Lasala & Santoleri, 2022). Despite numerous efforts such as motivation, side-effect management or medication adherence-enhancing interventions (MAEI) adherence estimates remain suboptimal (Burhenn & Smudde, 2015; Finitsis et al., 2019; Puts et al., 2014; Rosenberg et al., 2020; Spoelstra & Sansoucie, 2015).

Table 1.2: Major consequences of non-adherence to OAC, adapted from (Spoelstra & Rittenberg, 2015; Weingart et al., 2008)

- Decrease in survival
- Ineffectiveness of OAC regimen
- Potential for unnecessary treatment change
- Increased use of healthcare resources and costs; drug waste or increased hospitalizations
- Clinical trials: Misleading results, inconsistent response rates
- Increased toxicities
- Decreased patient satisfaction
- Poor healthcare provider relationship and communication

Even though evidence exist that medication adherence to OAC is far from optimal and the efforts to enhance adherence, through motivation, MAEI, healthcare provider (HCP) involvement, medication adherence remains neglected in daily practice in the field of oncology (Foulon et al., 2011; Levit et al., 2022)**.**

1.2.1 Breast cancer and adherence to adjuvant endocrine therapy

Breast cancer (BC) is the most commonly diagnosed cancer among women worldwide (Bray et al., 2018; Sung et al., 2021). During the acute phase of treatment, BC patients are treated with a combination of surgery, radiotherapy and/or chemotherapy. Survivorship is defined as the post-acute treatment period of a cancer patient (Pollastro, 2017; Vaz-Luis et al., 2022).

About three-quarters of breast cancer tumours are estrogen and/or progesterone-receptor-positive (Yip & Rhodes, 2014). For those, the post-acute phase is managed with adjuvant endocrine therapy (AET) in order to reduce the risk of breast cancer recurrence (Burstein et al., 2019; Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005). Tamoxifen and aromatase inhibitors,

two AETs, decrease the risk of BC recurrence by about 30% (Davies et al., 2013; Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005).

AET treatment regimen is taken orally and contains one dose once a day, and it is strongly associated with the recommended duration of use (5-10 years) (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005; Partridge et al., 2003). Even though 5 years of AET was shown to reduce BC recurrence by 50% and mortality by a third, non-adherence to AET is continuously reported (Davies et al., 2013; Inotai et al., 2021; Makubate et al., 2013; Pistilli et al., 2020).

Accordingly to the literature, 31%-73% discontinue AET before the recommended 5 years of treatment, depending on the AET drug (aromatase inhibitor or tamoxifen) and method of measurement (Huiart et al., 2011, 2013; Mao et al., 2020; Murphy et al., 2012). In addition, Huiart et al. showed in earlier work that shorter temporary discontinuation in AET is strongly associated with an increased likelihood of restarting oral therapy (Huiart et al., 2014). A recent study by Lambert-Coté identified five AET adherence trajectory groups among BC: (1) quick decline and stop, (2) moderate decline and stop, (3) slow decline, (4) high adherence, and (5) maintenance of very high adherence (Figure 1.5). This study is interesting as it shows the dynamism of AET adherence across a population and with each trajectory (Table 1.3). For example, 30% of the studied population belonged to the 'high adherence' trajectory, meaning the first year this population is 100% adherent (according to the method of measurement used) however over the course of time adherence estimates decrease. These findings are important while developing MAEI, highlighting the time aspect of medication adherence within and across breast cancer survivors (BCS) as well as the need for personalization.

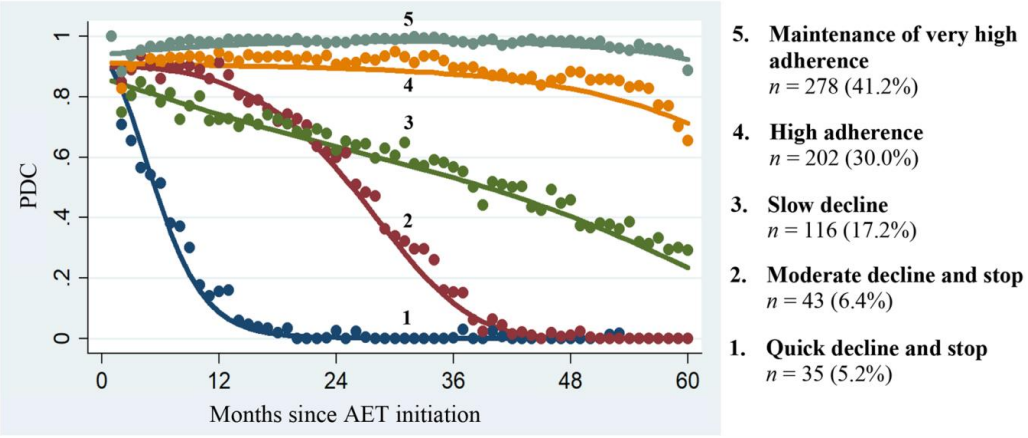

Figure 1.5: Illustration of a 5-group model for AETadherence trajectories Source: (Lambert-Côté et al., 2020)

Table 1.3: Adherence measures according to AET adherence trajectory group Source: (Lambert-Côté et al., 2020)

Adherence measure	AET adherence trajectory group					Total
	Quick decline and stop	Moderate decline and stop	Slow decline	High adherence	Maintenance of very high adherence	
Persistence	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
At the end of year 1[a]	10 (28.6)	42 (97.7)	107 (94.7)	199 (100.0)	263 (100.0)	621 (95.1)
At the end of year 2[b]	1 (3.0)	32 (74.4)	104 (98.1)	196 (99.5)	252 (100.0)	585 (92.7)
At the end of year 3[c]	1 (3.2)	15 (34.9)	98 (92.5)	188 (99.5)	243 (100.0)	545 (89.1)
At the end of year 4[d]	0 (0.0)	2 (5.1)	88 (86.3)	184 (98.9)	238 (100.0)	512 (85.9)
At the end of year 5[e]	0 (0.0)	0 (0.0)	61 (61.0)	152 (84.0)	226 (97.8)	439 (75.7)
PDC	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Year 1[a]	0.46 (0.26)	0.90 (0.15)	0.79 (0.19)	0.93 (0.10)	0.96 (0.07)	0.89 (0.18)
Year 2[b]	0.03 (0.07)	0.73 (0.25)	0.70 (0.24)	0.93 (0.10)	0.99 (0.03)	0.85 (0.26)
Year 3[c]	0.00 (0.00)	0.36 (0.32)	0.61 (0.23)	0.92 (0.08)	0.99 (0.02)	0.81 (0.30)
Year 4[d]	0.01 (0.02)	0.04 (0.08)	0.48 (0.18)	0.87 (0.14)	0.98 (0.03)	0.75 (0.34)
Year 5[e]	0.00 (0.02)	0.00 (0.01)	0.34 (0.20)	0.81 (0.19)	0.96 (0.07)	0.69 (0.36)
Total[f]	0.10 (0.06)	0.41 (0.11)	0.59 (0.13)	0.89 (0.06)	0.97 (0.02)	0.80 (0.25)

Analysis for each period excluded censored data (death, metastasis, or another cancer)

AET Adjuvant endocrine therapy, *PDC* Proportion of Days Covered, *SD* standard deviation

[a]21 women excluded in year 1 ($n=653$)

[b]43 women excluded in year 2 ($n=631$)

[c]62 women excluded in year 3 ($n=612$)

[d]78 women excluded in year 4 ($n=596$)

[e]94 women excluded in year 5 ($n=580$)

[f]94 women excluded in 5-year analysis ($n=580$)

Hence, lack of adherence to the treatment may play an important role in the risk of cancer recurrence, survival and quality of life of BC patients. (Inotai et al., 2021; Sabaté, 2003).

1.2.2 Barriers and facilitators to adjuvant endocrine therapy adherence

It is crucial to understand and study the barriers and facilitators to AET adherence in BCS. These barriers are associated with the above-mentioned 5 dimensions of adherence (1.1.2 Medication adherence determinants). The shift from the acute treatment phase to the post-acute treatment phase has been associated with social (e.g stigma), psychological (e.g anxiety and fear) familial (lack of support and understanding) and professional issues and medical issues (e.g medication

management; adherence and side-effects) during their survivorship (Hurtado-de-Mendoza et al., 2018; Kantsiper et al., 2009; Ringwald et al., 2017; Yussof et al., 2022). Additionally, younger age, side-effect burden, medication safety concerns, and resource barriers (e.g cost or accessibility of drug and support) (Gast & Mathes, 2019; Mathes et al., 2014; Spencer et al., 2020; Verbrugghe et al., 2013).

Literature reported that older age, establishing a routine of medication taking, leaving the medicine in a visible or easily accessible place, taking the medication with other medications, reducing the cost of medicine, using a pillbox, understanding the negative consequences of lack of adherence, and having positive interactions with physicians are the driving facilitators for AET adherence (Lambert-Côté et al., 2020; Sarradon-Eck et al., 2012; Spencer et al., 2020; Wells et al., 2016).

These findings underscore the importance of developing multi-faceted, patient-centred interventions that address a diverse range of barriers to AET adherence.

1.2.2 Role of healthcare provider in adjuvant endocrine therapy management

'Stop blaming the patient!' - For a long time, medication adherence was seen to be a patient's challenge rather than a contribution of a multidisciplinary healthcare team (Bandiera et al., 2022; Brown & Bussell, 2011; M. P. Schneider & Burnier, 2022). In the absence of an integrated and coordinated approach to care, each healthcare provider supports medication adherence in their silo rather than reinforcing an interprofessional healthcare ecosystem (Figure 1.6) (M. P. Schneider & Burnier, 2022; Schünemann et al., 2022). Thus defining roles and responsibilities, while remodelling the organisation of care and increasing efficiency and accessibility to evidence-based medication adherence interventions.

Schneider et al. propose a partnership and interprofessional healthcare providers along the multifaceted journey to medication adherence (M. P. Schneider & Burnier, 2022). Hence, treatment management is the interplay between healthcare providers (e.g physicians, specialists, pharmacists, and nurses) together with the patient. Especially in more complex areas such as oncology where the patient already underwent challenging acute treatments, it is important to act

as a team to support the patients and foster health outcomes. In such models, providers' prescribing and dispensing behaviours, and quality of care tend to improve (S. M. Smith et al., 2021).

In the scenario of AET, the BCS usually do not visit their oncologist for a relatively long time during which they might be facing side-effects, psychological distress, and daily confrontations related to their AET (Ringwald et al., 2017). The role of the pharmacist and or the nurse have risen in importance regarding medication management. Most often pharmacists and or nurses are perceived as more accessible (Felton et al., 2016). In the case of BC, nurses are implicated in the patient treatment since the acute treatment phase and can connect with the patient and build a trustworthy relationship (Bedell, 2003). Thus it is of utmost importance to have a good patient healthcare provider relationship, patients are sufficiently educated on their treatment and are comforted and supported in case of need (Finitsis et al., 2019; Kini & Ho, 2018; Mårtensson & Hensing, 2012; Pouls et al., 2021; Riva et al., 2015). Consequently, they need autonomy in managing their medication and when dealing with symptoms and side-effects associated with their disease and treatment (Zhang et al., 2014). Thus the value of HCP supporting BCS is undebatable for medication adherence and disease management.

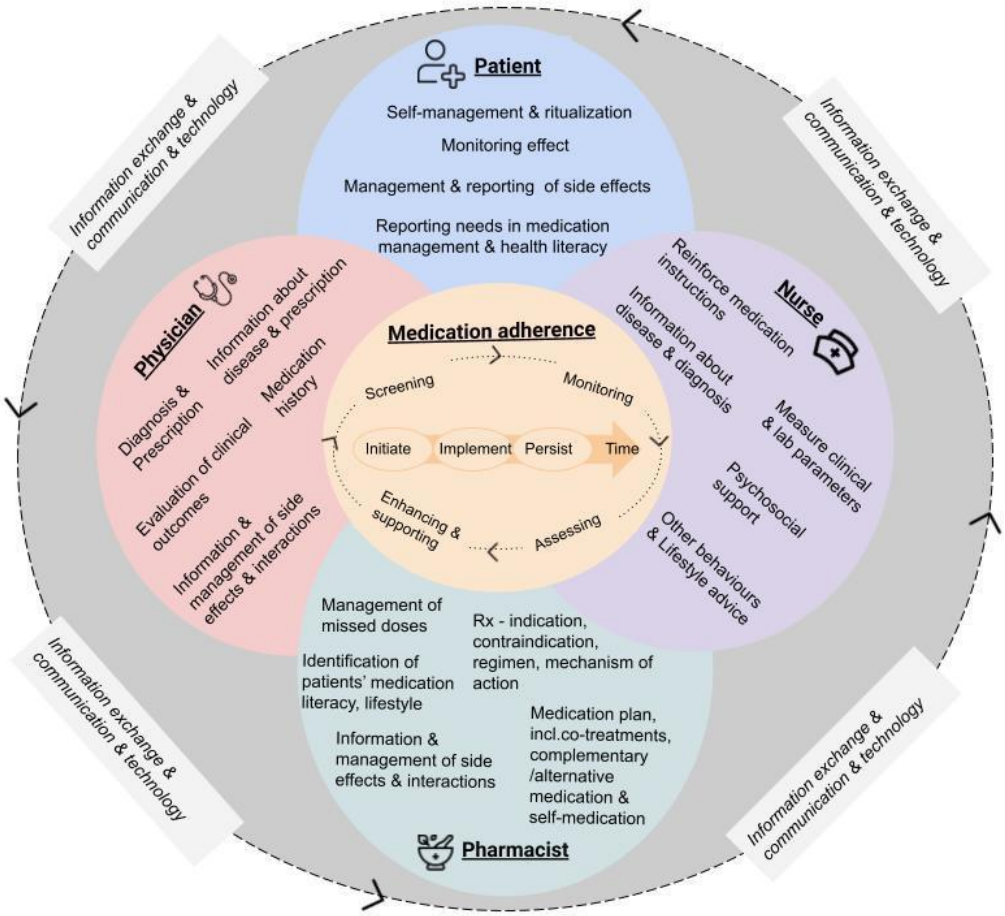

Figure 1.6: Interprofessional healthcare ecosystem for medication adherence adapted from (M.-P. Schneider et al., 2016; Vrijens et al., 2012a) Source: Goetzinger, Schneider; Chapter 3.5.5 Interventions to improve medication adherence - Drug Utilization research book, 2023 (in external review)

Understanding the dynamic pattern of AET adherence, its barriers as well as the social and psychological challenges of BCS is crucial to develop effective MAEI and improve health outcomes (reduced rates of BC recurrence, improved quality of life).

1.3 Enhancing medication adherence

Concerning the field of medication adherence research and eHealth, medication adherence technologies (MATech) such as electronic pillboxes or smartphone applications have been developed (Ahmed et al., 2018). Car et al. highlighted that these MATechs are the future for self-management of treatment and medication adherence monitoring (Car et al., 2017). A systematic review by Nieuwlaat et al. showed that MATechs are most effective if multiple components, trying to overcome barriers to adherence using tailored ongoing support from allied health professionals are used (Nieuwlaat et al., 2014).

A 2018 review by Ahmed et al. identified over 600 medication adherence apps on Google Play and Apple App Stores. However, most of them lacked evidence of effectiveness and did not involve healthcare professionals (HCPs) during their development thus implementation in the real-world setting remains scarce (Clyne & McLachlan, 2015).

1.3.1 A scoping review of medication adherence-enhancing interventions (MAEI) for chronic diseases

The source of the following paragraph: Goetzinger, Schneider; Chapter 3.5.5 (Section 3) Interventions to improve medication adherence - Drug Utilization research book, 2023 (in external review)

During the last decades, medication adherence enhancing interventions have witnessed a shift from simple (e.g one-time education interventions) to multidimensional, multifaceted interventions. They are delivered and evaluated from individual to societal levels. Multidimensional interventions combine two or more successful intervention content components (e.g cognitive behavioural therapy, educational material, reminders) and collaborative components (e.g. patient partnership, shared-decision making, motivational interviewing). Some interventions are disease-specific whereas others are disease-agnostic. They can impact not only one medication but several (e.g polypharmacy). Overall, medication adherence-enhancing interventions need to consider determinants affecting medication adherence while also considering other health behaviours (e.g.

tobacco, physical activities, diet) thereby increasing the reach of clinical outcomes and reducing the costs of delivering healthcare (Khan & Socha-Dietrich, 2018).

The authors of this chapter conducted a scoping review to identify current medication adherence-enhancing interventions and to synthesize their effectiveness regarding the questions mentioned above. Eligible studies were reviews, systematic reviews or meta-analyses investigating the effectiveness of medication adherence-enhancing intervention using various designs from randomised controlled trials to cohort data. Additional inclusion criteria were medication adherence as the primary outcome, chronic diseases and adults older than 18 years. In total 1187 titles and abstracts were screened, and 67 were eligible for full-text reading. After careful consideration and to avoid bias in reporting results, we decided only to include reviews published after December 31, 2016. Thus, 8 systematic reviews/meta-analyses were retained (Conn & Ruppar, 2017; Cornelissen et al., 2020; Finitsis et al., 2019; Kini & Ho, 2018; Pouls et al., 2021; Rosenberg et al., 2020; S. M. Smith et al., 2021; Wiecek et al., 2019). Study characteristics such as the patient population, sample size and study duration, definition and measurement of medication adherence and the quality measurements of the reviewed studies are available in Appendix 1.1.

Despite the publication of a vast array of studies reporting on medication adherence-enhancing interventions, no conclusive evidence exists regarding their effectiveness. All reviews reported high heterogeneity in the study methodology, sample sizes and study duration (ranging from 4 weeks to 2 years). Some studies had multiple follow-up time points whereas others followed up at the beginning and the end of the study. Five reviews focused on long-term conditions in general whereas three reviews were disease-specific. Medication adherence definition and measurements changed across studies. If a definition was reported, the majority used the definition from Cramer et al. followed by Vrijens et al. (Cramer et al., 2008; Vrijens et al., 2012a). Furthermore, most studies considered a variety of medication adherence measurements both subjective (e.g self-reported) and objective (e.g digital pillboxes or databases). The majority of the reviews used the Cochrane risk of bias tool to evaluate the quality of the study.

The literature lacks conclusive evidence regarding the effectiveness of medication adherence-enhancing interventions:

a. Which theoretical framework is the intervention built upon?
b. What are the effective components of an intervention?
c. How does the intervention involve patients and informal caregivers?
d. What is the mode of delivery of the intervention?
e. What is the duration/iteration of the intervention components and how long does the effect of the intervention last?
f. Is the intervention disease-specific or translatable among pathologies, patient populations and settings?
g. Are interventions built upon interprofessional collaborations more effective?
h. How could this intervention be integrated into the healthcare setting?

Main results of the included reviews on the effectiveness of medication adherence enhancing interventions

Regarding the phases of medication adherence addressed, studies most often address implementation adherence, followed by discontinuation and only very few studies mentioned initiation (Cornelissen et al. 2020). According to a meta-analysis of 771 trials, only 18% were associated with a theory or model (Conn et al., 2016). A summary of the main results is highlighted in table 1.4.

All studies agreed that multicomponent studies (e.g. educational, attitudinal and technical) tend to be more effective than single-component studies. Wiecek et al. classified studies regarding their follow-up periods and illustrated that multicomponent medication adherence enhancing intervention usefulness might increase over time compared to single-component interventions (Wiecek et al., 2019). Another trend that seems to be effective in enhancing medication adherence

is the use of interactive 2-way communication strategies, thus reinforcing the active patient's role (Conn & Ruppar, 2017; Finitsis et al., 2019; Kini & Ho, 2018; Pouls et al., 2021; Rosenberg et al., 2020).

The following categories - contents and processes- were used to describe the components of medication adherence interventions (results of the scoping review):

- Education
- Cognitive -, behavioural -, or habit-based strategies
- Medication Regimen Management
- Technical components intended to simplify the medication-taking process (e.g reminder)
- Incentives to improve adherence (e.g reducing co-payments and paying patients and clinicians for achieving disease management goals)
- Monitoring and supervision
- Interprofessional collaboration

Overall, only a few studies reported a positive effect on medication adherence and clinical outcomes. Thus no conclusive evidence could be revealed on which intervention components are more effective than others. Nevertheless, the included reviews can provide promising trends and give recommendations and perspectives for future research (For in-depth information see Appendix 1.2).

Table 1.4: Summary of included reviews; main results and recommendations for future medication adherence enhancing intervention research

Main Results	Recommendations
1. Most MAEIs used educational and counselling-based components regardless of the mode of delivery(e.g analogue, face-to-face or digital technology)(Cornelissen et al., 2020; Kini & Ho, 2018; Pouls et al., 2021; Rosenberg et al., 2020; S. M. Smith et al., 2021; Wiecek et al., 2019) 2. MAEI should be tailored to the needs of the patient population (risk factors, management, support,...). Tailoring enhances medication adherence and increases adherence to intervention use(Rosenberg et al., 2020; Wiecek et al., 2019) 3. MAEI components such as interactivity and bi-directional communication seem to be most effective to enhance medication adherence(Conn & Ruppar, 2017; Finitsis et al., 2019; Pouls et al., 2021) 4. Multicomponent MAEI interventions seem to be more effective than single-component interventions(Cornelissen et al., 2020; Wiecek et al., 2019) 5. The MAEI components needed to enhance medication adherence in patients might change over time(Wiecek et al., 2019).	Raise medication adherence awareness among stakeholders (Kini & Ho, 2018) Construction of the interventions: ● Patient-provider involvement for MAEI development(Cornelissen et al., 2020) ● Consider medication adherence as a time-dependent behaviour(Cornelissen et al., 2020; Wiecek et al., 2019) ● Find the best combination MAEI components considering the dynamic behaviour of medication adherence(S. M. Smith et al., 2021; Wiecek et al., 2019) ● Tailoring MAEI to the needs of the study population(Rosenberg et al., 2020; S. M. Smith et al., 2021) ● Basing interventions on validated theories and/or frameworks and implementation research approaches(Finitsis et al., 2019; Kini & Ho, 2018; Pouls et al., 2021; Rosenberg et al., 2020; Wiecek et al., 2019) ● Interprofessional approaches among end-users need to be clarified to indicate each provider's role and responsibility in enhancing medication adherence together with patients.(Kini & Ho, 2018; Rosenberg et al., 2020) Evaluation of the interventions: ● Rethink the methodology for evaluating MAEI (study design, selection bias, health outcomes)(Conn & Ruppar, 2017; Finitsis et al., 2019; Pouls et al., 2021; Wiecek et al., 2019) ● Evaluate the cost-effectiveness of MAEI(Wiecek et al., 2019)

Recommendations for future research in medication adherence-enhancing interventions

Future research on medication adherence-enhancing interventions should focus on new methods to design medication adherence-enhancing interventions, which are directly embedded in usual care. A summary is illustrated in Table 1.4.

Construction of the interventions:

- Interventions have to consider medication adherence as a time-dependent behaviour, with medication adherence management needs evolving inter- and intra-individually throughout the different phases of initiation, implementation and persistence.

- Basing interventions on validated theories and/or frameworks are instrumental in validating the content of the intervention and increasing their implementability into daily practice. The Smile project is a good example of how to use theory-based frameworks to develop an intervention (Ribaut et al., 2020).

- Interprofessional approaches among end-users need to be clarified to indicate each provider's role and responsibility in enhancing medication adherence together with patients. For this interprofessional approach to take place, intensive work needs to be done in the context of raising awareness among healthcare providers, healthcare policy-makers and insurers. Education curriculums need to be adapted to teach the next generation of healthcare providers the importance of medication adherence in health outcomes and how to do so. Thus, the fidelity of healthcare providers towards interventions will increase.

Evaluation of the interventions:

- Traditional randomized controlled trials require blinding and concealment of study participants to reduce the risk of bias, yet this action is often not possible at the patient level. Alternatively, using cluster randomization at the setting level becomes more relevant, solving the ethical difficulties in recruiting adequate control groups of patients.

- Selection bias in including participants who are already adherent to their treatment - as adherent patients are more open to participating compared to non-adherent - is high if medication adherence interventions are not embedded into the regular flow of patients' follow-up at the setting level. Neither is the necessary follow-up of patients guaranteed with an appropriate sample size if not embedded in the regular activity flow, thus jeopardizing statistical power.

- Health outcomes such as cost-effectiveness and patient-reported outcomes such as quality of life have to be incorporated when evaluating medication adherence-enhancing interventions. In this perspective, drug utilization research provides useful methodology, techniques and tools, especially regarding data collection on patient drug use and measurement of medication adherence and outcomes, evaluation of the intervention (mixed method methodology) and implementation methodology.

Use of digital technology for medication adherence interventions

Digital technologies have gained importance in healthcare, disease self-management and data science. Also in the field of medication adherence, these digital technologies are beneficial. On the one hand, digital tools facilitate the measurement of medication adherence and on the other have innovated the way of delivering medication adherence interventions.

Research on the impact of digital interventions is growing rapidly. Pouls et al. systematic review showed that interactive digital technologies have a positive effect on medication adherence in patients taking long-term treatments. The review showed that there is a positive effect of interventions using SMS text messages or interactive voice response, mobile apps, and calls as the mode of providing adherence tele-feedback. Regarding the strategies used by this digital MAEI, they found that digitalisation facilitates medication management skills, improves healthcare quality by coordinating medication adherence care between professionals and facilitates communication or decision-making between patients and healthcare providers.

Hence digital technologies are reforming healthcare and representing a huge area of research and opportunity for medication adherence interventions while ensuring stronger care coordination and human collaborations between patients and interprofessional care providers.

Digital interventions may be a game changer as they offer new ways for measuring adherence, collecting patient-reported outcomes and experiences, and providing intervention directly in the patient ecosystem, thus limiting patient burden. Another beneficial aspect of digital medication adherence technology is the 'timing'. Digital medication adherence technology has the potential to intervene in the moment of need providing the intervention of need.

Another major strength of digitally-assisted enhancing medication adherence interventions is that patients are more strongly engaged in their health and self-management of their medication-taking by improving the accessibility of disease and treatment information and facilitating two-way communication with healthcare providers (Finitsis et al., 2019; Pouls et al., 2021). On the one hand, this is promoting interprofessionality and includes the patient as a partner in disease and treatment management. On the other hand, this is increasing patient empowerment as patients gain greater control and autonomy over the self-management of their disease and treatment.

Some limitations that future research needs to further investigate are concerns of 1. trustworthiness in terms of scientific and technical validity of digital technology, 2. accessibility issues, 3. Personal data protection and 4. Implementation into daily healthcare practice.

1.3.2 Medication adherence-enhancing intervention(s) for adjuvant endocrine therapy or oral cancer agents in general

MATech and digital MAEI allow cancer patients and survivors to manage their disease and treatment (e.g adherence and side-effects) (Car et al., 2017; Escriva Boulley et al., 2018). Digital interventions for cancer patients have already been successfully developed to provide support during the acute phase of cancer treatment as shown by Basch et al and Denis et al (Basch et al., 2016; Denis et al., 2017). They investigated the feasibility and effectiveness of MATech to

improve symptom management and surveillance as well as patient-physician communication. These personalized digital technologies increased the health-related quality of life as well as survival and decreased emergency room visits and hospitalizations. In the context of post-acute treatment, digital interventions were less effective ((Finitsis et al., 2019; Rosenberg et al., 2020). These digital interventions using educational material, online communities, reminder text messages or phone calls, did not significantly improve medication adherence in BCS(Finitsis et al., 2019; Rosenberg et al., 2020).

Regarding adjuvant endocrine therapy, adherence was most often defined as a medication possession ratio (MPR) of ≥80% (Murphy et al., 2012) however this estimate fails to identify the dynamic behaviour of medication adherence. Figure 1.7 illustrates how the traditional approach to measuring medication adherence misses the dynamic concept of medication adherence. This phenomenon might be one of the explanations why the current MAEI for AET in BCS are not yet reaching the wanted success and implementation into the real-world setting is scarce. Thus understanding this time aspect and the complex behaviour of medication adherence behaviour will be key in enhancing AET adherence in BCS and is crucial in the development of MAEI.

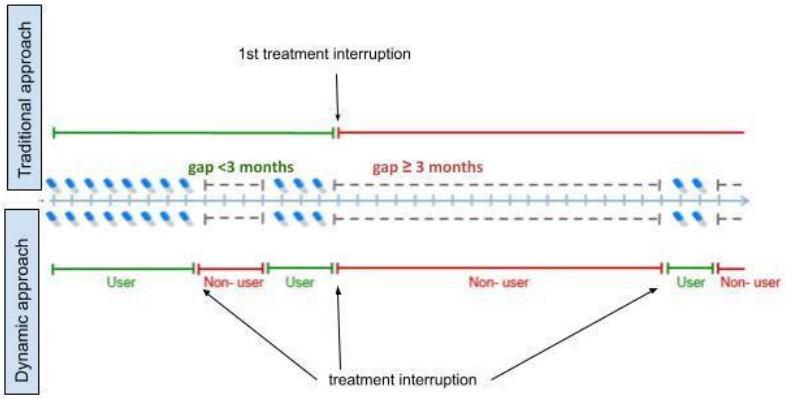

Figure 1.7: Difference in medication adherence using the traditional approach vs the dynamic approach.

1.4 Overview of the research presented in this thesis

As shown above most effective interventions did not lead to large improvements in adherence or clinical outcomes (Hadjiet al., 2013; Finitsis et al., 2019; Rosenberg et al., 2020). Most MAEI fail to identify the dynamic behaviour of medication adherence. This is because most of those interventions were created without the involvement of the end-user and or theory-based frameworks. Using Patient-provider involvement and interprofessional concepts to manage medication adherence is key in research and implementation of MAEI in the healthcare setting (De Geest et al., 2020; Aguayo et al., 2021).

Thus taking this complex behaviour of medication adherence, understanding in-depth patient and healthcare providers' needs, and beliefs during the AET and the acceptance and usability regarding MATech and MAEI while using theory-based frameworks will be key in enhancing AET adherence in BCS and is crucial to developing MAEI to implement it into the real-world setting. **Therefore, the overall aim of the present thesis was to use a patient-provider involvement approach and a theory-based framework to develop a digital MAEI for AET in BCS**.

In total, this thesis includes seven chapters. Chapter 1, the introduction highlights the literature on medication adherence, MAEI research and more precisely using the case of AET in BCS. To accomplish the overall aim of this research project chapter 2 to 6 were divided into a contextual analysis of AET management in Luxembourg, established usability patterns and acceptability of current MATech and MAEI for AET in BCS followed by a behaviour theory-based framework to finally construct a digital MAEI for AET in BCS and develop a feasibility study. These chapters amount to 4 major research steps that were performed consecutively. Chapter 7 gives a critical evaluation of the major findings from the present research project and its take-home messages. In addition, it gives future perspectives and a final conclusion. Table 1.5 illustrates the overview of the research project's steps, objectives, research questions, methodology used and where to find the results.

First, a scoping review aimed to identify current MAEI and synthesize their effectiveness. To elucidate the purpose of this objective the following research questions were investigated:

1. Which theoretical framework is the intervention built upon?
2. What are the effective components of an intervention?
3. How does the intervention involve patients and informal caregivers?
4. What is the mode of delivery of the intervention?
5. What is the duration/iteration of the intervention components and how long does the effect of the intervention last?
6. Is the intervention disease-specific or translatable among pathologies, patient populations and settings?
7. Are interventions built upon interprofessional collaborations more effective?
8. How could this intervention be integrated into the healthcare setting?

Second, we performed a contextual analysis of AET use in BCS and to analyse current digital health usability patterns and level of acceptance towards a digital MAEI supporting AET in BCS and HCP. In this phase a qualitative and qualitative study answered the following research questions:

1. What are patients' and healthcare providers' beliefs, attitudes and expectations towards AET management in Luxembourg?
2. To what extent do patients and healthcare providers accept an eHealth intervention to monitor AET?
3. What are perceived barriers and facilitators to using an eHealth intervention to monitor AET?

Third, we aimed to define the problem of AET adherence in behavioural terms, to identify intervention options and to determine content and implementation options using a theory-driven framework.

1. What is the AET adherence behaviour problem? (where does it occur, who is the target group, and who is involved)
2. What needs to change for the behaviour change to occur?
3. What intervention functions enhance the target behaviour change?

4. What are the implementation options? (behaviour change techniques, mode of delivery)

Fourth, we constructed a digital MAEI in BCS taking an AET and developed a feasibility study. The following research questions were tackled:

1. What is the impact of the digital MAEI on the BCSs' quality of life?
2. What are the estimates of AET adherence in BCS?
3. Are there technical occurrences with the MATech used in the intervention?
4. What behaviour change techniques were used by the BCN in case of non-adherence?

Table 1.5: Overview of the research project's steps, objectives, research questions, methodology used and where to find the results

Research project steps	**Objective**	**Research question(s)**	**Research method used**	**Chapter**
Step 1	To identify current MAEI and to synthesize their effectiveness.	1. What are the effective components of an intervention? 2. How does the intervention involve patients and informal caregivers? 3. What is the mode of delivery of the intervention? 4. What is the duration/iteration of the intervention components and how long does the effect of the intervention last?	Scoping review	Chapter 1-1.3.1

		5. Is the intervention disease-specific or translatable among pathologies, patient populations and settings? 6. Are interventions built upon interprofessional collaborations more effective? 7. How could this intervention be integrated into the healthcare setting?		
Step 2	To analyse current digital health usability patterns and level of acceptance towards a digital MAEI supporting AET in BCS.	1. What are patients' and healthcare providers' beliefs, attitudes and expectations towards AET management in Luxembourg? 2. To what extent do patients and healthcare providers accept an eHealth intervention to monitor AET? 3. What are perceived barriers and facilitators to using an eHealth intervention to monitor AET?	Mixed method approach (Qualitative study & Quantitative study)	Chapter 2, 3, 4
Step 3	To define the problem in behavioural terms, to identify intervention options and to determine the content and implementation options, using a theory-driven framework.	1. What is the AET adherence behaviour problem? (where does it occur, and who is the target group, who is involved) 2. What needs to change for the behaviour change to occur? 3. What intervention functions enhance the target behaviour change? 4. What are the implementation options? (behaviour change techniques, mode of delivery)	Theory-based framework - behaviour change wheel (COM-B model and TDF)	Chapter 5

Step 4	To construct and explore the feasibility of the digital MAEI for BCS taking their AET	1. What is the impact of the digital MAEI on the BCSs' quality of life, 2. What are the estimates of AET adherence in BCS, 3. Are there technical occurrences with the MATech used in the intervention 4. What behaviour change techniques were used by the BCN in case of non-adherence?	Feasibility study (Protocol)	Chapter 6

In-depth explanations regarding the methodology used for the different steps are found within the respective chapters.

Chapter 2

eHealth technology to support breast cancer survivors during their adjuvant endocrine therapy: a qualitative study

Title: eHealth technology to support breast cancer survivors during their adjuvant endocrine therapy: a qualitative study

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2.1 Abstract

Purpose:

This qualitative study aims to assess breast cancer survivors (BCS) and healthcare providers (HCP) beliefs, attitudes, needs and expectations during breast cancer (BC) survivorship with a specific focus on the use and acceptability of eHealth intervention to support adjuvant endocrine therapy (AET) adherence

Patients and Methods:

Semi-structured individual interviews were conducted among 14 BCS and 10 HCPs (oncologists, breast cancer nurses and pharmacists) in Luxembourg. Eligible BCS were female, outpatient, taking an adjuvant endocrine therapy and have proficiency in one of the national languages. The face-to-face interviews were recorded, transcribed, anonymized, and analyzed with the thematic analysis approach.

Results:

At the time of the interviews, BCS were, on average, 54.5 years old (SD=6.9) and 50% took Tamoxifen. Half of the included HCP had over 20 years of experience while 70% were female. The interviews with BCS identified the following topics: *"AET", and "HCP implication into medical follow-up"*. HCP interviews determined *"Post-acute treatment follow-up needs", and "Patient-Provider communication",* as topics. *"eHealth technologies as support tools"* was a common topic for both BCS and HCP. BCS claimed to increase support from HCP during the initiation, increase social and private assistance during the shift from patient to survivor and better information regarding the AET. During implementation AET management strategies were declared. Overall, BCS pointed out the need for improved patient-provider communication. HCP urged the need for a systematic post-acute treatment follow-up integrated into the clinical setting and emphasized the necessity of real-time AET monitoring, encouraging targeted and personalized consultations.

Conclusion:

eHealth technology as a BC survivorship companion could link the gap between BCS claimed needs and integrate the lack of a systematic post-acute treatment follow-up for AET management in a clinical setting. Key components of this eHealth technology should be patient-provider interaction, support, information and remote AET monitoring while encouraging multidisciplinary teamwork.

Keywords: Cancer survivorship, digital health, eHealth, medication adherence, breast cancer, oral hormone therapy, behaviour science, patient preferences

2.2 Introduction

Breast cancer is the most common type of cancer in women worldwide. Survivorship is defined as the post-acute treatment period of a cancer patient (Pollastro, 2017). After the acute treatment period, most BC patients may not see their health provider for long. Consequently, they need autonomy in managing their medication and when dealing with symptoms and side-effects associated with their disease and treatment. In order to accomplish this, patients need skills and knowledge related to finding and using information about their own health situations (Mårtensson & Hensing, 2012; Riva et al., 2015). However, this transition period from cancer patient to survivor is associated with anxiety and fear, thus increased support during this period is claimed by breast cancer survivors (BCS) (Hurtado-de-Mendoza et al., 2018; Kantsiper et al., 2009). BCS experience challenges during the period of survivorship, ranging from social, familial and professional issues. Thus, BCS report specific medical issues during their survivorship such as medication management adherence and side-effects (Kantsiper et al., 2009).

Medication adherence, which is a dynamic behaviour, is influenced by socio-economic-related factors, healthcare team- and system-related factors, condition- and therapy-related factors, and patient-related factors (Kardas et al., 2013). The common definition for medication adherence, developed by the ABC taxonomy, is 'the process by which patients take their medication as prescribed' and consists of three main phases; 1. *initiation* (patient takes the first dose of prescribed medication), 2. *implementation* (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken) and 3. *discontinuation* (occurs when the patient stops taking the prescribed medication, for whatever reason(s) (Vrijens et al., 2012a). During the period of survivorship, hormone receptor-positive BC patients will be assigned to take adjuvant endocrine therapy (AET) for 5-10 years, which has the potential to decrease the risk of BC recurrence by over 30% (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005). However, the efficacy of these therapies is strongly associated with the recommended duration of use (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005; Partridge et al., 2003). Suboptimal adherence measures ranging from

30-50% are reported in former studies, depending on the drug and method of measure (Huiart et al., 2011, 2014; Mao et al., 2020).

The last decade has witnessed an increased interest in innovative mobile and digital technology. Digital health allows cancer patients and survivors to manage their disease, treatment and the occurring side-effects (Car et al., 2017; Escriva Boulley et al., 2018). Recent research focuses on the feasibility and usability of these technologies including applications and Internet-mediated interventions to provide personalized support to BCS. Digital interventions for cancer patients have already been successfully developed to provide support during the acute phase of cancer treatment as shown by Basch et al and Denis et al (Basch et al., 2016; Denis et al., 2017). They investigated the feasibility and effectiveness of digital technologies to improve symptom management and surveillance as well as patient-physician communication. These personalized digital technologies increased the health-related quality of life as well as survival and decreased emergency room visits and hospitalizations. In the context of post-acute treatment, digital interventions were less effective (Finitsis et al., 2019; Rosenberg et al., 2020). These digital interventions using educational material, online communities, reminder text messages or phone calls, did not significantly improve medication adherence in BCS (Finitsis et al., 2019; Rosenberg et al., 2020).

To date, researchers face the challenge to conceive effective eHealth support tools to increase adherence to medication during BC survivorship. The efficacy of ‘traditional’ methods is limited and eHealth interventions are still lacking the ability to adapt to each individual. This might be due to a lack of in-depth understanding of BCS' beliefs, attitudes, needs and expectations towards an eHealth support tool to improve AET adherence in a personalised real-time manner during BC survivorship. Therefore, the present study investigates BCS’ and healthcare providers (HCPs)’ beliefs and needs during BC survivorship and their expectations and acceptance of an eHealth tool to support AET management.

2.3 Research Design and Method

2.3.1 Study design

We used a qualitative study, to conduct individual semi-structured interviews from June 2019 to February 2020. The Luxembourgish national ethical committee (Comité national d'éthique de recherche (N◦201811/01 Version1.1) and the Luxembourgish Ministry of Health (82bxll634) granted ethical approval.

2.3.2 Recruitment

We recruited BCS from several national cancer centers (Centre hospitalier du Luxembourg, Centre hospitalier Emile Mayrisch, and Centre François Baclesse) with the help of volunteering oncologists. Eligible BCS were female, outpatient, within the adjuvant treatment phase and have proficiency in either Luxembourgish, French, or German. Eligibility was not based on age or menopausal stage. Thus, volunteering oncologists and BC nurses were recruited through national hospitals. The national pharmacist association ('Syndicat des Pharmaciens Luxembourgeois') helped us to recruit volunteering pharmacists. Hereafter, the descriptor 'HCPs' is used to group the oncologist, BC nurses and pharmacists.

2.3.3 Data collection and study procedure

The interview guide was established by CG and MKBD. An overview of the interview questions is outlined in Appendix 2.1. The semi-structured interviews for BCS were divided into three major sections. The first part was dedicated to the BCS disease history and experience with the treatment during the acute treatment phase. The second part focused on AET management. Lastly, the third section evaluated BCS expectations and acceptance of digital health technologies. The semi-structured interviews for the HCP were also divided into three sections: patient-provider relationship, AET management, and digital health technology. Each section had a leading question to start the discussion. Stimulus questions were identified but only asked in case the discussion had been silenced or the participant did not touch upon the topic themselves.

Once the informed consent was signed in duplicate, the interviewer (CG) started the semi-structured interviews. These were conducted face-to-face in either Luxembourgish, French or German and lasted up to 60 min. The interviews were recorded, transcribed verbatim and anonymized. InqScribe was used to perform the transcription. The quotes used for the present work were translated into English.

After the first two interviews, the research team decided to adapt their interview guide. During the interviews, we noted that the participants had difficulties discussing their needs for and using eHealth tools. Therefore, we decided to show them already existing applications. This helped them to have an idea about digital health technologies to promote medication adherence. We checked for accessible and positively reviewed medication adherence applications available in the apple store. After consideration, we retained the application called 'pill reminder' (Licea, n.d.). Participants were introduced to the applications and were then asked about their opinion, preferences and concerns regarding the app. In addition, we asked the participants what is currently missing in the app and what they would need to make it acceptable for them to use on a regular basis to manage their AET.

2.3.4 Data analysis

We used thematic analysis, the most commonly used approach in qualitative research, to explore the data. This approach follows five major steps: Compiling, Disassembling, Reassembling, Interpreting, and Concluding (Castleberry & Nolen, 2018). Thus, all the information was compiled and then separated based on common ideas, themes and subthemes. After we merged themes, to finally interpret their meaning and draw conclusions.

In qualitative research, no gold standard toward the 'right' sample size does exist. Therefore, the general rule of thumb is to follow the principle of saturation. This entails that data is collected as long as there is new information (Teddlie et al., 2009).

2.4 Results

2.4.1 Characteristics of Interviewees

In total, we interviewed 24 participants; 14 BCS and 10 HCP. Table 1 highlights the study participants' descriptive characteristics. BCS' age ranged between 42 and 68 years (mean age 54.5 SD+- 6.9) and the majority were Luxembourgish, married and took at least one other chronic treatment besides their AET. Half of the BCS were on tamoxifen and 29% on aromatase inhibitors, and 29% had at least experienced one AET switch. Regarding the post-acute treatment phase, one-third of the BCS were in their 1st year of AET, 50% were between 1-5 years and 21% took their AET for more than 5 years. Detailed characteristics for each BCS are shown in Appendix 2.2. Additionally, we interviewed four oncologists, three BC nurses and three pharmacists. Most (70%) of the HCP were female and half of them had professional experience of over 20 years in their domain respectively. Both BCS and HCP would accept to use the potential eHealth solution to manage and enhance AET (Table 2.1).

Table 2.1: Descriptive characteristics of breast cancer survivors and healthcare professionals

Participant characteristics	**Participants, n (%)**
Patients	**14 (100%)**
General Information	
Age (years):	4 (29%)
41-50	8 (57%)
51-60	2 (14%)
61-70	5 (36%)
Working (yes)	9 (64%)
Marital status (yes)	6 (42%)
Nationality:	4 (29%)
Luxembourgish	4 (29%)
Portuguese	
Other	
Medical History	
Family history (yes)	3 (21%)
Other chronic medication (yes)	8 (57%)
Breast cancer acute treatment	
Chemotherapy (yes)	5 (36%)
Radiotherapy (yes)	13 (93%)
Post-acute treatment (adjuvant endocrine therapy (AET))	
Tamoxifen (yes)	7 (50%)
Aromatase Inhibitors (Yes)	4 (29%)
Unknown	3 (21%)
AET Phase	
<1 year since AET initiation	4 (29%)
≥1 - <2 years	4 (29%)
≥2 - <5 years	3 (21%)
≥5 years	3 (21%)
AET switches (Yes)	4 (29%)
Healthcare professionals	**10 (100)**
Oncologist	4 (40%)
Breast cancer nurse	3 (30%)
Pharmacist	3 (30%)
Years of experience	
≤20 years	5 (50%)
>20 years	5 (50%)
Gender (Female)	7 (70%)

2.4.2 Breast cancer survivors' and healthcare providers' beliefs and needs during breast cancer survivorship

The interviews focused on identifying BCS' and HCPs' beliefs and needs during BC survivorship and their expectations and acceptance of an eHealth solution to support AET management. Figures 2.1a and 2.1b are hierarchical sunburst graphs presenting BCS and HCP key topics, categories, themes and subthemes that were revealed during the thematic analysis of the interviews. . The interviews with BCS identified the following topics: *"Adjuvant Endocrine Therapy", "HCP implication into medical follow-up", and "eHealth technologies as support tool"*. The interviews with the HCPs revealed the hereafter mentioned topics: *"Post-acute treatment follow-up need", "Patient-Provider communication" and "eHealth technologies as support tool"*. These topics will be described below with supporting quotes from interviewees. As both BCS and HCP have *"eHealth technologies as support tools"* as a common topic this will be discussed together. Appendix 2.3 illustrates the quotes from BCS and HCP interviews.

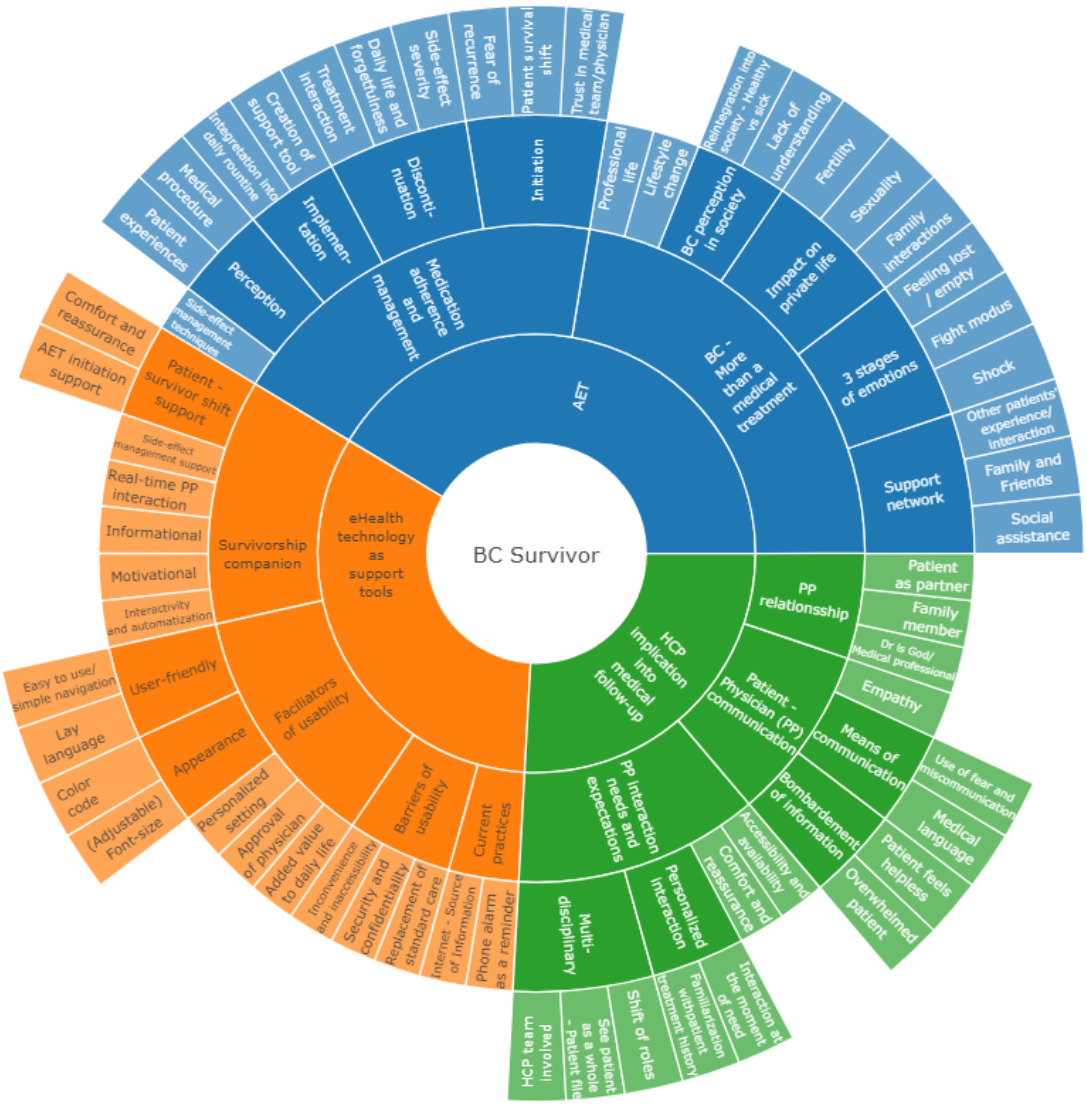

Figure 1a: Hierarchical clusters of BCS interviews grouped into Topics, Categories, Themes and Subthemes.

Figure 1b*: Hierarchical clusters of HCP interviews grouped into Topics, Categories, Themes and Subthemes.*

2.4.3 Breast cancer survivor- "Adjuvant endocrine therapy"

This topic revealed 2 distinct categories and 11 themes.

Breast cancer: More than a medical treatment

All BCS highlighted that AET not only is a medical challenge but also largely impacts other areas in their life. Thus, the first category is "BC- More than a medical treatment". They report that BC encourages lifestyle changes, to on the one hand change bad habits and on the other hand to cope mentally with their situation. *'I took up running, I hated it before my disease. But now it kind of gives me peace of mind. And even when I am angry with what happened to me I run a little faster to get it all out of the system' (Participant 8).*

Other participants declared the need for a solid support network to overcome personal and social challenges. A few experienced financial issues; *'I had social assistance helping me sort out financial matters because I was in a really bad situation' (Participant 6).* Others reported to be supported by family and friends.

Findings showed also that BC patients go through three distinct phases of emotions: 1. Shock 2. Fight modus and 3. Feeling empty and lost. For most patients, the diagnosis announcement is a huge shock and their world collapses. *'At the beginning, it [diagnosis of breast cancer] was a shock' (Participant 3)* This stage lasts longer for some patients than for others. Eventually, they move on to the fight modus, meaning that they accepted the disease and now want to battle it. *'After a few days of the announcement, which probably was the hardest time in my life, I told myself that I have to fight. I have a daughter and I will fight for her.' (Participant 4).* Finally, when they shift from acute treatment, where they see their healthcare team on a regular basis and are closely followed up, into the post-acute treatment phase, where they only see their physician once to twice a year, BCS start feeling lost and empty, hence experience anxiety and depression. *'During my treatment in the hospital I did not realize what I was going through, this happens during the*

treatment at home, where you are alone and you do not easily find your way back to your daily life, it would have been helpful to have support (...) (Participant 5)'.

Moreover, BCS reported that BC impacts private life in terms of family interaction, sexuality and fertility. *'I considered stopping treatment because I still wanted children. (...) Now I froze my eggs. But it is very difficult (...)' (Participant 12).* Some participants had to change their jobs due to a lack of resilience and understanding of their social network; *'I had to change my job. I was no longer as resilient and also needed a part-time job' (Participant 8).* Thus, BC perception in society is still linked to a lack of understanding, and confusion about whether BCS should be considered healthy or sick. *'My husband thinks that because I had an operation, it [breast cancer] is gone and I should be fine.' (Participant 3).*

Medication adherence and management

BCS reported different medication adherence challenges in different phases of treatments. The initiation of treatment turned out to be the most challenging phase. Initiation is impacted by

1. The trust in the medical team or the physician, *'I told my oncologist I do what needs to be done. So he prescribed me the treatment. I started immediately, I completely trust him.' (Participant 2),*

2. The patient to survivor shift; *'At the beginning, when I had my 1st prescription, I really doubted to start. I felt alone. I did not know if this treatment was worth the risk of side-effects. I would really have needed some reassurance at that time.' (Participant 4),*

3. The fear of recurrence; *'(...). It is true, I have thought of not taking the pills, but I am too afraid of it [cancer] to come back so I continue and I endure the side-effects.' (Participant 5).*

During implementation, BCS claimed to create habits and try to integrate the treatment into their daily routine. Participant 1 reported that she '*gets up, like every morning, and takes her medication. It is a habit like drinking a cup of coffee or eating dinner'.* Most of the participants need to create

a support tool to be reminded to take their AET. *'I bought myself pillboxes, I fill them with my treatment and put them on my nightstand, that way I know that I have to take 1 pill every morning after waking up.' (Participant 2).*

Those participants that have issues with discontinuation of their AET are highly affected by severe side-effects, forgetfulness and other daily activities as well as polypharmacy issues. *'I must admit I forget my medication from time to time, (...). I get up in the morning, (...) I take a shower, get dressed, feed the cats and dogs and then drive to work. In the car I asked myself, did you take your pill?' (Participant 10).*

Medication adherence is affected by the perception of the BCS as some see the treatment as a medical procedure and others rely on experiences they have seen or heard. *'I already went through the whole procedure with my mum, so yes it is scary to be affected yourself but also she had a good experience with hormone therapy so for me I knew I do it it will be the same' (Participant 2).*

Finally, BCS reported experiencing mild to severe side-effects, which they start to eventually manage by creating coping strategies such as: *'If I have an important thing the following day it happens that I do not take my pill to avoid side-effects.' (Participant 4).*

2.4.4 Breast cancer survivor - "Healthcare provider implication into medical follow-up"

This topic revealed three categories: 'Patient-Physician (PP) communication', 'PP relationship' and 'PP interaction needs and expectations' and 10 themes.

PP communication

During the PP communication, with regard to the post-acute treatment phase, BCS mentioned that their physician bombards them with information, leaving them feeling helpless and overwhelmed. *'He [oncologist] used so many terms I did not understand or I did not always follow, so I couldn't help myself but follow his instructions. In the end, he is the medical doctor so he should know what*

he talks about.' (Participant 5). BCS reported that this might be due to the means of communication. BCS reported that their physician often uses medical language and uses statistics as references *'My oncologist always says in your case in the American literature and he used words and statistics I don't even remember.' (Participant 7).* Some participants claimed that their oncologist would use fear to motivate them to take their AET; '*He [oncologist] told me to continue taking my treatment after 5 years so the cancer is not coming back' (Participant 5)*. Lastly, participants stated that their oncologists do not show empathy towards them and their disease/treatment situation; *'My oncologist called it ' your little cancer' I was shocked I had 5 tumours and mastectomy done (...) I don't know, maybe he can not put himself in my shoes as he is a man' (Participant 7).*

PP relationship

BCS interviews disclosed three different types of PP relationships:

1.'Dr is God / Medical professional'; *'If my doctor tells me to do something, I do it.' (Participant 5)*

2.'Family Member': *'He [oncologist] is like a brother to me' (Participant 1)*

3.'Patient as a Partner': *'I asked my oncologist for explicit information regarding the adjuvant endocrine therapy, why this treatment, I wanted to understand and also to clarify the information I found online to be correct that you are healed, which is not the case, so it was good I asked' (Participant 14)*

PP interaction needs and expectations

BCS addressed specific needs and expectations they have for PP interaction such as more personalized interactions and multidisciplinary. BCS expect their physician to be familiarized with their disease and treatment history and claim more time-specific interactions. *'Every time I come to the consultation I have to restart explaining my case. This annoys me. He should at least take 5 min before calling me in to familiarize himself with my history. (Participant 7)'*

Interviews showed that BCS desperately need healthcare providers to work closer together, like a multidisciplinary team. BCS accept HCP in their survivorship follow-up that were included since the diagnosis and the acute treatment phase. Patients claim the need to introduce a shared patient file to foster closer collaboration between HCP, allowing HCP to be informed about the patient's BC and treatment history as well as other diseases. *'To each physician, I go to, tell me something else [...] It is like if you go to a mechanic, he tells you to change the brakes, the other one tells you to change the filters and the next one wants you to do an oil change, so annoying.' (Participant 7)*

Overall, BCS expect their HCP to give them comfort and reassurance during the post-acute treatment phase and be available and accessible at specific time points: need of reassurance, information on treatment, etc *'I would have needed someone who reassured me that the treatment will be fine, as it is now, this reassurance would have been great, yes' (Participant 4)*

Finally, we asked the interviewee if they would accept to be followed up for their AET from another HCP such as the BCN or the pharmacist. In this study, BCS would overall accept BCN to take over parts of the AET follow-up, especially side-effect management and AET adherence. However, participant 10 experienced that her BCN was not certain about taking responsibility to share side-effect coping strategies. *'I remember that I asked the nurse during the radiotherapy to help me with the burning and she had to go ask the doctor. So I think they should be educated for the special needs of us and then I think BCN could actually take up parts of the follow-up but they need to take responsibility otherwise I can ask the physician myself'.* Thus, BCS highlighted that in order for this responsibility shift to occur, BCN should follow specific training. Patients expressed only mild trust in pharmacists and see them more as "sellers" of a product. *'No no I don't talk to the pharmacist about my disease. No, not at all, I don't tell him about my life. He sells me my treatment' (Participant 6)*

2.4.5 Healthcare providers - "Post-acute treatment follow-up need"

This topic revealed two categories: 1. 'Lack of post-acute treatment structure' and 2. 'AET complexity'.

Lack of post-acute treatment structure

HCPs' interviews revealed a major lack of a systematic follow-up structure for the post-acute treatment phase in BCS. This leads to, on the one hand, that HCP are confused about or even neglecting their roles in the follow-up of BC survivorship and AET management. Some HCP share their practices and experience with other fellows but overall they expressed the need for a multidisciplinary teamwork environment. '*Collaborating with other physicians would be great and is partially done but as we don't have a systematic structure of the BCS follow-up patients can see other physicians without me knowing. Another advantage would be to work closer with BCN, however, to date, we only have 1 per hospital and thus the workload would not be possible.' (Oncologist 1).*

On the other hand, interviews showed that a shift in responsibilities could help create a structure for BCS follow-up as oncologists claimed to be willing to give up some of their post-acute treatment responsibilities to BCN, who themselves are willing to pick up more responsibilities. *'Breast cancer nurses could take over parts of the AET follow-up in BCS. On the one hand, we got formed in psychology and social work, are aware of clinical matters regarding AET and are in close contact with oncologists. On the other hand, we already get to know the patients during the acute phase of the treatment.' (Nurse 3)*

The main concern for integrating BC survivorship follow-up into the clinical pathway is the potential increase in workload. To date, only one BCN is hired per hospital making it unattainable to shift more responsibilities to BCN. *'We would most definitely be able to take over a good part of BCS follow-up, however, we are only one breast cancer nurse per hospital, so if we would need to follow up every single patient plus our daily work it would simply not be possible. In that case, we need to form more breast cancer nurses' (Nurse 2).* According to the oncologists, the more in-depth follow-up would increase their workload and thus unlikely to be implemented. Pharmacists on the contrary would welcome more engagement in the AET management as they stated to be unrecognized for their qualifications. *'I really think that the role of the pharmacist needs to shift,*

we need to be recognized as those responsible, in collaboration with the physician, for the follow-up of treatment. We are not only product sellers.' (Pharmacist 1).

AET complexity

Results from the interviews revealed that HCP tend to neglect the issue of AET non-adherence and the related management challenges. Some believe that the worst part of BC patients' treatment is over and that taking one pill a day should be easy. Nevertheless, HCP admit that there is a lack of systematic follow-up regarding AET management and adherence.

Thus, HCP claim increased sensitization for AET, by using specific communication techniques. '*I try to use a schematic illustration to explain the mechanism of the adjuvant endocrine therapy. I think using this schematic illustration helps the patient to better understand how the treatment works and also why it is important.' (Oncologist 3)* This helps to simplify the understanding of the AET importance. Oncologist 2 and Nurse 1 believe that the timing of communicating the AET is important and repetition of this communication should be considered. *'I noticed that the timing of introducing the AET is crucial. (…) some patients are not able to listen and capture all the AET information. Therefore I started to introduce the AET during the acute phase.' (Oncologist 2) 'Often we share the task of informing the patient. So the oncologist tells the patient about the adjuvant endocrine therapy during the consultation. Then we [breast cancer nurses] repeat it one more time when we see them.'(Nurse 1)*

Finally, oncologists highlighted that they rely completely on patients' collaboration regarding AET adherence and thus highlighted the need for better management and monitoring of the AET. '*Indeed monitoring adherence in real-time would definitely benefit my consultations because I could target patients that are non-adherent, this would improve the quality of the consultations and saves time. Patients often hesitate to tell the truth about whether they took their pill. (Oncologist 2)'*

2.4.6 Healthcare providers - "Patient-provider communication"

This topic revealed three categories: 1.'personalized communication', 2.'Lack of training' and 3. 'Availability'.

Oncologists announced that AET management challenges require personalized consultation, and adapting to each patient's health literacy and level of information understanding *'I notice that my patients differ in how they take up the information about their disease and treatment, so I have to adapt from my side how I communicate the information to that patient in order for her to understand it.' (Oncologist 1)*

Nevertheless, patient-provider communication is challenging for most providers as it is not included in the curriculum of their education and most of them rely on practice scenarios and experience; *'The things we learned at school are so different to what actually happens in reality.' (Pharmacist 1)*

Besides, oncologists and BCN highlight that BCS expects them to be available all the time which once again points out the urgent need for a BC survivorship follow-up structure within the clinical pathway; *'My patients call me and write emails while on vacation, there is a limit and I believe that such an eHealth tool could support me for example in this regard as the breast cancer nurse or my colleague could then handle patients needs' (Oncologist 4)*

2.4.7 BCS & HCP common topic "eHealth technology as a support tool"

BCS categorized this topic into 'current practices', 'survivorship companion', 'barriers of usability' and 'facilitators of usability'. HCP's interviews revealed three categories; 'real-time remote monitoring', 'barriers of usability' and 'facilitators of usability'.

BCS stated that to date they mostly use the Internet as a source of information regarding their treatment and/or disease and phone alarms to be reminded to take their AET. *'Every morning at 9*

my phone rings, then I know that I have to take my pill. So I set this reminder on my phone myself' (Participant 1)

If BCS were to use an eHealth technology that supports them during BC survivorship and more precisely with their AET management, they would expect it to be a survivorship companion. Especially, during the initiation phase of AET, BCS claimed increased support and the need for reassurance. *'At the beginning of my treatment, I would have needed to be reassured more often because I was on my own. (...) an application could potentially help to reassure us.' (Participant 6).* Therefore, such an eHealth technology could provide reinforced support and assistance during the shift from the acute treatment phase to the post-acute treatment phase, while supporting AET initiation and side-effect management. Furthermore, eHealth technology including real-time patient-provider interaction with intervention strategies that are informational, and motivational are the most preferred intervention component among BCS. *'I know my oncologist has a lot of work sometimes I hesitate to contact him, in that case, direct communication would help' (Participant 2)*

HCP stated that such eHealth technologies could positively impact their consultations by remotely monitoring in real-time AET management (eg adherence and side-effects) thus personalizing consultations to the individual BCS. *'I rely on what my patients tell me, some are so nervous and scared that they forget their questions, so it is hard to intervene or support them. (...) With a monitoring system of patients' health-related data as in this context, treatment adherence could ameliorate our consultations.' (Oncologist 1)*. Nevertheless, HCP are firm that this monitoring aspect should not be time-consuming and thus propose an integrated alert system that notifies non-adherence behaviour and/or occurrence of side-effects. *'I think that this monitoring system needs to work with an integrated alert system because I won't be able to individually follow up who took their treatment and who reported side-effects (Nurse 3)*

Barriers and facilitators to using eHealth technologies to support BCS with their AET

Both BCS and HCP claimed barriers and facilitators related to the usability of eHealth technology, which is summarized in Table 2.2. A common facilitator is that the eHealth technology needs to be user-friendly, by allowing easy navigation and lay language. *'All these medical terms are so difficult to remember, or even to understand. Having a place with a 'normal' language would have helped me a lot' (Participant 7), 'The system needs to be easy to use, with one click I should have my information.' (Nurse 1).* Security and confidentiality are the common barriers to eHealth technology usability. *'Before implementing such a system I think we have to evaluate the data protection, who has access and how do we secure the access?' (Oncologist 4), 'If the security is not given I wouldn't like to use the application.' (Participant 14).* BCS are concerned that information provided within such an application could be shared for instance with their 3rd parties. Thus, BCS expect the eHealth tool to secure data and grant restricted access.

Table 2.2: Perceived eHealth usability facilitators and barriers in both BCS and HCP

	Barriers of usability	Facilitators of usability
BCS	• Inconvenience & inaccessibility • Security & confidentiality • Replacement of standard of care	• Personalized setting • Approval of Physician • User-friendly • Appearance • Added value to daily life
HCP	• Workload • Security & confidentiality • Patient blaming	• Real-time monitoring • User-friendly • Integration into the healthcare system

Furthermore, BCS declared that additional costs regarding the app would make such a tool non-accessible. It was important for BCS to raise the concern that such an eHealth intervention should

by no means be a replacement for the current standard of care. *'An app is nice but I want to keep the contact and consultations with my physician, I think this is important.' (Participant 8)*

Regarding HCP, they declared that additional workload and blaming BCS for non-adherence would be major barriers to eHealth technology usability. *'eHealth applications are awesome if they are a support and help the patient with taking their meds. However, I would not support these tools if their goal or intention is to control or even blame the patient when not taking the drugs, [...].' (Oncologist 3)*

In relation to other facilitators of usability, BCS interviews highlighted that they would welcome tailoring this eHealth support tool by modifying the timing of reminders, colours, text size and information. *'(...) using red or green could facilitate to know when I took my pill or not' (Participant 11)*

Other facilitators for HCP, regarding eHealth technology usability in the context of BC survivorship, are that the tool should allow real-time monitoring and be integrated into the healthcare system. *'I personally believe that the system must be integrated into our hospital in order to use it on a daily basis.' (Oncologist 3).*

Personae types of eHealth technology supporting AET management acceptance

Four different types of eHealth technology supporting AET management acceptance were identified based on the finding of the qualitative interviews. Each type was identified based on the reasoning for accepting eHealth technology to enhance AET.

- Type 1: Dr demands me to use this eHealth technology

'I would use this application only with the approval of my physician' (Participant 1)

- Type 2: Technology Admirer

'I love love love technology. I also have the newest iPhone and it helped me also a lot during my chemotherapy' (Patient 11)

- Type 3: Practical skills that add quality and value to BCS's life.

'All the apps I use so far need to be helpful, have purpose and facilitate my everyday life. I use an app called Doctena, you have a list of physicians available. You select a speciality and BAM all the relevant physicians.' (Participant 14)

- Type 4: Healthcare team connection, I feel reassured.

'A potential app should definitely be able to provide communication with my healthcare team in the hospital. Yes, that would be great. I would use this tool myself.' (Participant 4)

A proposed eHealth support application for breast cancer survivorship

The interviews provided an in-depth understanding of BCS's and HCP's needs, expectations and acceptance of an eHealth support tool during BC survivorship, improving AET management in a personalized real-time manner. Figure 2.2, schematically illustrates components and features that would meet those needs thus rendering the tool suitable to use in practice.

Figure 2.2: eHealth support application for breast cancer survivorship

Figure 2.2 demonstrates a BC survivorship companion with an integrated interactive interface with BCS's healthcare team. This BC survivorship companion comes in the form of an application and entails four significant components; 'AET management', 'Medical information', 'Social support network' and 'Communication with healthcare team'.

The proposed real-time interface application collects BCS health data such as medication adherence and side-effect measures or specific questions and connects those to the clinical healthcare structure. In case of abnormal measures, HCP are notified and able to intervene with BCS in the moment of need. HCP and BCS accepted phone calls or direct messages as means to communicate.

Also, the proposed real-time interface application offers personalization facilities, and a real-time interface, and provides information and motivation for the BCS as well as comfort and reassurance. Meanwhile, this application needs to guarantee data security, confidentiality and accessibility.

2.5 Discussion

The present study investigated BCS and HCPs' needs and expectations during BC survivorship as well as their expectations and acceptance of an eHealth technology to support AET management.

BCS claimed increased support during the initiation phase of the AET and the acceptance that survivorship is more than solely a medical threat. Indeed, previous literature highlighted the recurrent request from BCS regarding increased support during BC survivorship, as they report anxiety, fear, and struggle to find their way back into everyday life (Hurtado-de-Mendoza et al., 2018; J. M. Jacobs et al., 2020; Kantsiper et al., 2009). The results of this study point out the importance of using the ABC taxonomy by Vrijens et al as the need, between the different adherence stages, differs (Sarradon-Eck et al., 2012; Vrijens et al., 2012a) 22). In the context of BCS and AET, results observed specific challenges during the initiation phase as patients are overwhelmed and often unaware of the importance of the treatment (Clancy et al., 2020). During the implementation phase of BCS struggle to integrate their AET into their daily routines and develop adequate coping strategies.

Unawareness of AET importance mostly goes back to a lack of communication skills among HCP and the lack of an integrated post-acute follow-up structure for BCS within the clinical setting. This lack is the major barrier for HCP to answer to the needs of BCS during AET. Even though it is suggested that healthcare systems, HCP and BCS should work closely together while promoting medication adherence and overall AET self-management (Wagner, 1998), no systematic follow-up is put in place and AET management remains often the patient's matter. For adequate AET initiation, implementation and persistence, HCP should provide appropriate and systematic education and behavioural support to increase BCSs' during the post-acute treatment phase of BC survivorship (Clancy et al., 2020; Finitsis et al., 2019; Rosenberg et al., 2020). Though HCP claim to use lay language to explain AET complexity, patients stated that HCP could make a bigger effort in using lay language and more empathy (Moore et al., 2018; Wilkinson et al., 2002). Improving communication skills not only increases the correct message delivery but also has the potential to reduce consultation by 12% shorter (Wilkinson et al., 2002). Thus, it is undebatable that good patient-provider communication is essential during the post-acute treatment phase (Finitsis et al., 2019; Kantsiper et al., 2009; Lowe et al., 2011; Ringwald et al., 2017).

BCS from this study favour increased interaction with their BCN because they on the one hand already build a close connection during the acute phase of treatment and on the other hand are aware of the busy time schedule of their

oncologist. This goes hand in hand with the beliefs of the HCP, as oncologists claimed to be willing to shift some of their AET follow-up responsibilities to BCN, who themselves are willing to take up some of this responsibility. However, the biggest constraint at this stage is the lack of a clear post-acute treatment structure for AET management and BC survivorship within the clinical pathway. This means that neither BCN nor oncologists claim to have time to take more of these activities. Therefore, healthcare policymakers are addressed to take this challenge up on their agenda. Literature showed that pharmacists do have the potential to play an active role in medication management. In order for this model to be effective clear guidelines need to be set and multidisciplinary teamwork encouraged (De Geest et al., 2020; Gagné et al., 2022; M. P. Schneider & Burnier, 2022). Oncologists, BCN, pharmacists and potentially other stakeholders involved in the BC survivorship follow-up such as generalists, gynaecologists and the patient himself should be working hand in hand to develop a personalized AET management plan including all of the relevant providers at the moment of need at specific follow-up time points.

In this study, BCS and HCP both claimed to accept an eHealth technology to support post-acute treatment follow-up, AET management being one component. BCS expect an eHealth technology to operate as a survivorship companion focusing on adjuvant endocrine therapy management (eg adherence and side-effects), medical information, social support network, and interaction with healthcare providers. Indeed, recent literature showed the positive impact interactive eHealth interventions can have on medication adherence (Finitsis et al., 2019; Lin et al., 2017; Paranjpe et al., 2019; Pouls et al., 2021). Regarding HCP, the eHealth technology needs to provide a real-time AET monitoring component to allow personalized follow-up consultations with BCS. HCP's major concerns with an eHealth technology supporting BCS post-acute treatment phase are the potential workload and patient shaming.

Finally, eHealth could be the key to ameliorating patient-provider communication, supporting post-acute treatment and being the link to structure the post-acute treatment phase for BCS within the clinical pathway by using remote monitoring thus and encouraging multidisciplinary teamwork.

Strengths, limitations and future research perspective

The main strength of the present study is that both HCP' and BCS' beliefs and attitudes were investigated respectively, based on guidelines and recommendations to ensure that patients' needs and expectations were taken into account. This allowed revealing similarities and differences in needs and acceptance regarding eHealth support technology in the context of BC survivorship and AET management. This study additionally helps to determine crucial requirements and assets for an eHealth support technology regarding its usability and implementation within the healthcare sector.

The present study had a rather heterogeneous population, providing a global picture of the current AET management needs and challenges. Even though the results are not generalizable due to the qualitative nature of the study, the data allow for the comparison of similarities and differences between research contexts.

Interviewees were volunteering participants, thus they might, in general, be already more implicated in their health and have better medication adherence and may be more positive about monitoring medication adherence using eHealth technology than the wider population of BCS and HCPs. Excluding male participants from the study could be seen as a limitation, yet we believe that the needs of men are different and thus need their specific investigation.

Nevertheless, this study points out some key take-home messages (Text box 1) for future research in the context of BC survivorship and the use of eHealth technology as a support tool. Therefore, future research should focus on improving BCS and HCP communication and AET management, specifically during the initiation and implementation phases. Co-design principles should be used to develop a first prototype and beta-test its efficacy. Vo et al showed in their review that to date only a few studies have investigated user expectations or perceptions of a digital health solution prior to its use(Vo et al., 2019). In addition, current literature focusing on medication adherence-enhancing interventions observes a major gap in theory-based interventions (Conn & Ruppar, 2017; Finitsis et al., 2019; Rosenberg et al., 2020; S. M. Smith et al., 2021; Wiecek et al., 2019). Therefore using the results of this study and applying existing taxonomies and frameworks (Lowe et al., 2011; Michie et al., 2011; Ribaut et al., 2020; Skivington et al., 2021; Vrijens et al., 2012a) should be the next step in developing personalized, implementable and effective interventions that will improve AET adherence among BCS. Meanwhile, clear post-acute treatment strategies need to be discussed by healthcare policymakers to allow for multidisciplinary teamwork in the context of BC survivorship and AET management. Also, clear roles for implicated HCP need to be set and patient-provider communication strategies promoted.

2.6 Conclusion

Even though AET management is challenging for BCS, they are also experiencing psychosocial difficulties that make BCS often feel overwhelmed and isolated. This is mostly perceived as insufficient information and support from HCP. This study showed that the major barrier for HCP to answer to the needs of BCS during AET is the lack of an integrated post-acute treatment structure within the clinical setting. Due to the absence of a systematic follow-up, AET management remains often the patient's matter.

Therefore, eHealth technology as a BC survivorship companion could link the gap between BCS claimed needs and integrate the lack of a systematic post-acute treatment follow-up for AET management in a clinical setting. Key components of this eHealth technology should be patient-provider interaction, support, information and remote AET monitoring while encouraging multidisciplinary teamwork.

2.7 Acknowledgements

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Take home messages from Chapter 2

Breast cancer survivors needs during post-acute treatment phase

- Increase support from healthcare provider during the initiation and implementation phase of the adjuvant endocrine therapy
- Increase social and and private assistance during the shift from patient to survivor
- Improved communication with healthcare provider

Breast cancer survivors eHealth technology expectations and acceptance

- eHealth technology should be a BC survivorship companion in addition to standard of care
- Promote real-time interaction with healthcare provider
- Be multifaceted; adjuvant endocrine therapy management (e.g adherence and side-effects), medical information, social support network, interaction with healthcare provider

Healthcare provider needs during post-acute treatment phase

- Restructuring and integrating post-acute treatment follow-up in clinical setting
- Shift of responsibilities between healthcare providers (e.g. Breast cancer nurses should have increased responsibility in the management of the adjuvant endocrine therapy)
- Increased multidisciplinary teamwork

Healthcare provider eHealth technology expectations and acceptance

- Real-time monitoring of adjuvant endocrine therapy for more personalized consultations
- Avoid shaming the patient
- Allow for better allocation of resources to avoid added workload
- Integration into the clinical setting

Link with the following chapter

This Chapter provided sound information on the BCS' and HCPs' beliefs and needs during BC survivorship and their expectations and acceptance of an eHealth tool to support AET management. Thus the next chapter can dive into the identification of the current usability of eHealth technologies and determine differences in BC survivors accepting a medication adherence-enhancing eHealth technology to support their AET to BC survivors that do not accept such a medication adherence-enhancing eHealth technology.

Chapter 3

Analysing breast cancer survivors' acceptance profiles for using an electronic pillbox connected to a smartphone application using Seintinelles, a French community-based research tool

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Title: Analysing breast cancer survivors' acceptance profiles for using an electronic pillbox connected to a smartphone application using Seintinelles, a French community-based research tool

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3.1 Abstract

Introduction:

Up to 50% of breast cancer (BC) survivors discontinue their adjuvant endocrine therapy (AET) before the recommended 5 years, raising the issue of medication non-adherence. eHealth technologies have the potential to support patients to enhance their medication adherence and may offer an effective way to complement healthcare. In order for eHealth technologies to be successfully implemented into the healthcare system, end-users need to be willing and accepting to use these eHealth technologies.

Aim:

This study aims to evaluate the current usability of eHealth technologies and to identify differences in BC survivors accepting a medication adherence enhancing eHealth technology to support their AET to BC survivors that do not accept such a medication adherence enhancing eHealth technology.

Methods:

This study was conducted in 2020 including volunteering BC survivors belonging to the Seintinelles Association. Eligible participants were women, diagnosed with BC within the last 10 years, and been exposed to, an AET. Univariable and multivariable logistic regression analyses were performed to investigate medication adherence enhancing eHealth technology acceptance profiles among BC survivors. The dependent variable was defined as acceptance of an electronic pillbox connected to a smartphone application (hereafter: medication adherence enhancing eHealth technology).

Results:

Overall, 23% of the participants already use a connected device or health application on a regular basis. The mean age of the participants was 52.7 (SD 10.4) years. In total, 67% of 1268 BC survivors who participated in the survey declared that they would accept medication adherence-enhancing eHealth technology to improve their AET. BC survivors accepting a medication adherence enhancing eHealth technology for their AET, are younger (OR = 0.97, 95% CI [0.95; 0.98]), do take medication for other diseases (OR = 0.31, 95% CI [0.13; 0.68]), already use a medication adherence enhancing eHealth technology or technique (OR = 1.74, 95% CI [1.06; 2.94]) and are willing to possess or currently possess one or more connected devices or health applications (OR = 2.89, 95% CI [2.01; 4.19]).

Conclusion:

Understanding the acceptance profiles of BC survivors is fundamental for conceiving an effective eHealth technology enhancing AET among BC survivors. Hence, such profiling will foster the development of personalized medication adherence-enhancing eHealth technology.

Keywords: breast cancer; eHealth; medication adherence; medication adherence enhancing interventions; patient adherence; user-centered design.

3.2 Introduction

Breast cancer (BC) is the most common cancer among women, as 355,000 are estimated to be diagnosed with BC each year in Europe (International Agency for Research on Cancer et al., 2020). The majority (80%) of BC patients are hormone receptor–positive and most (>90%) have stage I to III and are eligible for adjuvant endocrine therapy (AET) (Partridge et al., 2003).

The shift, that BC survivors experience from the acute phase of treatment (e.g., surgery, chemotherapy, radiotherapy) to the post-acute phase (e.g., AET), is associated with social and medical challenges (Goetzinger et al., 2021; Hurtado-de-Mendoza et al., 2018; Kantsiper et al., 2009). Patients recurrently reported the need for increased support in terms of AET management (adherence and side-effects) as well as increased patient–healthcare provider communication and follow-up (Finitsis et al., 2019; Pouls et al., 2021). During this post-acute treatment period, most BC survivors report anxiety, fear, and struggle to find their way back into everyday life. In addition, BC survivors usually do not visit their oncologist for a relatively long period during the post-acute treatment phase (Goetzinger et al., 2021; Ringwald et al., 2017). Thus the value of HCP support during this survivorship period of BC patients is undebatable for medication adherence and disease management (Kini & Ho, 2018).

Medication adherence is a dynamic behaviour influenced by various factors (Kardas et al., 2013; Sabaté, 2003) and is defined as the process by which patients take their medication as prescribed. This medication adherence process is further categorized into three distinct phases: 1. *Initiation* (patient takes the first dose of prescribed medication), 2. *Implementation* (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken) and 3. *Discontinuation* (occurs when the patient stops taking the prescribed medication, for whatever reason(s)) (Vrijens et al., 2012a). Previous work demonstrated that 30%–50% of BC survivors discontinue their AET before the recommended 5 years end depending on the AET agent and method of medication adherence measurement (Huiart et al., 2011) Moreover, it was shown that AET reduces BC recurrence rate by 50% and mortality by a third (Early Breast Cancer Trialists' Collaborative Group (EBCTCG) et al., 2011; Pistilli et al., 2020). Therefore, it is key to identify AET non-adherence, to reduce the risk or poorer health outcomes (Pistilli et al.,

2020). To date, there is no gold standard to identify non-adherence. Indirect methods such as pharmacy prescription refills or patient-administered questionnaires are mostly used, yet fail to measure the real medication intake or even overestimate adherence (Lu et al., 2018).

The World Health Organization defines eHealth 'as the cost-effective and secure use of information and communications technologies in support of health and health-related fields, including health-care services, health surveillance, health literature, and health education, knowledge and research (World Health Organization, 2023). Concerning the field of medication adherence research and eHealth, medication adherence technologies (MATech) such as electronic pillboxes or smartphone applications have been developed(Ahmed et al., 2018). Car et al. highlighted that these MATechs are the future for self-management of treatment and medication adherence monitoring (Car et al., 2017). A systematic review by Nieuwlaat et al. showed that MATechs are most effective if multiple components, trying to overcome barriers to adherence by means of tailored ongoing support from allied health professionals are used (Nieuwlaat et al., 2014). Nevertheless, the most effective interventions did not lead to large improvements in adherence or clinical outcomes (Finitsis et al., 2019; Hadji et al., 2013; Rosenberg et al., 2020). This is because most of those interventions were created without the involvement of the end-user, whereas patient involvement is key in research and implementation in the healthcare setting (Aguayo et al., 2021; Ribaut et al., 2020). Thus, BC survivor involvement is key to conceiving effective MATechs to enhance AET. In order to personalize medication adherence-enhancing interventions for subtypes of BC survivor users, it is important to profile the acceptance of BC survivors to use medication adherence-enhancing eHealth technology for AET enhancement.

Therefore, the present study aims to 1) evaluate the current usability of eHealth technologies in BC survivors and to 2) identify differences in BC survivors accepting medication adherence enhancing eHealth technology to enhance their AET to BC survivors that do not accept such a medication adherence enhancing eHealth technology. In this study, we define medication adherence-enhancing eHealth technology as an electronic pillbox connected to a smartphone application.

3.3 Method

3.3.1 Study design

A cross-sectional, e-survey was conducted from July to December 2020 among BC survivors from the French Seintinelles platform (www.seintinelles.com). Seintinelles is a non-profit community-based research platform, developed in collaboration with psycho-oncologists to facilitate the implication of patients in cancer research (Bauquier et al., 2017; Pannard et al., 2020). Volunteering citizens, regardless of their current health condition and/or cancer type, can participate in this platform, comprised of over 8000 BC patients (in 2020), the target population of the present study. Thus, this platform has the ability to recruit a large number of participants in a very limited time.

3.3.2 Recruitment and study population

Seintinelles sent an email to all its BC members, informing them about the study objectives, along with the information sheet (Appendix 3.1). If they were interested in participating, they were asked to complete a short questionnaire on the website to verify that they met all the inclusion criteria (Appendix 3.2). Inclusion criteria for this e-survey were:

- Women
- BC diagnosed within the last 10 years
- At least temporarily exposed to an AET

If participants met all inclusion criteria and still wanted to participate, they signed an e-consent form before starting the e-survey.

3.3.3 e-survey

The e-survey used within the present study aims to establish a state of art on current eHealth usability and potential acceptability of medication adherence enhancing eHealth technology in BC survivors.

The e-survey consists of about 30 questions and required participants' attention for at least 20 min. They had the option to interrupt the questionnaire and could save their answers to continue later. There were no incentives given to participants. BC survivors (N = 2) proofread the final version of the e-survey. CG and CA as well as employees of Seintinelles pre-tested the e-survey with respect to technical errors and incorrect utilisation of question filters. While conducting the e-survey, participants could only see one question at a time. It was mandatory to answer the question in order to get to the next. This method was used to ensure that no questions were left unanswered.

3.3.4 Measurement

The e-survey was subdivided into five sections to collect data on socio-demographic characteristics, health status and disease experience, medication adherence, eHealth utilization and a specific section on medication adherence enhancing eHealth technology. For more information, Appendix 3.3 illustrates the structure and definitions of the e-survey.

Sociodemographic characteristics

The first section of the e-survey collected data on participants' age, marital status, having children and the number of children. In addition, participants responded to questions asking about their educational, professional and financial status. These items were adapted from the questionnaire used in Vican 5, a French nationwide population-based questionnaire aiming to explore life 5 years after cancer diagnosis (Bauquier et al., 2017).

Health status and disease experience

The second section investigated participants' general health status and their experience with BC in the acute phase of treatment. These questions were either developed by CA and CG or taken from Vican 5 (Bouhnik et al., 2015).

AET adherence

The third section analyzed adherence to AET in terms of persistence and if discontinuation for which reasons. In addition, this third section investigated experienced side-effects and the use of

support by psychologists or alternative medicine. Furthermore, current techniques or eHealth technologies used to support participants with their AET intake were investigated.

This section sums up by evaluating the patient–physician relationship and communication. CA and CG developed these questions.

eHealth utilization

Section 4 evaluated current eHealth utilisation. This section of the questionnaire-survey was based on a self-administered qualitative questionnaire used in social psychology science in the DISCO trial (DISpositif COnnecté', connected device in English) investigating the use and acceptability of connected devices in breast cancer (Touillaud et al., 2021). As in the questionnaire from the DISCO trial, we provided the participant with two definitions, explaining 'connected device' and 'mobile application'. In contrast to the DISCO trial questionnaire, the present study focuses more precisely on adherence to OHT in BC survivors, thus additional items, created by CG and CA, were based on the results found by (Goetzinger et al., 2021).

Medication adherence enhancing eHealth technology

The fifth section investigated acceptability and related barriers and facilitators to acceptability and usability of a proposed medication adherence enhancing eHealth technology supporting AET management in BC survivors. This paper will only focus on the first question of this section, as it is the dependent variable used for the univariable and multivariable logistic regression analyses.

3.3.5 Dependent variable

The dependent variable 'Acceptance of a Medication adherence enhancing eHealth technology (electronic pillbox connected to a smartphone application)'' (1 = yes, 0 = no) was computed from 'Would you accept to use an electronic blister connected to an application on your phone to support your AET treatment'. Hence, we categorized the following answers together to receive a binary variable;

'Yes' includes the following answer options:

- 'Yes, I accept voluntarily',

- ‘Yes, if my Doctor asks me to’,
- ‘Yes, depending on the information provided’.

‘No’ includes these answer options;

- ‘No, I do not trust connected devices’,
- ‘No, I don’t know how to use new technology’,
- ‘No, I don’t have a smartphone and I don’t want one’,
- ‘No, for other reasons’.

3.3.6 Ethical provision

The study received approval by the National Commission for Information and Freedoms (Commission nationale de l’informatique et des libertés, CNIL: 1955704) and the Sud-EST II data protection committee (Comité de Protection des données, Numéro EudraCT: 2020-A00665-34).

3.3.7 Statistical analysis

This study uses descriptive statistics to characterize the study population and to highlight current patterns of eHealth use in BC survivors. Univariable and multivariable logistic regression analyses were performed to evaluate differences in BC survivors that accept an electronic blister connected to an app to support AET adherence with those that do not. Odds ratios were used as the measure of association to compare the strength of the correlation between ‘Medication adherence enhancing eHealth technology acceptance’ and relative predictors. We performed a both-way stepwise logistic regression analysis to investigate factors that are significantly associated with accepting an electronic blister connected to the app to support AET adherence. The final model was retained as the lowest AIC was achieved. Significance was accepted at a *p*-value lower than 0.05, with a 95% Confidence Interval. We used the R software version 4.0.3 including the ‘ISwR’, ‘oddsratio’, ‘StepReg’, ‘forestplot’ and ‘dyplr’ packages to analyse the data and conceive the figure. This study used only completed questionnaires in order to avoid weighing and computation of missing values.

3.4 Results

Overall, 1,516 eligible Seintinelles members started the questionnaire, and 1268 BC survivors responded to the complete online questionnaire and were used for the analysis. No missing values were recorded in our dataset as participants could only proceed with the questionnaire when the previous question was answered.

The overall study sample is on average 52.7 years (SD 10.4) old, over half are married (73.9%), and employed (60.3%) (Table 3.1). Furthermore, 46% of the overall sample reported good general health, and more than half of the study sample did not use any other medication for other diseases (52.8%). 21% of the participants were diagnosed with BC before 2012, 12% in 2015 and 21% after 2018. About a third (32.6%) of the BC survivors state that their BC does have 'some effect' on their life. Only 7.7% of the BC survivors evaluate themselves to be able to control their disease and almost 40% claim to have very good knowledge about the disease. Moreover, 88% highlighted that they had no BC recurrence up to the date of the questionnaire completion.

At the time of the questionnaire, 69.6% of the BC survivors were taking an AET, 91.5% experienced side-effects and 9.2% interrupted their AET. Most women stated that their GP is somewhat implicated in their BC follow-up. A third (33.8) of the BC survivors stated that the information provided by their physician regarding the benefits of their AET is satisfying.

Table 3.1: Descriptive characteristics of BCS (Seintinelles study, 2020)

	Overall (N=1268)	Acceptance of an Electronic Blister Connected to an App		
		YES (N=845)	NO (N=423)	P-value
Total	100%	66.6%	33.4%	
Sociodemographic characteristics				
AGE (mean, SD)	52.7 +-10.4	51.4 +- 10.3	55.3 +- 10.3	<0.001
MARITAL STATUS Single Married Widow Divorced	 156 (12.3%) 937 (73.9%) 34 (2.7%) 141 (11.1%)	 95 (11.2%) 646 (76.4%) 19 (2.3%) 85 (10.1%)	 61 (14.4%) 291 (68.8%) 15 (3.6%) 56 (13.2%)	0.031
CHILDREN Yes No	 1021 (80.5%) 247 (19.5%)	 686 (81.2%) 159 (18.8%)	 335 (79.2%) 88 (20.8%)	0.443
EDUCATION High school degree Bachelor or equivalent Master equivalent Professional diploma Other	 205 (16.2%) 390 (30.8%) 554 (43.7%) 94 (7.4%) 25 (1.9%)	 128 (15.2%) 268 (31.7%) 371 (43.9%) 66 (7.8%) 12 (1.4%)	 77 (18.2%) 122 (28.8%) 183 (43.3%) 28 (6.6%) 13 (3.1%)	0.144
PROFESSIONAL STATUS Employed Sick leave Job hunting Retired Self-employed Other	 764 (60.3%) 61 (4.8%) 49 (3.7%) 248 (19.6%) 78 (6.2%) 68 (5.4%)	 538 (63.7%) 36 (4.3%) 31 (3.7%) 138 (16.3%) 51 (6.0%) 51 (6.0%)	 226 (53.4%) 25 (5.9%) 18 (4.3%) 110 (26.0%) 27 (6.4%) 17 (4.0%)	< 0.001

FINANCIAL STATUS At ease Difficult	948 (74.8%) 320 (25.2%)	627 (74.2%) 218 (25.8%)	321 (75.9%) 102 (24.1%)	0.560
Health status and experience with breast cancer				
GENERAL HEALTH STATUS Very good Good Ok Bad	164 (12.9%) 586 (46.2%) 462 (36.4%) 56 (4.5%)	108 (12.8%) 403 (47.7 %) 295 (34.9%) 39 (4.6%)	56 (13.2%) 183 (43.3%) 167 (39.5%) 17 (4.0%)	0.379
MEDICATION FOR OTHER DISEASE Daily Regularly In case of need No	456 (35.9%) 39 (3.1%) 104 (8.2%) 669 (52.8%)	294 (34.8%) 15 (1.8%) 69 (8.2%) 467 (55.2%)	162 (38.3%) 24 (5.6%) 35 (8.3%) 202 (47.8%)	<0.001
YEAR OF DIAGNOSIS <2012 2013 2014 2015 2016 2017 >2018	261 (20.6%) 119 (9.4%) 144 (11.4%) 153 (12.1%) 154 (12.1%) 169 (13.3%) 268 (21.1%)	164 (19.4%) 76 (9.0%) 93 (11.0%) 95 (11.2%) 101 (12.0%) 121 (14.3%) 195 (23.1%)	97 (22.9%) 43 (10.2%) 51 (12.1%) 58 (13.7%) 53 (12.5%) 48 (11.3%) 73 (17.3%)	0.113
QUALITY OF LIFE /BC IMPACT ON LIFE No effect at all Does not affect much Some effect Does effect Does effect severely	163 (12.9%) 363 (28.6%) 414 (32.6%) 245 (19.3%) 83 (6.6%)	97 (11.5%) 231 (27.3%) 283 (33.5%) 180 (21.3%) 54 (6.4%)	66 (15.6%) 132 (31.2 %) 131 (30.9%) 65 (15.4%) 29 (6.9%)	0.027
CONTROL OVER BC No control Not very much control Some control Control A lot of control	194 (15.3%) 302 (23.8%) 414 (32.6%) 260 (20.5%) 98 (7.7%)	115 (13.6%) 217 (25.7%) 289 (34.2%) 165 (19.5%) 59 (7.0%)	79 (18.7%) 85 (20.1 %) 125 (29.5%) 95 (22.5%) 39 (9.2%)	0.027

KNOWLEDGE OF BC				0.262
No knowledge	33 (2.6%)	20 (2.4%)	13 (3%)	
No real knowledge	65 (5.1%)	42 (4.9%)	23 (5%)	
Some knowledge	270 (21.3%)	190 (22.5%)	80 (19%)	
Good knowledge	412 (32.5%)	283 (33.5%)	129 (300%)	
Very good knowledge	488 (38.5%)	319 (36.7%)	178 (42%)	
BC RECURRENCE				0.683
Yes	149 (11.8%)	102 (12.1%)	47 (11.1%)	
No	1119 (88.2%)	743 (87.9%)	376 (88.9%)	
Treatment adherence				
TAKING AN OHT				0.042
Yes	882 (69.6%)	604 (71.5%)	278 (65.7%)	
No	386 (30.4%)	241 (28.5%)	145 (34.3%)	
SIDE-EFFECTS				0.598
Yes	1160 (91.5%)	776 (91.8%)	384 (90.8%)	
No	108 (8.5%)	69 (8.2%)	39 (9.2%)	
OHT INTERRUPTIONS				0.183
Yes	117 (9.2%)	71 (8.4 %)	46 (10.9%)	
No	1151 (90.8%)	774 (91.6%)	377 (89.1%)	
Patient-Physician communication				
GP IMPLICATION IN BC FOLLOW-UP				0.197
Yes, regularly	383 (30.2%)	261 (30.9%)	122 (28.8%)	
Yes, occasionally	287 (22.6%)	202 (23.9%)	85 (20.1%)	
Yes, exceptionally	239 (18.9%)	149 (17.6%)	90 (21.3%)	
No, never	359 (28.3%)	233 (27.6%)	126 (29.8%)	

BCS' SATISFACTION ON PHYSICIANS INFORMATION GIVEN REGARDING THE:				
NATURE OF THE TREATMENT				0.067
Very unsatisfying	87 (6.9%)	51 (6.0%)	36 (8.5%)	
Unsatisfying	196 (15.5%)	132 (15.6%)	64 (15.1%)	
Correct	433 (34.1%)	273 (32.3%)	160 (37.8%)	
Satisfying	353 (27.8%)	250 (29.6%)	103 (24.4%)	
Very satisfying	199 (15.7%)	139 (16.5%)	60 (14.2%)	
EXPECTED BENEFITS OF THE TREATMENT				0.017
Very unsatisfying	58 (4.6%)	34 (4.0%)	24 (5.7%)	
Unsatisfying	143 (11.3%)	93 (11.0%)	50 (11.8%)	
Correct	405 (31.9%)	249 (29.5%)	156 (36.9%)	
Satisfying	429 (33.8%)	306 (36.2%)	123 (29.1%)	
Very satisfying	233 (18.4%)	163 (19.3%)	70 (16.5%)	
TREATMENT SIDE-EFFECTS				0.077
Very unsatisfying	198 (15.6%)	125 (14.8%)	73 (17.3%)	
Unsatisfying	342 (27.0%)	227 (26.9%)	115 (27.2%)	
Correct	364 (28.7%)	231(27.3%)	133 (31.4%)	
Satisfying	247 (19.5%)	182 (21.5%)	65 (15.4%)	
Very satisfying	117 (9.2%)	80 (9.5%)	37 (8.7%)	

3.4.1 Current eHealth use among breast cancer survivors

Approximately 38% of the included BC survivors did already possess one or more connected devices or health applications and 39% of those use these tools every day (Table 3.2). 18.7% of these women use these tools to motivate themselves, followed by 14.3% to monitor their health. Current techniques or devices to help BC survivors to adhere to their AET are specific locations to store their AET blister (47.2%), phone alarm (13.0%) and Pillbox (13.3%). About 12% of BC survivors use at least two of those aids regularly. Most participants (90.3%) claim that these aids help them to adhere to their AET.

Table 3.2: Current eHealth use of BCS and acceptance to use a connected electronic blister with an app to manage OHT (Seintinelles study, 2020)

	Overall (N=1268, %)
Do you possess 1 or more connected devices or health applications?	603 (47.6%)
No, it doesn't interest me	105 (8.3%)
No, but I know someone close to me who uses them and I am interested	76 (6.0%)
No, but I plan to get one within the next 6 months	102 (8.0%)
Yes but I do not use them	92 (7.2%)
Yes I use them for 1 year	290 (22.9%)
Yes I use them already longer than a year	
If yes, how often did you use the connected device or health app in the last 3 months? (N=382)	
Never	24 (6.3%)
Less than once a month	52 (13.6%)
1-3x a month	51 (13.4%)
Once a week	27 (7.1%)
Twice a week	16 (4.2%)
3x a week	20 (5.2%)
More than 3x a week	43 (11.2%)
Everyday	149 (39.0%)
If used at least less than once a month, how do these tools help you? (N=358)	
To manage my health	19 (5.3%)
To motivate me	67 (18.7%)
To monitor my health	51 (14.3%)
To motivate me & monitor my health	20 (5.6%)
Other reason(s)	52 (14.5%)
No reason	149 (41.6%)
During your OHT, do you use any devices or specific techniques to help you with your treatment? (multiple answers possible)	
Phone alarm (yes, %)	165 (13.0%)
Pillbox (yes, %)	168 (13.3%)
A specific location to store the blister (yes, %)	599 (47.2%)
The implication of closed one (yes, %)	73 (5.8%)
Application (yes, %)	15 (1.2%)
Other (yes, %)	59 (4.7%)
None (yes, %)	452 (35.7%)
Nr of medication adherence support devices/specific techniques used.	
0	452 (35.7%)
1	607 (47.9%)
2	153 (12.1%)
>3	56 (4.3%)
If at least 1-support device/specific technique is used, do these tools help you to adhere to your medication? (N=816)	
Yes	737 (90.3%)
No	30 (3.7%)
I don’t know	49 (6.0%)

Which of the following features/facts are important for you regarding your medication adherence? (Multiple answers possible)	
Auto Surveillance (yes)	459 (36.2%)
Information disposition (yes)	554 (43.7%)
Real-time side-effect declaration (yes)	630 (49.7%)
Real-time follow-up by health care professional (yes)	499 (39.4%)
Patient-Physician communication (dematerialised) (yes)	522 (41.2%)
Pharmacy Refill Alarm (yes)	304 (24.0%)
Reduce face-to-face consultations (yes)	298 (23.5%)
Personalized follow-up (yes)	518 (40.9%)
Adherence management (yes)	213 (16.8%)
Exchange with others on treatment (yes)	344 (27.1%)
None (yes)	164 (12.9%)
Would you accept an electronic pillbox connected to an app on your phone to follow your OHT (Dependent variable)?	
Yes, voluntarily	344 (27.1%)
Yes, if asked by my Doctor	109 (8.6%)
Yes, depending on the information I receive	392 (30.9%)
No, I have no confidence in connected health devices	59 (4.7%)
No, I do not know how to use new technologies	17 (1.3%)
No, because I don't want a smartphone	28 (2.2%)
No, for other reasons	319 (25.2%)

3.4.2 Medication adherence support tool acceptance

Specific features that support medication adherence and are important for BC survivors to use real-time side-effect declaration (49.7%), information disposition (43.7%) and dematerialised patient-physician communication (41.2%) among others. Finally, the study showed that 27.1% of the participants would voluntarily accept to use of an electronic pillbox connected to an app on their phone to manage their AET.

3.4.3 Factors associated with breast cancer survivors' acceptance of an eHealth tool to manage adjuvant endocrine therapy

Table 3.3 illustrates the univariable logistic regression analysis, which analysed factors associated with accepting an electronic pillbox connected to an app to enhance AET among BC survivors. Some of the factors associated with accepting an electronic pillbox connected to an app were age (OR = 0.96, 95% CI 0.95, 0.98), being married (OR = 1.43, 95% CI 1.00, 2.02), retired (OR =

0.53, 95% CI 0.39, 0.71), taking regular medication for other diseases (OR = 0.34, 95% CI 0.17, 0.67) and using more than one support tool for AET adherence (OR = 1.53, 95%CI 0.18, 0.67).

Table 3.3: Factors associated with accepting an eHealth tool to manage OHT in BCS (Seintinelles study, 2020)

	Acceptance of an Electronic Blister Connected to an App		
Univariable logistic regression analysis	OR	95% CI	P-value
Age	0.96	0.95-0.98	<0.001
Marital status			
Single	Ref		
Married	1.43	1.00-2.02	0.047
Widow	0.81	0.39-1.74	0.589
Divorced	0.98	0.61-1.56	0.914
Professional Status			
Employed	Ref		
Sick leave	0.61	0.36-1.04	0.065
Job hunting	0.72	0.40-1.34	0.291
Retired	0.53	0.39-0.71	<0.001
Self-employed	0.79	0.49-1.31	0.816
Other	1.26	0.73-2.29	0.427
Medication for other diseases			
Daily	Ref		
Regularly	0.34	0.17-0.67	0.002
In case of need	1.09	0.70-1.72	0.718
No	1.27	0.99-1.64	0.061
Quality of life			
No effect at all	Ref		
Does not affect much	1.19	0.81-1.74	0.367
Some affect	1.47	1.01-2.14	0.044
Does affect	1.88	1.24-2.88	0.003
Does affect severely	1.27	0.74-2.21	0.398

Control over breast BC			
No control at all	Ref		
Not very much control	1.75	1.20-2.57	0.004
Some control	1.59	1.11-2.27	0.011
Control	1.19	0.81-1.75	0.365
A lot of control	1.04	0.63-1.71	0.879
Taking an adjuvant endocrine therapy			
Yes	Ref		
No	0.77	0.60-0.98	0.036
Number of medication adherence support devices/specific techniques used			
1	Ref		
2	2.09	1.36-3.28	0.001
>3	2.00	1.05-4.14	0.047
0	0.71	0.55-0.92	0.008
BCS' Satisfaction On Physicians Information Given regarding the:			
Nature Of The Treatment			
Very unsatisfying	Ref		
Unsatisfying	1.46	0.86-2.45	0.157
Correct	1.20	0.75-1.92	0.437
Satisfying	1.71	1.05-2.78	0.029
Very satisfying	1.64	0.97-2.76	0.065
Expected Benefits Of The Treatment			
Very unsatisfying	Ref		
Unsatisfying	1.31	0.70-2.45	0.394
Correct	1.13	0.64-1.96	0.676
Satisfying	1.76	0.99-3.07	0.050
Very satisfying	1.64	0.90-2.97	0.100
Treatment Side-Effects			
Very unsatisfying	Ref		
Unsatisfying	1.15	0.80-1.66	0.446
Correct	1.01	0.71-1.45	0.938
Satisfying	1.64	1.09-2.46	0.017
Very satisfying	1.26	0.78-2.06	0.346
Possession of connected devices or health applications			
No, it doesn't interest me	Ref		
No, but I know someone close to me who uses them and I am interested	1.37	0.87-1.92	<0.001
No, but I plan to get one within the next 6 months	0.70	0.20-1.23	0.008
Yes but I do not use them	1.40	0.89-1.97	<0.001
Yes I use them for 1 year	1.35	0.82-1.93	<0.001
Yes I use them already longer than a year	1.11	0.79-1.43	<0.001

Figure 3.1 highlights the stepwise multivariable logistic regression, presenting factors that are significantly associated with accepting an electronic pillbox connected to an app to enhance AET among BC survivors. The final adjusted model includes 'Age', 'Medication intake for other diseases', 'Number of medication adherence support devices used', 'BC survivors satisfaction on physicians information given on expected benefits of the treatment' and 'Possession of connected devices or health applications'. We performed both forward and backward stepwise regression and both methods selected the same variables.

Hence, accepting an electronic pillbox connected to an app to enhance AET among BC survivors is inversely associated with age (OR = 0.97, 95% CI 0.95, 0.98) and the use of regular intake of other medication compared to no other medication intake (OR = 0.31, 95% CI 0.13, 0.68) (Figure 3.1). Using at least two medication adherence support tools increases the odds of accepting an electronic pillbox connected to an app to enhance AET among BC survivors (OR = 1.74, 95% CI 1.06, 2.94). Finally, BC survivors using connected devices for more than a year is 2.89 times (95% CI 2.01, 4.19) more likely to accept an eHealth tool to enhance AET compared to those that do not possess or are not interested in connected devices or health applications.

Acceptance profiles in breast cancer survivors

Variables	Level	OR	95% lower	95% upper
Age		0.97	0.95	0.98
Medication for other diseases	Daily	Ref		
	Regular	0.31	0.13	0.68
	In case of need	0.83	0.48	1.44
	No	1.05	0.76	1.43
Nr of support tools used	1	Ref		
	2	1.74	1.06	2.94
	>3	1.92	0.88	4.55
	0	0.79	0.58	1.07
Physicians information given on the	Very unsatisfying	Ref		
expected benefits of treatment	Unsatisfying	1.20	0.57	2.49
	Correct	1.10	0.57	2.11
	Satisfying	1.66	0.85	3.18
	Very satisfying	1.71	0.85	3.42
eHealth tool possession	No, it doesn't interest me	Ref		
	No, but I know someone and I am interested	3.39	1.97	6.13
	No, but I plan to get one within the next 6 months	2.17	1.20	4.08
	Yes, but not in use	4.21	2.30	8.19
	Yes, since 12 months	4.00	2.17	7.90
	Yes, since more than 12 months	2.89	2.01	4.19

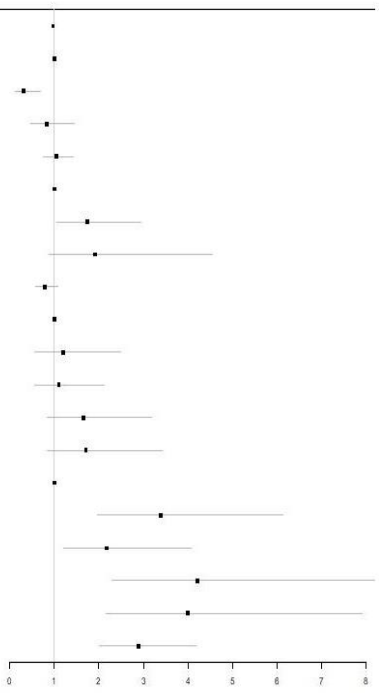

Figure 3.1: Acceptance profiles in breast cancer survivors

3.5 Discussion

This study investigated differences in BC survivors that accept an electronic pillbox connected to an app to enhance AET with those who do not.

Drewes et al. analysed the correlation between sociodemographic factors, the health status of BC patients and the willingness to use the Internet and apps (Drewes et al., 2016). They found that decisive factors influencing BC patients' willingness to use new communication technologies are younger, have a large number of people per household, and having a short time since breast cancer diagnosis. Other commonly reported barriers to medication adherence across diseases, are patient beliefs/perceptions, comorbidities and poor patient–provider communication among others (Konstantinou et al., 2020). We found similar results and add to the current knowledge that polypharmacy positively effects acceptance of a medication adherence-enhancing eHealth

technology. Furthermore, we found that those patients that have already created an AET adherence habit/technique or are willing to use a smartphone or health applications are more likely to use an AET-enhancing eHealth tool. Similar eHealth acceptance trends can be found for patients with cardiometabolic diseases, mental health disorders, and infectious diseases (AshaRani et al., 2021; Gire et al., 2021; Talal et al., 2019). In our study, we found that at the time of the survey, only 1.2% actively used an app yet 67% of the BC survivors would accept to use of the proposed electronic pillbox connected to an app to enhance their AET. As Car et al. mentioned, eHealth is the future of medication management in terms of personalisation, monitoring and adherence (Car et al., 2017). To date, digitally delivered interventions including components such as medication and condition education, motivational interviewing, reinforcement and motivational messages led to improvements in medication adherence (Finitsis et al., 2019; Hadji et al., 2013; Nieuwlaat et al., 2014; Pouls et al., 2021; Rosenberg et al., 2020). In addition, qualitative papers showed that patients are ready and willing to integrate eHealth technologies into their daily life to monitor and enhance their health status and medication intake (Currie et al., 2015; Goetzinger et al., 2021). Yet, the challenge we face is to conceive effective eHealth interventions for end-users and implement them in the healthcare sector (Car et al., 2012). Thus integrating patients into the development phase of these eHealth technologies is key to creating feasible tools for the end-user that are implementable in the healthcare setting (Bauquier et al., 2017; Pannard et al., 2020; Ross et al., 2016).

Understanding the disease and/or patient profiles will allow for personalised healthcare in the future. Characterising patient groups will allow for defining new strategies for individual patients benefiting their needs to optimise health outcomes. Recent research, using profiling principles, found that healthcare for patients with the cardiometabolic disease could benefit from more targeted and tailored strategies for the prevention of cardiometabolic diseases at a population level (Fagherazzi et al., 2021). Eventually, post-acute treatment for BC survivors using a medication adherence enhancing eHealth technology can move from a “one-size-fits-all” vision to a tailored follow-up strategy, personalizing care to each BC survivor.

This study evaluated the association between BC survivors' characteristics and the acceptance of an eHealth intervention among BC survivors. Hence, the results produced will be fundamental

when conceiving an eHealth support tool to enhance AET among BC survivors. Using patient acceptance profiling strategies will allow them to provide them with personalised care and develop effective, sustainable, and implementable eHealth support tools. Future studies should have a closer look into the specific features of such an AET support tool, examine the acceptable time point(s) of intervention and evaluate the implication of HCP. In addition, implementation strategies to adopt these eHealth technologies into the healthcare system need to be investigated.

3.6 Limitations

The present study entails several limitations. Also, the present study deals with selection bias, as the Seintinelles platform only includes volunteering members. Meaning the participants showed interest in the study topic, and also observed a high educational level among the study sample. The present study thus provides only a snapshot of characteristics for accepting eHealth tools. Some categories have a small sample and should be regarded with caution.

3.7 Conclusion

This study found that although 1.2% currently used health-related apps over two-thirds would accept to use of medication adherence-enhancing eHealth technology to enhance their AET. BC survivors are accepting and willing to be supported during their AET, yet, the medication adherence enhancing eHealth technology needs to fit their needs and profiles. Thus, understanding acceptance profiles among BC survivors is fundamental for conceiving an effective medication adherence-enhancing eHealth technology-enhancing AET among BC survivors.

3.8 Author contributions

CG contributed to the study conception and design, data analysis and interpretation, and manuscript preparation. CG, CA, MP, and LH contributed to the study conception and design. AS and BV contributed to the data analysis and interpretation. GF contributed to manuscript preparation and editing. All authors contributed to the manuscript review.

Take home messages from Chapter 3

- 1.2% currently used health-related apps over two-thirds would accept to use of medication adherence-enhancing eHealth technology to enhance their AET

- BC survivors accepting a medication adherence enhancing eHealth technology for their AET, are younger (OR = 0.97, 95% CI [0.95; 0.98]), do take medication for other diseases (OR = 0.31, 95% CI [0.13; 0.68]), already use a medication adherence enhancing eHealth technology or technique (OR = 1.74, 95% CI [1.06; 2.94]) and are willing to possess or currently possess one or more connected devices or health applications (OR = 2.89, 95% CI [2.01; 4.19]).

Link with the following chapter

Chapter 3 evaluated the association between BC survivors' characteristics and the acceptance of an eHealth intervention among BC survivors. The next chapter presents results from the same study but dives into specific intervention content and features of such an AET support tool. In addition, Chapter 4 adds major barriers and facilitators to a proposed digital MAEI.

Chapter 4

Barriers and Facilitators towards the acceptability and usability of an adjuvant endocrine therapy enhancing eHealth technology during breast cancer survivorship

Title: Barriers and Facilitators towards the acceptability and usability of an adjuvant endocrine therapy enhancing eHealth technology during breast cancer survivorship

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Currently in co-author review in order to submit to journal

4.1 Abstract

Purpose

Breast cancer (BC) survivors experience medical and psychosocial challenges during survivorship requiring a patient-co-designed eHealth intervention to meet BC survivor's needs. The present study investigated barriers and facilitators to the acceptability and usability of an AET-enhancing eHealth intervention for BC survivors.

Methods

The subjects were 1268 BC survivors recruited from the Seintinelles, a french platform facilitating the implication of patients in research. We collected study data using self-administered e-questionnaires. Eligible participants were women diagnosed with BC within the last 10 years, and have been exposed to AET. Descriptive statistics assessed the barriers and facilitators to the acceptability and usability of a proposed AET-enhancing eHealth intervention among BC survivors.

Results

The case-scenario revealed that BCS found that 86% of the study population would accept to transfer their AET adherence and side-effect data collected on the connected eHealth technology to their already implicated HCP once to twice a week. The preferred mean of side-effect reporting is a questionnaire and patient-HCP interaction should be in form of text messages or phone calls. Gamification did not make the application more favourable to be used by the participants. Finally, the main facilitators to use the proposed eHealth intervention was the possibility to report on side-effects and having a patient-HCP interaction. Having to pay for the application, not owning a smartphone as well as a lack of data protection and confidentiality were highlighted as the main barriers to using the proposed AET-enhancing eHealth intervention among BCS.

Conclusions

Implicating BC survivors in the development of an AET-enhancing eHealth intervention allows conceiving acceptable and implementable interventions that benefit the patient in the real-world setting. Understanding patient preferences regarding features help developers, and clinicians to better respond to their patient needs hence providing better healthcare services for the patient and improving health outcome.

Keywords: eHealth, Breast cancer, medication adherence, cancer survivorship, patient-physician communication, data sharing

4.2 Introduction

Over the past 40 years, cancer survival has improved and a population of cancer survivors has emerged (L. A. Jacobs & Shulman, 2017). Survivorship, the transition period from acute treatment to post-acute treatment, is different for every individual and those close to them (Mayer et al., 2017; National Cancer Institute-Division of cancer control and population science, 2022; Pollastro, 2017).

Often cancer survivors do not feel prepared for the post-acute treatment period. Accordingly, survivors have repeatedly claimed unique needs during survivorship ranging from medical to social and psychological challenges (Hewitt et al., 2007; Mayer et al., 2017; Park et al., 2018; Pollastro, 2017). In breast cancer (BC), specifically, BC survivors reported psychosocial and communication issues as well as fear and anxiety shifting from the acute treatment phase to the post-acute treatment phase (Goetzinger et al., 2021; Hurtado-de-Mendoza et al., 2018; Kantsiper et al., 2009; Lubberding et al., 2015).

A qualitative study by Goetzinger et al highlighted that these medical and psychosocial challenges frequently impact oral adjuvant endocrine therapy (AET) management (Goetzinger et al., 2021). BC survivors have difficulties initiating their AET due to a lack of or inappropriate communication regarding the treatment's importance and purpose. As BC survivors are in a state of transition, they often fall into a state of psychological distress, having the risk of delaying the initiation or not initiating AET. Due to recurrent and sometimes severe side-effects impacting the quality of life, wrong beliefs about AET and lack of patient-physician communication, BC survivors are not correctly implementing their treatment (skipping doses, performing drug holidays) or even deciding to discontinue their AET. Most of the time, AET management challenges and psychological distress remain the matter of the BC survivors. Hence, HCP often remain unaware of these difficulties as a result of no systematic AET follow-up strategies in healthcare settings (Goetzinger et al., 2021; Lubberding et al., 2015).

AET adherence is important to avoid negative health consequences. Adherence is defined as the ‘process by which patients take their medications as prescribed, composed of initiation (patient

takes the first dose of prescribed medication), implementation (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen) and discontinuation (patient stops taking the prescribed medication) (Vrijens et al., 2012a). Results showed that AET non-adherence to breast cancer treatments increased the likelihood of BC recurrence, and worse disease-free survival and mortality (Inotai et al., 2021; Pistilli et al., 2020).

Over 600 medication adherence applications exist in the App store and Google Play store yet implementation in real-world settings such as clinical practice remains scarce (Ahmed et al., 2018). Systematic reviews, reporting on AET-enhancing interventions, revealed inconclusive results on the effectiveness of these interventions (Ekinci et al., 2018; Finitsis et al., 2019; Heiney et al., 2019; Hurtado-de-Mendoza et al., 2016). Mostly these interventions are developed without the involvement of the end-users (e.g. BCS and HCP) (Ahmed et al., 2018; Vo et al., 2019). It is of utmost importance therefore to understand end-users barriers and facilitators for using an AET-enhancing eHealth intervention during BC survivorship (Grol & Wensing, 2004; Simblett et al., 2018; Svendsen et al., 2020; van den Wijngaart et al., 2018). Thus analysing in-depth key intervention components (features, tools, interventionists) that are acceptable by BCS is crucial. Therefore, the present study investigated barriers and facilitators to the acceptability and usability of an AET-enhancing eHealth intervention for BC survivors.

4.3 Methods

4.3.1 Study design

A cross-sectional, online survey among BC survivors was carried out in BC survivors from the French Seintinelles platform from July to December 2020 (www.seintinelles.com). Seintinelles is a non-profit community-based research platform, which was created in conjunction with psycho-oncologists. Seintinelles' aim is to facilitate patient implication in cancer research as well as to provide the possibility to recruit a large number of participants in a very limited time (Bauquier et al., 2017; Pannard et al., 2020). In 2020 Seintinelles counted around 8000 BC patients, who are the target population of this study.

4.3.2 Study population & Recruitment

Volunteering Seintinelles BC survivor members were recruited to participate in the present study. The Seintinelles platform sent an email to all its BC members to inform them about this study and its objectives. In addition, Seintinelles disseminated the study information in form of a newsletter on their social media channels. Both the email and the newsletter contained study information and a link to the online questionnaire. More information can be found elsewhere (Goetzinger et al., 2022). Eligible participants were female BC patients, diagnosed with BC within the last ten years, and who have been exposed, at least temporarily, to an AET. if all inclusion criteria were met, the participant was asked to sign the e-consent form before starting to answer the questionnaire anonymously.

4.3.3 Online Questionnaire - A Case-scenario approach

As this study is part of a co-design strategy to conceive an AET-enhancing eHealth intervention for BC survivors during the post-acute treatment phase, we use a case-scenario strategy. During a qualitative study, we experience that it can be difficult for participants to imagine and give feedback on an eHealth intervention that does not yet exist (Goetzinger et al., 2021). The case-scenario approach helps to facilitate the investigation of a complex scenario within a certain scenario (Erel et al., 2022). Thus this study used the case-scenario approach to set the scene for AET intake during the post-acute treatment phase in BC survivors. The full case-scenario is illustrated in Appendix 4.1. In addition, the provided case-scenario allows the participants (BC survivors) to relate to the fictitious character thus being able to answer as if the proposed AET-enhancing eHealth intervention was given to them.

Once the scene is set, the participant is guided through the proposed AET-enhancing eHealth intervention: an electronic pillbox connected to a smartphone application (Figure 4.1). The purpose of this AET-enhancing eHealth intervention is to monitor and follow AET intake behaviour and connect the BC survivor with the healthcare team.

Hence, the online questionnaire's aim was to investigate in-depth:

- Which features are relevant to enhance and/or support AET management (e.g adherence, side-effects)?
- Which features are relevant to communicate with the healthcare team (patient-HCP interaction)?
- Acceptance of medical data sharing?
- Who would you allow to be implicated in the AET monitoring?
- What are the means, mediums and frequency of communication?
- The usability acceptance of a proposed eHealth intervention?
- What are (other) barriers to this eHealth intervention usability?
- What are (other) facilitators to this eHealth intervention usability?

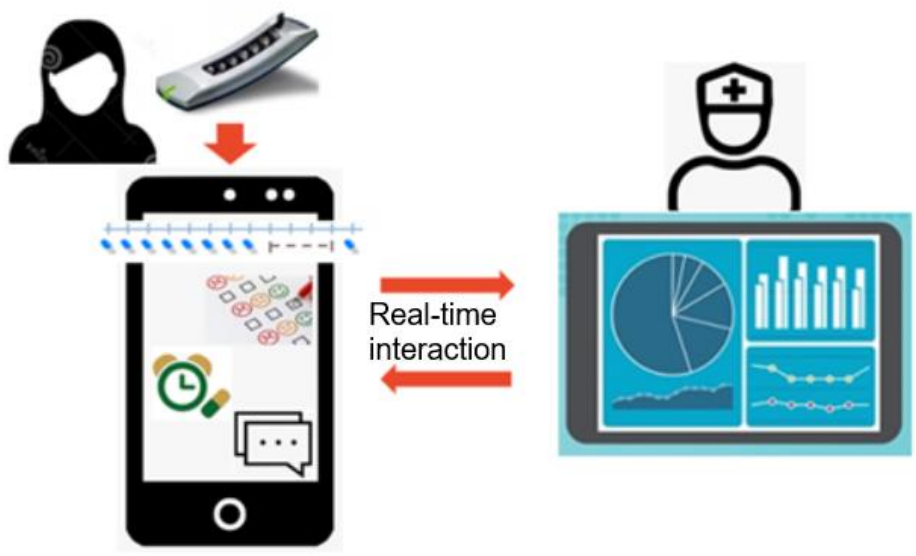

Figure 4.1: AET-enhancing eHealth intervention: an electronic pillbox connected to a smartphone application

4.3.4 Ethical provision

The study received approval from the National Commission for Information and Freedoms (Commission nationale de l'informatique et des libertés, CNIL: 1955704) and the Sud-EST II data protection committee (Comité de Protection des données, Numéro EudraCT: 2020-A00665-34).

4.3.5 Statistical analysis

We used descriptive statistics (frequency and proportions (n (%)), mean +- standard deviation (SD) and median) to characterize the study population and to elaborate on BCS's barriers and facilitators for using a connected eHealth technology to support their AET. Statistics were conducted using the R Study, version 4.0.3, including the 'ISwR' and 'dyplr' packages to analyse the data.

4.4 Results

4.4.1 Descriptive characteristics of study participants

Of the 1516 participants that started the online questionnaire, 1268 participants completed the full e-survey. In table 4.1 the descriptive characteristics of the study sample are highlighted. The majority of the participants are married (73.9 %), have children (80.5 %) and are currently employed (66.4 %). BCS reported being in rather good general health. Results showed that at the time of the survey, 69.6% of the participants were taking an AET and 91.5% disclosed experiencing side-effects, (articular pain (21%), tiredness (19%) and heat waves (19%) due to their AET. Almost a third of the BCS reported having interrupted their AET during the last 15 days at the time of the survey.

About 45% of the participant claimed to have consulted special care for their side-effects due to AET and for 35% this helped them to continue taking their AET. Almost 25%, received psychological support during their survivorship and for 18% these consultations helped them to persist with their AET. Furthermore, results revealed that for a third of the included participants, a healthcare provider is regularly implicated in their BC follow-up.

Overall, 67 % of the participants would accept using the proposed eHealth intervention (Figure 4.1). More precisely, 27% would accept using it voluntarily, 9% if asked by their doctor, and 31%if they would receive the right information. Those not accepting the eHealth intervention either do not trust new technologies (5%) or have other reasons for not accepting (28.7%).

Table 4.1: Descriptive characteristics of BC survivors (Seintinelles study, 2020)

	Overall (N=1268)
Sociodemographic characteristics	
AGE (mean, SD)	52.7 +-10.4
MARITAL STATUS Single Married Widow Divorced	 156 (12.3%) 937 (73.9%) 34 (2.7%) 141 (11.1%)
CHILDREN Yes No	 1021 (80.5%) 247 (19.5%)
PROFESSIONAL STATUS Employed Sick leave Job hunting Retired Other	 842 (66.4%) 61 (4.8%) 49 (3.9%) 248 (19.6%) 68 (5.4%)
Health status and AET managment (adherence & side-effects)	
GENERAL HEALTH STATUS Very good Good Reasonable Bad	 164 (12.9%) 586 (46.2%) 462 (36.4%) 56 (4.5%)

TAKING AN OHT	
Yes	882 (69.6%)
Yes, but temporarily interrupted	38 (3%)
No, finished prescription	241 (19%)
No, decided to discontinue	56 (4%)
No, with the shared decision with doctor	51 (4%)
AET INTERRUPTION WITHIN THE LAST 15 DAYS	
No	632 (72%)
Yes	250 (28%)
SIDE-EFFECTS, yes (%)	1160 (91.5%)
Articular pain	913 (21%)
Tiredness	866 (19%)
Heat waves	855 (19%)
Nausea	138 (3%)
Weight gain	638 (14%)
Libido Loss	621 (14%)
Other	419 (9%)
Survivorship and AET management	
SPECIAL CARE FOR side-effect MANAGEMENT	
Yes, and it helped to continue my AET taking	444 (35%)
Yes, and it did not help to continue my AET taking	128 (10.1%)
No	696 (54.9%)
PSYCHOLOGICAL FOLLOW-UP	
Yes, it helped me to continue my AET	228 (17.9%)
Yes, but it did not help to continue my AET	67 (5.3%)
No	973 (76.7%)
HEALTHCARE PROVIDER IMPLICATION IN BC FOLLOW-UP	
Yes, regularly	383 (30.2%)
Yes, occasionally	287 (22.6%)
Yes, exceptionally	239 (18.9%)
No, never	359 (28.3%)

CONNECTED PILLBOX CONNECTED TO SMARTPHONE APPLICATION ACCEPTANCE	
Overall yes	845 (66.6%)
Yes, voluntarily	344 (27.1%)
Yes, if asked by the doctor	109 (8.6%)
Yes, depending on the explanation given	392 (30.9%)
No, no confidence in connected devices	59 (4.7%)
No, don't know how to use new technology	17 (1.3%)
No, don't have and don't want a smartphone	28 (2.2%)
No, other reasons	319 (25.2%)

4.4.2 Real-time interaction between BC survivors and their Healthcare providers

Part of the case-scenario was to find out how and whom to implicate in the real-time follow-up of BC survivors taking their AET. Our results showed that 86% of the study population would accept to transfer their data collected on the connected eHealth technology to their referral hospital (Table 4.2). The preferred frequency of this data transfer was once to twice a week (31.9%).

Table 4.2: Real-time interaction between BCsurvivors and healthcare provider (Seintinelles study, 2020)

	Overall (N=1268)
Real-time interaction with Healthcare Provider (HCP)	
How often should the medication data recorded on the application be sent to the hospital?	
1. Everyday	142 (11%)
2. Multiple times a week	61 (5%)
3. Once a week	367 (29%)
4. 1-2 times a week	404 (32%)
5. Less often	112 (9%)
6. Never, I would not accept sharing my data with my referral hospital	182 (14%)
Who would you prefer as a contact person:**	
1. My general practitioner	450 (35%)
2. An HCP already implicated in my medical follow-up	870 (67%)
3. Any HCP	125 (10%)
4. A closed person, to whom I would give access to my data regarding my OHT	21 (2%)

5. A random person, regardless of their status (Anyone)	49 (4%)
6. No one, I don't want to be contacted	67 (5%)
How would you like to be contacted?*	
1. By phone call	313 (26%)
2. By text message or notification on my phone	361 (30%)
3. E-mail	184 (15%)
4. Scheduled consultation	132 (11%)
5. A questionnaire on the application	146 (12%)
6. Other	65 (5%)
When would be the best moment to contact you?*	
1. After one day without AET intake	131 (11%)
2. After 2 days without OHT intake	252 (21%)
3. 3 days within the same week without OHT intake	348 (29%)
4. After one whole week without OHT intake	207 (17%)
5. At least 10 days within a month (even non-consecutive)	82 (7%)
6. Other	181 (15%)
Which mediums of follow-up would you prefer?**	
1. Phone call	482 (27%)
2. Text message, notification or mail	552 (30%)
3. Access to a 'forum' to interact with other BCS taking an OHT	378 (21%)
4. The provision of videos and explanatory articles on the disease, OHT and side effects	331 (18%)
5. Other	70 (4%)

*N=1201
** Multiple answers were possible so 1 patient could vote for multiple options

Moreover, results showed that participants would prefer known HCP to get in contact with them (67%) rather than a family member or friend (2%) or a random person (4%) and only 5 % do not want to be contacted. This first contact should preferably be done using a text message (30%), or phone call (26%). Finally, BC survivors outlined that the right time for this first contact would be after 3 days (within the same week) without taking their AET(29%). A phone call (27%) or text message or notification or email (30%) were the most preferred medium of communication to be used during BC survivorship.

4.4.3 App features and usability functionalities of the described connected eHealth technology

Participants also reported their preferences and acceptance regarding different features within the app and how to use those (Table 4.3). Questionnaires were the preferred mean (41%) to communicate experienced side-effects or their health status on the proposed eHealth intervention.

Participants declared that once a week would be an acceptable time frame to report on their health status or side-effects (43%).

Table 3: Preferred features and usability functionalities of the electronic pillbox connected to the app on a phone

	Overall (N=1268)
App feature and usability functionalities	
In your opinion, information on the state of health should be provided in the form of:*	
1. A short questionnaire (about 5 questions) to be filled out regularly	720 (41%)
2. Emoji/smiley selected regularly by the patient and representing her state of health	391 (22%)
3. A free field where the patient can describe her state of health at any time	604 (34%)
4. Other	37 (2%)
At what frequency?*	
1. Once a day	105 (11%)
2. At least once a week	419 (43%)
3. At least once every 15 days	154 (16%)
4. At least once a month	251 (26%)
5. Other	46 (5%)
In your opinion, what would you do in case you are a week on vacation in another region and forget the electronic blister (Thus the tool records a week without taking medication):	
1. Call the treating hospital centre to inform them that you forgot your electronic blister and ask for advice	401 (32%)
2. Click the option “Do not send my information to the hospital” on the application (Temporarily)	509 (40%)
3. Click the option “Do not send my information to the hospital” on the application (Permanently)	13 (1%)
4. Nothing, you can explain the situation to the hospital in case they contact you	345 (27%)
Would you prefer using a gamification app (e.g avatars) to a generic app (both connected to an electronic pillbox)?	
1. Yes, more favourable	280 (22%)
2. Neutral, no preference	623 (49%)
3. No, less favourable	365 (29%)
For which reasons?**	
1. Because taking care of an avatar gives me a more active role in my treatment (Empathy)	113 (26%)
2. Because the "game" side of the application makes it easier for me to use it (Usability fidelity)	123 (28%)
3. Because the evolution of the character gives a concrete aspect to the effect of AET (Role model)	190 (43%)
4. Other reason	11 (3%)

Would you stop using the electronic pillbox connected to the app when you would not experience any side effects and take the AET every day?	242 (19%)
1. Yes, no need anymore	54 (4%)
2. Yes, the electronic pillbox connected to the app could now on the contrary decrease the motivation to take AET	553 (44%)
3. No, the electronic pillbox connected to the app remains an important support tool	419 (33%)
4. No, the electronic pillbox connected to the app can be useful again	

*N=975
**N=280 (but multiple answers were possible)

In case, BC survivors forget their electronic pillbox at home or pursue a 'drug holiday' they would like to see a button in the app that allows them to click 'Temporarily, do not send my information to the hospital".

Another feature tested was the "drug holidays". The preferred option to communicate the "drug holiday" was to have a button in the app that could be clicked temporarily to notify the referral hospital that no information is currently transmitted.

After we investigated whether a gamification version of the app would be preferred by the patient. In this case-scenario, the gamification entailed an avatar who had to take an AET once a day, thus the participant had to make sure this avatar took her AET every day and adhered to her (virtually) doctor appointments in case of pain or difficulties and indicate directly on the avatar the painful areas. The gamification aspect did not make the app more or less favourable to the participants. Results showed that this gamification can help the participant to understand the effect of AET and be seen as a role model (43%).

4.4.4 Barriers and facilitators to using a connected eHealth technology to support AET in BCS

The last part of this case-scenario was to investigate the barriers and facilitators to using a connected eHealth application to support AET in BCS. Both the facilitators and barriers are presented in Figure 4.2. On the one hand, BCS stated that side-effect reporting (51%) and fast HCP responses (55%) are the major factors that would facilitate them to use such a connected eHealth tool to be supported in their AET. On the other hand, not owning a smartphone (53%) or having

to pay for the application (49%) are major BCS revealed barriers for BCS followed by lack of data protection and confidentiality thus hindering their use of such a connected eHealth application.

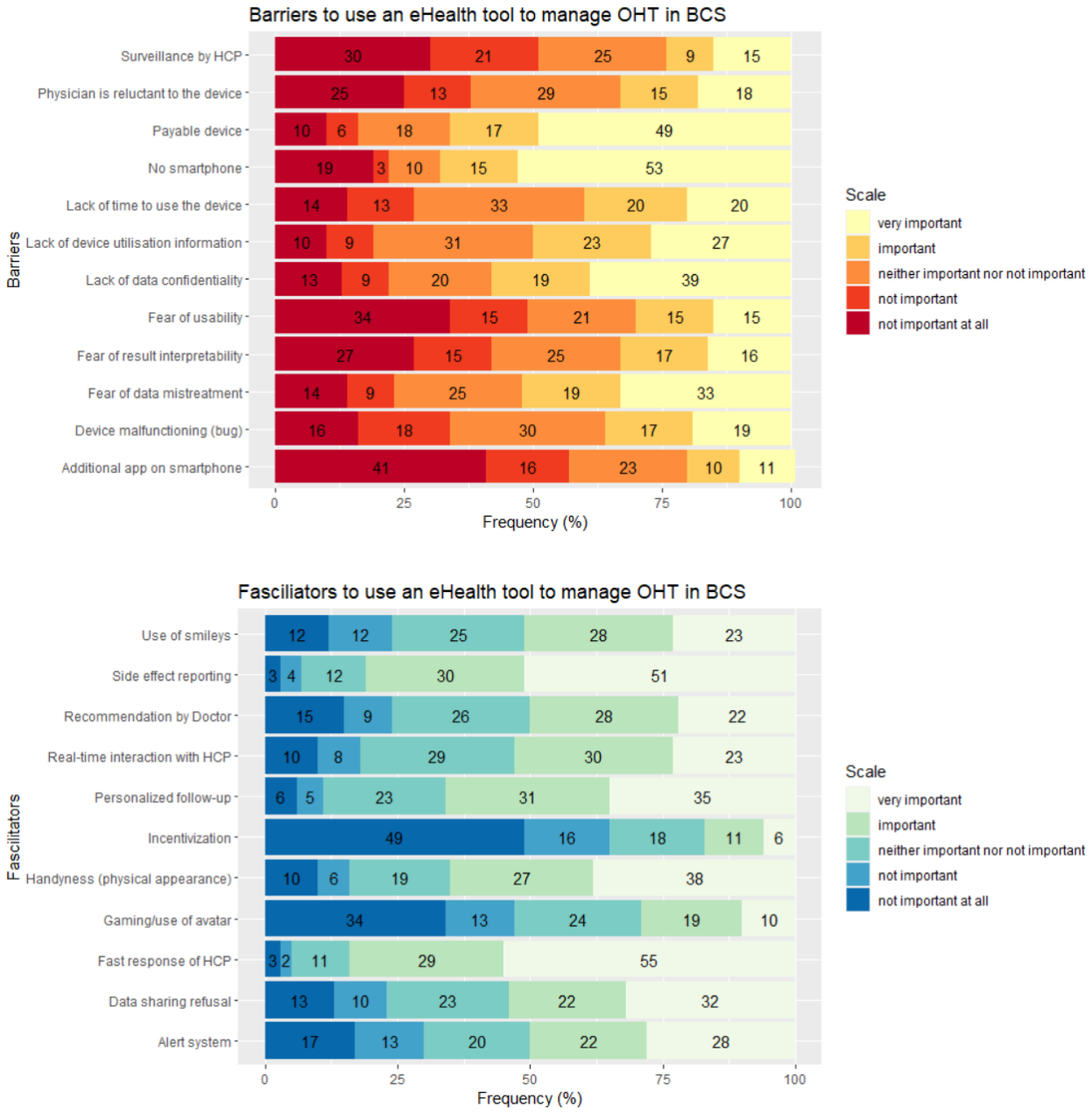

Figure 4.2: Barriers and Facilitators to use a connected eHealth technology to support OHT in BCS

4.5 Discussion

Even though BCS claim to be open to using an eHealth intervention supporting AET (Baseman et al., 2017; Goetzinger et al., 2021; Hein et al., 2020; Lubberding et al., 2015), inconclusive results, regarding the effectiveness of these interventions, are found in the literature (Ekinci et al., 2018; Finitsis et al., 2019; Heiney et al., 2019; Hurtado-de-Mendoza et al., 2016). Previous literature emphasized key challenges with eHealth studies. Simblett et al and Jeffs et al. highlighted high dropout rates of 44-67% (Jeffs et al., 2016; Simblett et al., 2018). Another challenge consists of low adoption rates when implementing eHealth interventions (Escriva Boulley et al., 2018; Jeffs et al., 2016; Thies et al., 2017). And finally, these papers reveal issues with end-users accepting the tested eHealth intervention (Han et al., 2019; Simblett et al., 2018; Vo et al., 2019). These high dropout rates, low adoption ratio during implementation and low intervention acceptability result due to a poor fit of context and technology, usability issues and interoperability. Vo et al. conducted a meta- ethnographic review of qualitative studies to study patients' perception of mHealth Apps. They pointed out that only 5 out of the 43 included studies evaluated either patients' expectations or their perception of the study's app prior to its use (Vo et al., 2019). Co-designing eHealth intervention with both patients and HCP by involving them in the development phases of such eHealth intervention is crucial in driving engagement (Aguayo et al., 2021; Ahmed et al., 2018; Escriva Boulley et al., 2018; Vo et al., 2019).

The case-scenario approach used in the present paper allowed identifying key intervention components (features, tools, interventionists) that are acceptable by BCS in addition to major barriers and facilitators to the acceptability and usability of an AET-enhancing eHealth intervention for BC survivors. The majority (86%) of the study population would accept to transfer their AET adherence and side-effect data collected on the connected eHealth technology to their already implicated HCP once or twice a week. Thus the main facilitators revealed in the current paper were the reporting of side-effects and patient-HCP interaction. These results are in line with other studies that found that BCS expect their survivorship care to provide increased communication with their HCP, easily accessible information on disease and treatment and closer AET management follow-up by HCP, hence receiving tailored supportive care (Finitsis et al., 2019; Goetzinger et al., 2022; Lubberding et al., 2015; Pouls et al., 2021). Other papers highlight

that usability-accessibility; quality-quantity of content; tailoring-personalisation; and motivation-support are important facilitators of eHealth intervention usability (Hardiker & Grant, 2011; McCurdie et al., 2012; Svendsen et al., 2020).

Besides not owning a smartphone and having to pay for eHealth intervention the major barrier to the usability of the proposed eHealth intervention was the lack of data protection and confidentiality. Tadas et al. stated that to foster technology engagement, users need to have background knowledge of the technical functionalities as well as respect individual privacy (Tadas & Coyle, 2020). Simblett et al. additionally highlighted that technical malfunctions, are the most reported barriers to eHealth intervention usability (Simblett et al., 2018).

4.5.1 Strengths and Limitations

The present study entails several limitations. Due to the cross-sectional nature of the study, no generalisation of the results can be done. Also, the present study deals with selection bias, as the Seintinelles platform only includes volunteering members. Meaning the participants showed interest in the study topic. The present study thus provides only a snapshot for accepting eHealth tools.

The major strengths of the present study are end-user involvement in AET-enhancing interventions. Understanding patient preferences regarding features help developers and clinicians to better respond to their patient needs hence providing better healthcare services for the patient and improving health outcome.

Therefore, implicating BC survivors in the development of an AET-enhancing eHealth intervention allows conceiving acceptable and implementable interventions that benefit the patient in the real-world setting.

4.6 Conclusion

This case-scenario highlights barriers and facilitators regarding the usability of a connected pillbox to an application to enhance AET in BCS. Understanding BCS's preferences and needs will help app developers to patient-center and personalize eHealth interventions to enhance AET. Future research should employ the proposed and accepted features and components and test their feasibility in clinical practice.

4.7 Statement & Declaration

Funding: CG was supported by a PhD grant financed by the Action LIONS Vaincre le Cancer.

Competing Interest: The authors have no relevant financial or non-financial interests to disclose.

Author Contribution: CG contributed to the study conception and design, data analysis and interpretation, and manuscript preparation. CA & MP & LH contributed to the study conception and design. AS and BV contributed to the data analysis and interpretation. GF contributed to manuscript preparation and editing. All authors contributed to the manuscript review.

Data availability: The datasets presented in this article are not readily available because participants could be identifiable. The included tables provide the anonymized and summarized data. Requests to access the datasets should be directed to the corresponding author, catherine.goetzinger@gmail.com

Ethical approval: The study received approval from the National Commission for Information and Freedoms (Commission nationale de l'informatique et des libertés, CNIL: 1955704) and the Sud-EST II data protection committee (Comité de Protection des données, Numéro EudraCT: 2020-A00665-34).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Take home messages from Chapter 4

- Using a case-scenario is an innovative way to determine patient preference and avoid misunderstanding regarding terminology or interpretation of questions. The case-scenario methodology guides the survey participant through the survey while explaining a story, this way the patient can relate to the story, and better understand the questions.

- 86% of the study population would accept to transfer their AET adherence and side-effect data collected on the connected eHealth technology to their already implicated HCP once to twice a week.

- The preferred mean of side-effect reporting is a questionnaire and patient-HCP interaction should be in form of text messages or phone calls.

- Gamification did not make the application more favourable to be used by the participants.

- Main facilitators to using the proposed eHealth intervention: having the possibility to report on side-effects and having a patient-HCP interaction.

- Main barriers to using the proposed eHealth intervention: Having to pay for the application, not owning a smartphone and a lack of data protection and confidentiality

Link with the following chapter

Chapter 2, 3, and 4 gave an overview of the context of post-acute treatment in BC and the issues related to AET taking. The chapters additionally provided information on what BCS and HCP would accept to use on daily basis. In addition, various information was provided on intervention content and features, barriers and facilitators to use digital MAEI for AET. In order to respond to the gap in the literature that most MAEI were developed without using evidence-based theory. The following chapter will use the behaviour change wheel framework to guide the development of a digital MAEI for BCS taking AET.

Chapter 5

Developing a theory-driven eHealth intervention to support adjuvant endocrine therapy in breast cancer survivor

Currently in co-author review in order to submit to journal

Title: Developing a theory-driven eHealth intervention to support adjuvant endocrine therapy in breast cancer survivors

Authors

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5.1 Abstract

Introduction

Medication adherence to adjuvant endocrine therapies (AET) decreases the risk of breast cancer (BC) recurrence by over 30%. Depending on the drug and method of measurement, up to half of BC survivors discontinue their treatment before the recommended five years of treatment. This suboptimal persistence represents a major challenge to patients, healthcare providers and health systems, becoming a major public health priority. Despite the existence of numerous apps, there is a lack of successful and sustainable implementation and use.

Methods

This paper outlines a theory-driven development of an eHealth intervention to enhance medication adherence (or adjuvant endocrine therapy) in BC survivors. The Behaviour Change Wheel (BCW) and the Capability Opportunity Motivation and Behaviour (COM-B) model were applied to define the problem in behavioural terms, identify intervention options and determine intervention functions followed by implementation options.

Results

The present study identified four major target behaviours; initiation of AET, correct AET taking (implementation), Side-effect management and Psychological distress management (reduce stress & anxiety). Using the COM-B model we identified the following umbrella components necessary to influence the target behaviours; Capability (lack of knowledge regarding the importance of treatment, side-effect coping strategies or link AET, lack of routine,), Opportunity (lack of social support, lack or insufficient patient-physician communication) and Motivation (lack of problem-solving, beliefs). The following five intervention functions were chosen; education, persuasion, training, environmental restructuring, and enablement.

Conclusion

Digitalising healthcare, using eHealth technology and self-management apps as well as data science has the ability to remodel the post-acute AET follow-up in BCS, yet lacks development processes relying on evidence-based theories and patient involvement. Using theory-based intervention and co-design strategies to develop digital MAEI have the potential to account for the complex behaviour of medication adherence, hence improving overall health outcomes. The present work provides insight into a theory-driven analysis, enabling app developers to conceive a successful and sustainable eHealth intervention for BC survivors to enhance AET adherence.

5.2 Introduction

Tamoxifen and aromatase inhibitors are two adjuvant endocrine therapies (AET), that are eligible for BC patients that are hormone receptor-positive (80%) and in their post-acute treatment phase (Burstein et al., 2019; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) et al., 2011). AET is taken once a day for at least 5 years and is associated with significant side-effects, impacting breast cancer survivors (BCS) quality of life. Even though 5 years of AET was shown to reduce BC recurrence by 50% and mortality by a third, non-adherence to AET is continuously reported (Davies et al., 2013; Inotai et al., 2021; Makubate et al., 2013; Pistilli et al., 2020). Previous work revealed that up to 73% discontinued their AET before the recommended 5 years of treatment (Huiart et al., 2011; Mao et al., 2020; Murphy et al., 2012). Hence medication adherence is crucial in attaining favourable health outcomes (Inotai et al., 2021; Sabaté, 2003) in BCS.

Medication adherence, defined as '*the extent to which a person's behaviour corresponds with agreed recommendations from a healthcare provider*', is composed of three stages; *initiation* (starting to take prescribed treatment), *implementation* (taking the treatment as prescribed) and *persistence* (patient takes treatment as prescribed from the first dose until the last dose) (Vrijens et al., 2012a). If the patient stops taking the treatment it is called discontinuation. Thus medication non-adherence is a complex behaviour that is associated with over 700 determinants (Kardas et al., 2013). These determinants can be classified as patient-related, condition-related, socio-economic-related, therapy-related, healthcare team and system-related factors (Sabaté, 2003). In the context of BC, survivors reported that they do not feel ready for the post-acute treatment and the shift from patient to BCS (Lubberding et al., 2015) and associate negative emotions with AET, psychosocial issues and patient-provider communication concerns with this shift (Gallicchio et al., 2021; Goetzinger et al., 2021; Green et al., 2022; Hurtado-de-Mendoza et al., 2018; Jiang et al., 2022; Kantsiper et al., 2009; Ringwald et al., 2017; Spencer et al., 2020; Toivonen et al., 2020; Yussof et al., 2022). A qualitative study conducted by Goetzinger et al. found similar BCS needs and classified them using the ABC taxonomy (Figure 5.1). Hence BC and AET determinants are

more than purely medical and need to be considered when developing effective AET adherence-enhancing interventions and innovating BCS post-acute follow-up settings.

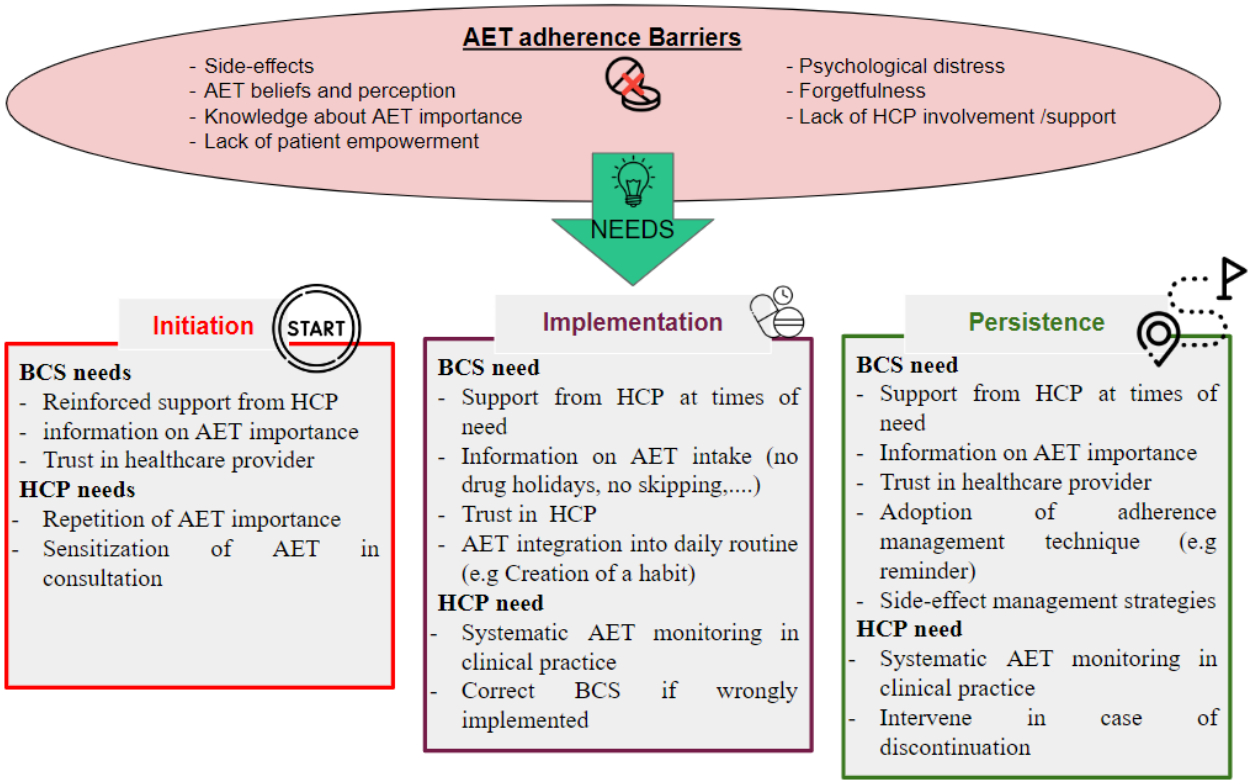

Figure 5.1: HCP & BCS needs with AET explained through the ABC taxonomy

Even though eHealth has the potential to bridge BCS and HCP needs with AET and post-acute BC follow-up healthcare and innovate the healthcare delivery structure (Car et al., 2017; Gee et al., 2015; Goetzinger et al., 2021), evidence from the literature remains inconclusive on the effectiveness. The reviews however raised promising trends that multi-component interventions seem to be more effective than single-component interventions (Ekinci et al., 2018; Finitsis et al., 2019; Heiney et al., 2019). The most studied intervention components were education material and counselling. Using eHealth technology and allowing bi-directional communication between providers and patients showed statistically significant effects while those relying only on providing information to the patient (one-way communication) did not (Finitsis et al., 2019). Similar results

were identified by Pouls et al highlighting that the remote interface between patient and healthcare provider has a significant impact on enhancing medication adherence (Pouls et al., 2021).

Even though over 600 apps were identified in the Apple App and Google play store, evidence remains missing and implementation in the real-world setting remains scarce (Ahmed et al., 2018). Hence the following major challenges of today's medications adherence enhancing interventions continue to be that (Zullig et al., 2019) (Nieuwlaat et al., 2014) (Morrissey et al., 2016; Vo et al., 2019):

- Most interventions are ineffective because they are inappropriately targeted and non-specific in terms of which adherence phase they target (ABC taxonomy).
- Most interventions need a multilevel structure yet most adherence interventions are focused on the patient
- Most interventions lack methodological accuracy
- Most studies are not based on validated theories and or frameworks
- Most studies do not include target end users (patients and healthcare providers) in the development process

To develop an effective and sustainable eHealth intervention enhancing AET adherence in BCS and providing a post-acute follow-up structure within the clinical setting, the intervention needs to be planned from the beginning with a clear focus on the central outcome of implementing the intervention in the post-acute treatment follow-up within the clinical setting (real-world setting). Hence the SMILe project is an excellent example of how to use theory-based frameworks to develop an intervention with the overarching goal of implementing it in a real-world setting (Ribaut et al., 2020) and will guide the methodology and process of the present study. The present study used a theory-driven approach (Behavioural Change Wheel (BCW) and the Capability-Opportunity-Motivation and Behaviour (COM-B)) to nourish the development of an eHealth intervention enhancing medication adherence in BC survivors.

5.3 Methodology

The present study describes the development of an eHealth intervention to support BCS and HCP during BC survivorship and more precisely with AET. A theory-driven approach (Behavioural Change Wheel (BCW) and the Capability- Opportunity-Motivation and Behaviour (COM-B)) were used to systematically characterise the target behaviours, intervention functions, behaviour techniques and modes of delivery of an eHealth intervention supporting AET management for BCS and HCP.

5.3.1 eHealth intervention design process - contextual analysis

The eHealth intervention design process was informed by previously performed qualitative and quantitative studies (E-dherence Quali, Seintinelles). These studies described the context and supplied an in-depth understanding of the environment and its circumstance (e.g setting, target population, infrastructure and motivation of all the stakeholders to be involved) to sustainably implement a digital MAEI supporting AET management for BCS and HCP (Chapter 2,3,4) (Goetzinger et al., 2021, 2022).

BCS raised the need for improved patient-provider communication, and support during AET initiation and implementation in form of social and private assistance. Thus they reported accepting an eHealth tool as a BC companion in addition to the standard of care including the following modules; remote patient-provider interaction in case of need, disease and treatment information, AET management (e.g adherence and side-effects) support and social support network. HCP communicated a lack of systematic AET follow-up in BCS during survivorship and hence would accept remote AET management monitoring.

5.3.2 The Behaviour change wheel (BCW)

Therefore BCW helps to develop the digital MAEI introducing a theory-driven approach (Michie et al., 2014). The BCW is a useful theory-based framework to identify, understand and explain behaviours and their influencing factors facilitating implementation in the real-world setting. The

BCW was developed from 19 frameworks of behaviour change and consists of 3 layers (Figure 5.2). The hub of the wheel elaborates on the problem at stake and identifies target behaviours for the intervention using the COM-B model and Theoretical Domains Framework (TDF). The TDF integrate several behavioural theories and has 14 domains of behavioural effect, which can be used in conjunction with the COM-B. Each domain refers to one COM-B component and represents theoretical constructs (e.g knowledge, skills, beliefs or goals). When used in tandem, the COM-B and TDF enable behavioural diagnosis thus facilitating the selection of efficient behaviour change interventions.

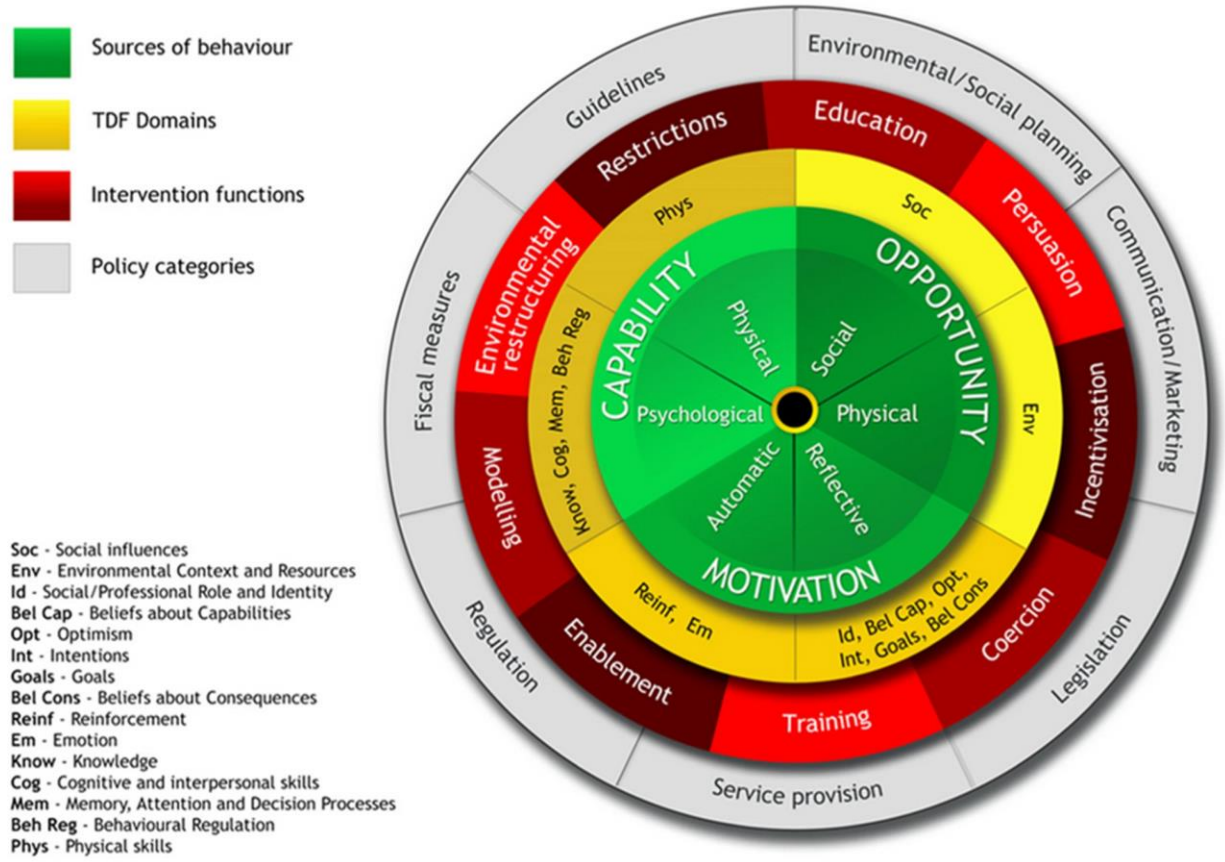

Figure 5.2: Behaviour change wheel (Michie et al., 2011) open access figure

The APEASE criteria are used to rate (i.e., ++ very promising, + promising, ± not promising but worth considering, − unacceptable) each target behaviour or intervention function while

considering existing evidence, HCP expertise, and results from the contextual analysis. The APEASE criteria was used within each Stage.

After, depending on the specific target behaviours and identified needs to change, one chooses between nine intervention functions (Education, Persuasion, Incentivisation, Coercion, Training, Enablement, Modelling, Environmental restructuring and Restrictions). Finally, policy types are associated in order the deliver the intervention functions. (Figure 5.3).

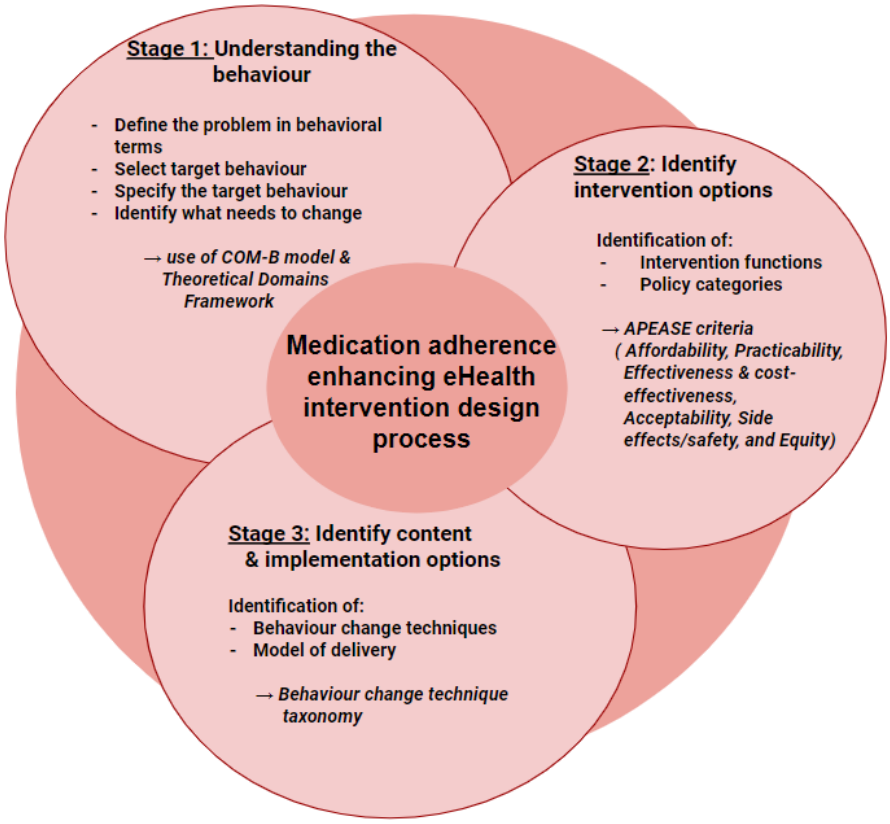

Figure 5.3: Three stages to design a MAEI. Adapted from: (Michie et al., 2011, 2014; Ribaut et al., 2020)

5.4 Results

5.4.1 Stage 1 - Understanding the behaviour

Using Step 1 of the BCW, the target behaviour for this intervention was medication adherence defined as "the extent to which the patient's action matches the agreed recommendations" (Vrijens et al., 2012a).

- *What is the problem?* Up to 73% discontinued their AET before the recommended 5 years of treatment (Mao et al., 2020; Murphy et al., 2012). However, taking AET as prescribed was shown to reduce BC recurrence by 50% and mortality by a third (Inotai et al., 2021; Pistilli et al., 2020).

- *Where does it occur?* Medication non-adherence to AET occurs during the post-acute treatment phase. This occurs outside the hospital at the patient's home or where they are when they have to take their AET. A contextual analysis (Chapters 2, 3, 4, (Goetzinger et al., 2021, 2022)) revealed that BCS claim increased support from their HCP. The qualitative study showed that the needs differ regarding the phase of medication adherence. During initiation, BCS need enforced encouragement and information on the importance of AET and help to create a habit of being reminded to take the treatment. While during the implementation phase, BCS rather need help with side-effect coping and demands patient-healthcare provider interaction (increased communication).

- *Who is involved?* The whole healthcare provider involved in the post-acute treatment of AET in BCS

- *Target group?* Breast cancer survivors (and HCP)

The second step of the BCW revealed a list of target behaviours that influence the initiation and implementation of AET based on the literature. Target behaviours ranged from initiation AET, taking and timing AET to refill prescriptions, coping with side-effects, adhering to follow-up

consultation, cope with psychological distress. Using a systematic selection we analysed each target behaviour by analysing if changing this behaviour would it have the best overall combination of direct impact on clinical outcomes, spillover effect on other behaviours and whether it is measurable. Therefore we selected *AET initiation*, *correct AET taking*, *managing side-effects and psychological distress* as target behaviours.

Table 5.1 presents step 3 of the BCW, specifying each target behaviour and putting it in context.

Table 5.1: Specification of target behaviours

Target behaviour	**Initiate AET (initiation)**	**Correct AET taking (implementation)**	**Side effect management**	**Psychological distress management (Reduce stress & anxiety)**
Who	BCS			
What	Fill prescriptions and take the AET for the first time	Take AET once a day	Be aware of side effects and find a coping strategy that helps them reduce or cope with the side effect	To be aware of the source of stress and anxiety and find a strategy to reduce it.
When	The patient is free to choose the time of intake at the initiation. After they are advised to take the AET once a day at that time.	A.m. or p.m.	Depending on the side-effect it can be a preventive coping strategy or at the time of need (occurrence of side effect)	This can be done in moments of need and preventative
Where	Patient location (home, work,...)	Patient location	Patient location	At home, work, supportive groups, specific location /institute

				(e.g. yoga institute)
How often	Once every day	Once a day for at least 5 years	As needed	During the 5 years of AET or at times of need
With whom	Alone	Alone	Alone (with support of BC nurse, support groups, oncologist, others)	Alone with the support of friends and family, dedicated professional

- *Who* needs to perform the behaviour?
- *What* do they need to do differently to achieve the desired change?
- *When* will they do it?
- *Where* will they do it?
- How *often* will they do it
- *With whom* will they do it

In order to perform step 4 to identify what needs to change the COM-B model is used, which is illustrated in the center of the BCW (Figure 5.2). This step elaborates on whether the behaviour is influenced by

- Capability (psychological and/or physical); the capacity to engage in a certain health behaviour
- Opportunity (Physical and/or social); determinants external to the patient that make the behaviour possible or not possible
- Motivation (reflective and/or Automatic); includes attitudes and beliefs about a behaviour

We combined the COM-B with theoretical domains framework (TDF) allowing to synthesize the behaviour. Using these two together helps to perform a 'behavioural diagnosis' thus facilitating the choice of effective behaviour change interventions (Michie et al., 2011; Ribaut et al., 2020).

Table 5.2 illustrates the results of the COM-B model and TDF. Barriers were identified using the literature and the results from the contextual analysis.

Table 5.2:COM-B model to identify the change that needs to happen to enhance AET adherence in BCS

COM-B	**TDF**	**What needs to happen for target behaviour to occur?**	**Is there a need for change? (Barriers)**
Physical capability	Physical skills	Being capable to swallow pill	No
Psychological capability	Knowledge	Knowledge of why intake and timing of AET is important (e.g reduce BC recurrence) Knowledge of coping strategies Knowledge that side-effect is linked to treatment	**Yes**, Lack of or unclear understanding of the importance of AET and the consequences of non-adherence **Yes**, Not being aware of side-effect magnitude and related coping strategies
	Cognitive and interpersonal skills	Developing a habit (e.g. correct AET intake,) Skills to ask for help (e.g. patients often feel afraid/ashamed to ask for help)	**Yes**, no habit, goals
	Memory, attention and decision process	Remember to take AET Notice when AET not taken	**Yes**, busy lifestyle, limitations in memory, Lack of self-monitoring
	Behavioural regulation	If-then-rule (if I take my AET I reduce my likelihood of BC recurrence)	**Yes**, lack of routine, busy lifestyle or

		Coping strategies development	**Yes**, lack of skills to develop coping strategies Lack of self-monitoring
Physical Opportunity	Environmental context and resources	Reminder cues to refill prescription/ take AET AET availability - interruptions in daily routine(both in the pharmacy but also when being away from home) Availability of systematic AET follow-up	**Yes**, Lack of support tools to remind AET intake, refill data, lack of systematic AET follow-up No, no known shortage of AET in Luxembourg
Social Opportunity	Social influences	Patient-HCP partnership - patient empowerment Lack of education on medication adherence in Healthcare providers and public Shift of responsibility (shared responsibility among all healthcare providers)	**Yes**, Lack of support both emotionally (family and /or friends can not relate) and instrumental **Yes**, Lack of healthcare provider support due to lack of awareness of AET non-adherence **Yes**, stigmatization (avoid taking AET in front of work colleagues) due to lack of awareness
Reflective Motivation	Beliefs about consequences	Correct beliefs about AET and its efficacy Correct beliefs of consequences of AET non-adherence	**Yes**, False beliefs about AET efficacy, consequences
	Intention	Lack of intention to initiate AET and or to correctly take AET	**Yes**, inadequate intentions

Automatic Motivation	Reinforcement	Lack of coping strategies	**Yes**, side-effects coping strategies
	Emotion	Positive emotions related to medication adherence, Positive experience with AET from loved one	**Yes,** Low relationship with health care provider

5.4.2 Stage 2 - Identifying intervention options

In Stage two the red (Step 5) and grey layer (Step 6) of the BCW are used (Figure 5.2). During this stage, a selection is done between the nine proposed intervention categories and 7 policy categories that would target the theoretical domains found to be most influential to AET medication adherence in Stage 1. The APEASE criteria assist in evaluating potentially appropriate intervention and policy categories (Table 5.3 and 5.4).

For the purpose of the present research project, the development of a MAEI for BCS taking AET and the results from the contextual analysis, five intervention functions (education, training, enablement, environmental restructuring and persuasion) and two policy categories (Service provision and regulation) were found effective.

Table 5.3: Selection of relevant Intervention functions using the APEASE criteria

Intervention functions	**APEASE***	**Include/ Exclude**
Education	A++, P++, E+, A++, S+, E+	**Include**; To raise knowledge on AET importance and potential consequences of non-adherence

Training	A++, P+, E++, A+, S+, E++	**Include**; solutions for self-monitoring, habits, pillboxes, reminder
Enablement	A++, P++, E++, A+, S+, E++	**Include**; provide skills for side-effect management
Environmental restructuring	A±, P+, E++, A+, S±, E+	**Include**; introduce medication adherence into clinical practice, into post-acute treatment follow-up
Persuasion	A++, P±, E±, A+, S±, E±	**Include**; To raise awareness on medication adherence, and make sure of the role of healthcare providers and society in medication adherence (e.g. patient - healthcare provider relationship)
Modeling	A-, P±, E±, A+, S±, E±	**Exclude**; not affordable and probably not effective, potentially wrong role models
Incentivisation	A-, P±, E±, A+, S±, E±	**Exclude**; not affordable and probably not effective
Coercion	A-, P-, E-, A-, S-, E-	**Exclude**; unacceptable

*Affordability, Practicability, Effectivness (Cost), Acceptability, Side-effect/ Safety, Equity

(++ very promising) (+ promising) (± not promising but worth considering) (− unacceptable)

Table 5.4 Selection of relevant Policy functions using the APEASE criteria

Policy category	APEASE*	Include/ Exclude
Service provision	A++, P++, E+, A++, S++, E++	**Include**; Establishing support services in workplaces, communities *Intervention functions: Education, training, enablement, persuation, environmental restructuring*
Legislation	A-, P-, E-, A-, S-, E-	**Exclude** (This policy category is applicable to the pupose of the intervention development in this projects context)
Regulation	A+, P+, E+, A±, S+, E+	**Include:** Establishing rules or principles of behaviour or practice *Intervention functions: Education, training, enablement, persuation, environmental restructuring*
Guideline	A±, P±, E+, A±, S+, E+	**Exclude:** it is not affordable nor in the scope of this project.
Fiscal measures	A-, P-, E-, A-, S-, E-	**Exclude**: not applicable in this context
Environmental/ social planning	A-, P-, E-, A-, S-, E-	**Exclude**: not applicable in this context
Communication/ marketing	A-, P-, E-, A-, S-, E-	**Exclude**: not applicable in this context

*Affordability, Practicability, Effectiveness (Cost), Acceptability, Side-effect/ Safety, Equity

(++ very promising) (+ promising) (± not promising but worth considering) (− unacceptable)

5.4.3 Stage 3 - Identify content and implementation options

The last Stage, in the theory-driven approach to developing an MAEI to enhance AET in BCS, identifies the intervention content (Step 7) and mode of delivery (Step 8). Here the behaviour change technique (BCT) taxonomy is used to identify techniques to change behaviour. This taxonomy entails 93 BCTs classified into 19 categories (Michie et al., 2014). The chosen BCT (Table 5.5) support the above-identified functions. Again the contextual analysis was used to inform both steps 7 and 8.

Table 5.5: Identification of BCTs and mode of delivery for the AET enhancing intervention in BCS

COM-B	**TDF domains**	**Identified intervention function**	**Identified BCTs**	**Mode of delivery**
Psychological Capability	Knowledge	Education Training Enablement	5.1. Information about health consequences	App - written information, interaction Phone interaction face-to-face
	Cognitive and interpersonal skills		8.3. Habit formation	Phone - interaction face-to-face

	Memory, attention and decision process		1.1. Goal setting 7.1. Prompts/ cues	App - reminder notifications
	Behavioural regulation		1.2. Problem solving (coping strategies) 2.3. Self-monitoring of behaviour	App - interaction, questionnaire Phone interaction face-to-face
Physical opportunity	Environmental context and resources	Environmental restructuring Training Enablement	4.1. Instruction on how to perform a behaviour 7.1. Prompts/ cues	App, face-to-face video, written info App, reminder, information, Website, -information
Social opportunity	Social influences	Persuasion Training Enablement	2.2. Feedback on behaviour 2.3. Self-monitoring of behaviour 3.2. Social support (practical) 3.3. Social support (emotional) 11.1. Pharmacological support	App - interaction, Phone interaction face-to-face
Reflective Motivation	Beliefs about consequences	Education Persuasion	9.2. Pros & Cons	App - interaction Phone interaction face-to-face

	Intention		9.1. Credible source	App - information, video face-to-face
Automatic Motivation	Reinforcement	Training	8.1. Behavioural practice/ rehearsal	App - interaction Phone interaction face-to-face
	Emotion	Enablement Persuasion	15.3. Focus on past success	App face-to-face

*Bold BCT are included in the AET enhancing intervention and only those have a mode of delivery BCT include the codes from the taxonomy (Michie et al., 2014)

5.5 Discussion

In summary, the BCW, combined results from a contextual analysis and a theory-driven approach to developing a digital MAEI for AET in BCS. The proposed intervention entails 5 intervention functions to enhance AET in BCS using an app and or phone interactions to deliver those interventions. These interventions function to influence the 10 target domains by using 15 selected BCTs.

Today over 600 apps exist for medication adherence and the number of newly released health apps is currently surpassing 200 per day (Ahmed et al., 2018), showing the growing recognition of digitalization in healthcare systems and HCP (Car et al., 2017; Fagherazzi et al., 2020, 2021; N. Linn et al., 2021). In spite of the inconclusive results of published interventions on medication adherence, there is a wide range of promising results that suggest further efforts are needed. Literature on MAEI need to rely on sound theory and frameworks as well as to involve patient and

healthcare providers in the development process of such MAEI (Aguayo et al., 2021; De Geest et al., 2022; Di Maio et al., 2022; Ribaut et al., 2020)

Another study developing a support intervention for BCS used mapping of behaviour using the Multiphase Optimisation Strategy (Green et al., 2022). They identified four major intervention targeting living with side-effects, medication and illness beliefs, forgetfulness and psychological distress. They chose SMS text reminders (targets memory and forgetting by creating a habit), information leaflets (targets illness and medication beliefs), ACT (Acceptance and commitment therapy), side-effect websites (targets to live with SE) thus improving/supporting AET adherence. As shown by Pouls et al and Rosenberg, BCS prefer 2-way interaction, the aspect where the present study adds to the current literature (Pouls et al., 2021; Rosenberg et al., 2020).

The present study provides meaningful information for app developers to conceive a successful and sustainable eHealth intervention for BCS taking an AET. Nevertheless, this project entails some limitations. The used framework neglects some national restrictions such as data protection legislation meaning that some identified functions could potentially not be used, even though they would positively influence our target behaviour. Despite the fact that a contextual analysis was performed and a consensus of national experts was achieved for the APEASE criteria and identification of BCTs it still remains a ‘subjective’ decision.

5.6 Conclusion

Digitalising healthcare, using eHealth technology and self-management apps as well as data science has the ability to remodel the post-acute AET follow-up in BCS, yet lacks development processes relying on evidence-based theories and patient involvement. Using theory-based intervention and co-design strategies to develop digital MAEI have the potential to account for the complex behaviour of medication adherence, hence improving overall health outcomes. The present work provides insight into a theory-driven analysis, enabling app developers to conceive a successful and sustainable eHealth intervention for BC survivors to enhance AET adherence.

Take home messages from Chapter 4

- 4 major target behaviours; initiation of AET, correct AET taking (implementation), Side-effect management and Psychological distress management (reduce stress & anxiety).
- Using the COM-B model we identified the following umbrella components necessary to influence the target behaviours;
    - Capability (lack of knowledge regarding the importance of treatment, side-effect coping strategies or link AET, lack of routine,),
    - Opportunity (lack of social support, lack or insufficient patient-physician communication) and
    - Motivation (lack of problem-solving, beliefs).
- 5 intervention functions were chosen; education, persuasion, training, environmental restructuring, and enablement.
- Using theory-based intervention and co-design strategies to develop digital MAEI have the potential to account for the complex behaviour of medication adherence, hence improving overall health outcomes

Link with the following chapter

Chapter 2, 3, 4 and 5 used theory-based intervention and co-design strategies to provide information to create (Chapter 6) a digital MAEI for BCS taking AET. Chapter 6 also proposes a methodology to test the developed digital AET-enhancing intervention for its feasibility.

Chapter 6

Improving Adjuvant Endocrine Therapy Adherence in Breast Cancer Survivors using a Medication Event Monitoring System: Protocol for a Feasibility Study

Submitted to JMIR - Methods and feasibility Studies (Status - in review)

Title: Improving Adjuvant Endocrine Therapy Adherence in Breast Cancer Survivors using a Medication Event Monitoring System: Protocol for a Feasibility Study

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Keywords: Cancer survivorship, digital health, eHealth, medication adherence, medication adherence enhancing intervention, breast cancer, oral hormone therapy, feasibility study

6.1 Abstract

Background:

Tamoxifen and aromatase inhibitors are two adjuvant endocrine therapies (AET) that decrease the risk of breast cancer recurrence by over 30 %. Former research demonstrated that half of the women on tamoxifen and a third of those taking aromatase inhibitors discontinue their treatment before the recommended 5 years. EHealth tools have already been successfully developed to provide support during the acute phase of cancer treatment however significant improvement in the post-acute phase of treatment is still lacking

Objectives:

The overall aim is to evaluate the feasibility of an electronic pillbox connected to an application (Medication Event Monitoring System (MEMS) tool and MEMS Adherence Software application), hereafter mentioned as a medication adherence enhancing eHealth intervention, to enhance AET adherence in BCS.

Method:

E-dherence Pilot is a single-arm feasibility study, including 15 BCS aged 18 or above, initiating their first prescription of AET. A medication adherence enhancing eHealth technology will monitor AET adherence and side-effect management in BCS in real-time. A breast cancer nurse (BCN) will digitally monitor the adherence behaviour of the BCS and contact the patient in case of non-adherence or reporting of side-effects.

Feasibility of the medication adherence enhancing eHealth intervention will be established by evaluating its acceptability, quality and medication adherence during the three months of follow-up. Acceptability is the adherence to and frequency of using the medication adherence enhancing eHealth intervention. The quality of the medication adherence enhancing eHealth intervention is rated by the ease of use, how well it functions and if it does what it purports to do. Medication adherence is the process by which patients take their medications as prescribed using a medication adherence-enhancing eHealth intervention.

Discussion:

This study evaluates the feasibility of the medication adherence enhancing eHealth intervention and serves as a preliminary trial to provide information about feasibility and effect estimates for a larger randomized controlled trial (RCT). This phase will advise which behavioural intervention components and MEMS tools should be retained for the medication adherence-enhancing eHealth intervention tested in a larger RCT.

6.2 Background

Today, cancer treatment offers a growing choice of oral forms of treatment. Compared to intravenous forms, these oral forms are perceived as an improvement in terms of delivery of care and comfort as well as simplify the logistics of treatment administration, yet raise the problem of adherence to the treatment (Banna et al., 2010; Ruddy et al., 2009). Therefore, medication adherence represents a major challenge to patients, healthcare providers and health systems, emerging into a new public health priority.

Breast cancer (BC) is the most commonly diagnosed cancer among women worldwide (Bray et al., 2018). During the acute phase of treatment, patients are treated with a combination of surgery, radiotherapy and/or chemotherapy. About three-quarters of breast cancer tumours are estrogen and/or progesterone-receptor-positive (Yip & Rhodes, 2014). For those, the post-acute phase is managed with adjuvant endocrine therapy (AET) in order to reduce the risk of breast cancer recurrence(Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005). Tamoxifen and aromatase inhibitors, two AETs, decrease the risk of BC recurrence by about 30% (Davies et al., 2013; Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005). Their efficacy depends however strongly on the duration of use (5 to 10 years), yet largely suboptimal adherence is reported (Murphy et al., 2012). Indeed, former studies found that 30-50% of BCS interrupt their treatment before the recommended five years (Huiart et al., 2013, 2014). Lack of adherence to the treatment may play an important role in the risk of cancer recurrence and hence in the survival of BC patients. Next to specific medical issues of medication management, BCS experience increased anxiety and fear with patients claiming increased support during this period (Hurtado-de-Mendoza et al., 2018; Kantsiper et al., 2009).

EHealth technologies may be a very effective mean to identify these interruptions in a real-time manner and to provide support at the time the person needs it (Car et al., 2017). Studies have demonstrated the benefits eHealth technologies can provide in the context of health status monitoring and disease management, as well as the promotion of healthy lifestyles. EHealth technologies have already been successfully used to provide support during the acute phase of cancer treatment. These personalized eHealth technologies increased survival, and health-related quality of life, and decreased emergency room visits and hospitalizations (Basch et al., 2016; Denis

et al., 2017). However, in the context of post-acute treatment, eHealth interventions were less effective. For instance, different eHealth initiatives promoting medication adherence, using educational material, online communities, reminder text messages or phone calls, did not improve medication adherence in cancer patients (Hadji et al., 2013; Ziller et al., 2013).

These interventions did not account for the dynamic process of medication adherence. Medication adherence is defined as 'the process by which patients take their medications as prescribed' and embeds three phases: 1. initiation (taking the first dose), 2. Implementation (patient's actual dosing corresponds to the prescribed dosing regimen), and 3. Persistence (length of time between initiation and the last dose) (Vrijens et al., 2012a). Moreover, medication adherence is a behaviour that is influenced by over 700 different factors ranging from patient-related to healthcare system factors (Kardas et al., 2013). Furthermore, Huiart et al. found that the longer BCS discontinue their AET the less likely they are to restart their treatment (Huiart et al., 2014). Therefore, a multifaceted intervention, identifying the moment of treatment interruption in real-time and being able to contact the patient at these specific time points may be key to enhancing adherence to AET in BCS.

In a study conducted by Goetzinger et al. they found that BCS in Luxembourg would accept personalized real-time communication between healthcare professionals and BCS (Goetzinger et al., 2021). BCS believe that an eHealth tool has the potential to provide information, motivation, reassurance and support during the survivorship period. In addition, they claim the importance of the interactive nature of such a medication adherence-enhancing eHealth intervention. Moreover, studies found that interventions that teach medication management skills, and/or facilitate communication (2-way) between patients and healthcare providers have a positive effect on medication adherence (Finitsis et al., 2019; Pouls et al., 2021).

Therefore, the present feasibility study (E-dherence Pilot) will evaluate a medication adherence enhancing eHealth technology that digitally monitors AET in BCS and provides a real-time interface between BCS and their breast cancer nurse (BCN).

6.3 Method

E-dherence Pilot is a single-arm study evaluating the feasibility of a medication adherence enhancing e-Health intervention (an electronic pillbox connected to an application (Medication Event Monitoring System (MEMS) tool and MEMS Adherence Software application).

6.3.1 Objectives

The overall aim of this study is to explore the feasibility of a medication adherence-enhancing e-Health intervention for BCS taking their AET. Secondary objectives will analyse 1. the impact of the medication adherence enhancing eHealth intervention on the BCSs' quality of life, 2. the management of side-effects (occurrence and coping strategies), 3. the technical occurrence of the eHealth technology and evaluate 4. the number and nature of the interaction between BCS and BCN.

6.3.2 Study population and setting

E-dherence Pilot will include 15 female, volunteering, outpatient BCS aged 18 or above. Eligible participants are followed-up either at 'Centre Hospitalier du Luxembourg (CHL)' or at 'Centre Hospitalier Emile Mayrisch (CHEM)', two local hospitals in Luxembourg. Furthermore, eligible patients should be at the initiation of their AET (1st prescription of AET), Included AET molecules are Nolvadex-D 20 mg and Arimidex 1 mg. Lastly, eligible BCS are Luxembourgish residents, fluent in either French or German and possess a smartphone (iOS or Android). Eligible participants need to meet all inclusion criteria to be enrolled on the study. We exclude male patients and patients with in situ or metastatic tumours or using an adjuvant treatment for ovarian suppression.

6.3.3 Study intervention

All participants receive (1) a Medication Event Monitoring System (MEMS®) tool and (2) access to the MEMS Adherence Software (Figure 6.1). These tools are manufactured and provided by AARDEX Group. Nolvadex-D 20 mg will be packaged in the MEMS® helping hand and Arimidex 1 mg is filled into the MEMS® cap. Both are electronic monitoring systems designed to compile dosing histories (date and time of medication intake). An integrated microelectronic

circuit records the dates and times every time the blister is removed and/or inserted (MEMS helping hand) or when the cap is opened and closed (MEMS cap) respectively.

In addition, the MEMS tools will be connected to the MEMS Mobile app on the participant's smartphones (iOS or Android). The MEMS Mobile app entails an integrated calendar to remind BCS to take their AET as prescribed and to transfer their data from the MEMS tool to the MEMS Mobile. Furthermore, the MEMS Mobile app includes questions on potential side-effects BCS could experience during the week and can be filled out if needed. For each side-effect, the BCS is asked to rate the severity from not severe at all to very severe.

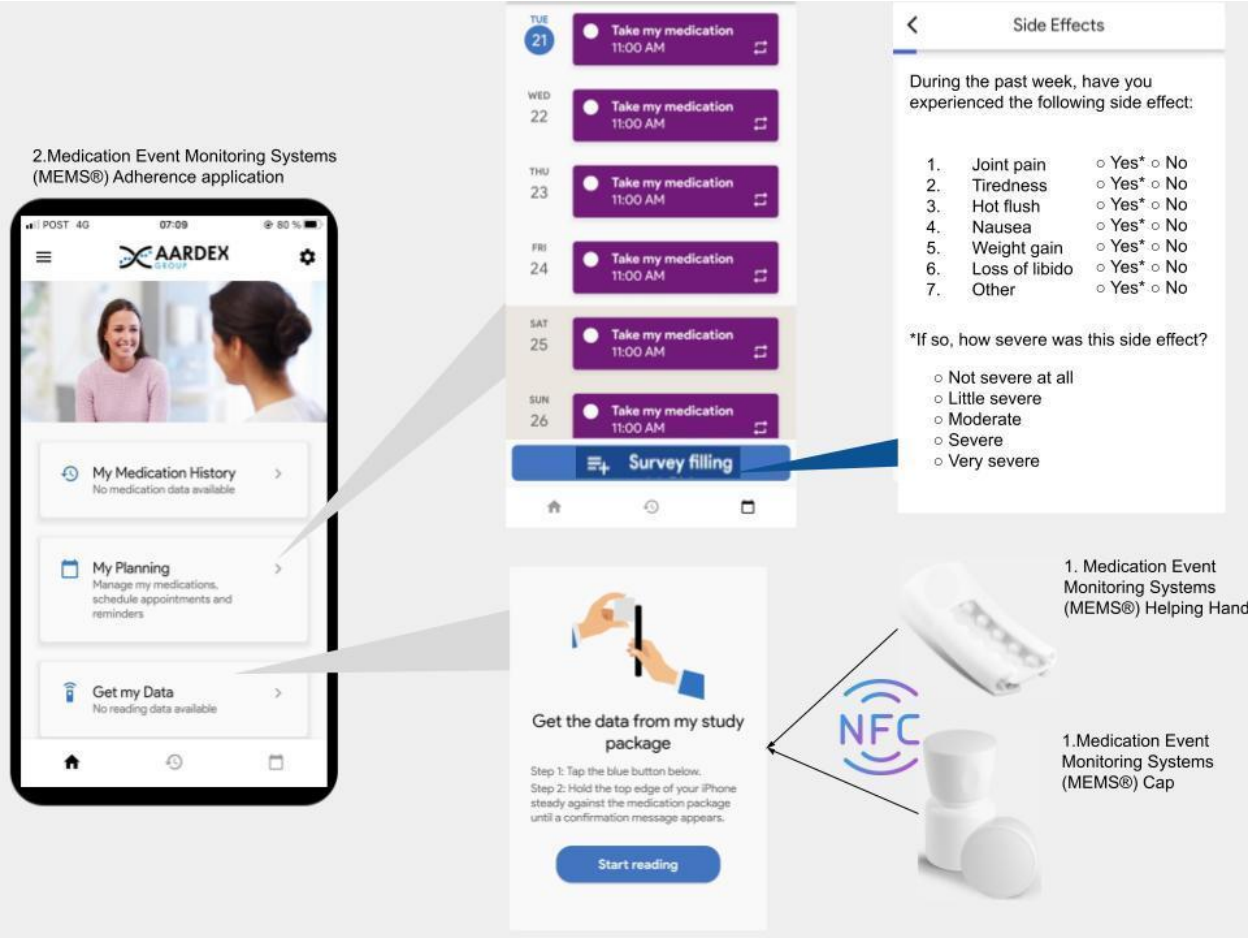


Figure 6.1:Medication Event Monitoring System (MEMS®) and MEMS Mobile

In the meantime, a clinical research nurse (CRN) digitally monitors the data collected in real-time (weekly) of both the AET intake and reported side-effects with the MEMS® Adherence Software

remotely. In case of an alert, such as recurrent non-adherence and/or reporting of side-effects and their severity, the CRN will contact the breast cancer nurse (BCN) in charge of the BCS, who will then contact the BCS by phone. If no alerts are registered, no further action is taken (Figure 6.2).

The intervention performed by the BCN was developed based on the theory of the behaviour change wheel by Michie et al. (Michie et al., 2011). The alert is triggered in case of 1. recurrent AET non-adherence, 2. side-effect occurrence and their respective severity, 3. a combination of recurrent AET non-adherence and the presence of side-effect(s). Figure 2 illustrates the behavioural interventions the BCN gives to the BCS depending on the motive of the alert. Once the BCN identified the motive of the alert she chooses between the - or a combination of - intervention functions: 1. Education - Feedback on behaviour and the potential outcome, 2. Training - Demonstrations & instructions on how to perform/enhance the behaviour, 3. Enablement - Giving prompts and cues to enhance the behaviour.

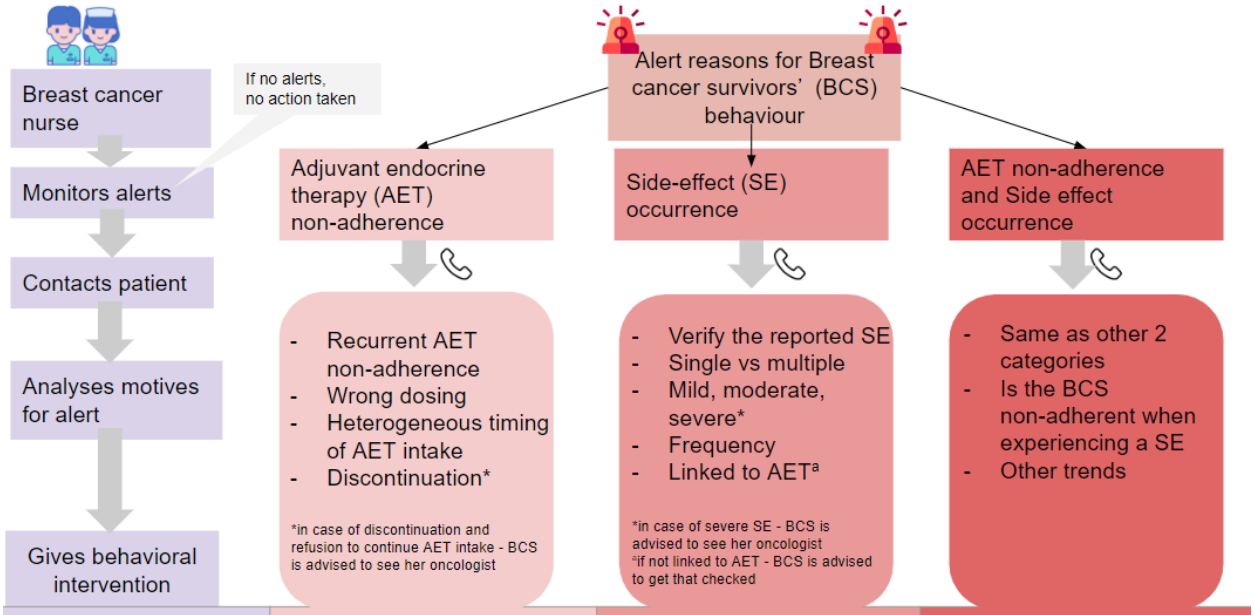


Figure 6.2: Behavioural interventions for AET management

In case the BCN, deems it relevant, she can advise the BCS to participate in support groups or to get an appointment with their oncologist. In the worst case, the BCN will refer the BCS to see the emergency department. BCS are free to contact their oncologist, BCN or other healthcare professionals at any point during the study if they wish to.

6.3.4 Study procedure

The E-dherence Pilot study consists of five main phases; screening, enrolment, first visit for inclusion, three months follow-up and end of study visit as illustrated in Figure 6.3.

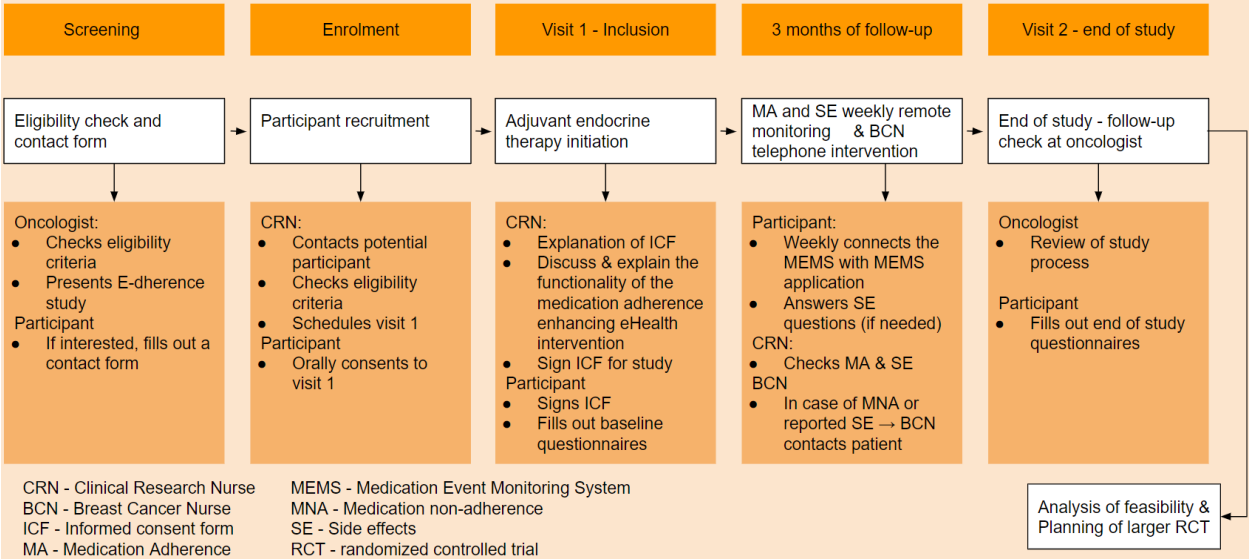


Figure 6.3 Overview of the E-dherence Pilot Study Intervention Procedure

Screening

During standard-of-care follow-up visits at CHL or CHEM hospitals, the oncologist screens potential BCS on eligibility to participate in the E-dherence Pilot study. In case the potential participant fits all the inclusion criteria, the oncologist introduces the E-dherence Pilot study and explains its procedures. Interested BCS thus accept to be contacted by the clinical research nurse (CRN) from the Luxembourg Institute of Health (LIH) and sign a contact form, including information on the BCS' name, phone number and oncologist name. The contact form is then sent to the CRN through a secured email pathway (password protected and encrypted).

Enrolment

Upon reception of the contact form, the CRN contacts the potential participant, double-checks the eligibility criteria again and clarifies the remaining questions regarding the study. If the participant agrees, a first visit is scheduled, which takes place either at the participant's home, at the clinical investigation center at LIH or in one of the two hospital centers. At this stage, the participant enters the 'table of correspondents' and receives a study identification number (pseudonymisation).

Visit 1 - Inclusion

During visit 1, the CRN and the participant go through the informed consent form (ICF), clarify questions and sign the ICF in double. Further, the CRN then demonstrates the use of the MEMS tool (depending on the patients' prescription) and MEMS application. The patient logs into the app for the first time in the presence of the CRN.

After the CRN left, the BCS is sent a link to RedCap to answer a baseline questionnaire about socio-demographic characteristics, beliefs about medication and quality of life. The CRN retrieves information about the participant's disease and treatment history from their medical record.

Three Months follow-up

During the 3 months follow-up after 'visit 1', the BCS takes her AET once a day using the MEMS tool and MEMS Adherence Software. BCS can choose the time that is most convenient for them. Once a week, the participant connects her MEMS to the MEMS Mobile app to read her AET intake. Throughout the 3 months, BCS can fill out as many SE questionnaires as needed and when applicable. The CRN weekly monitors the participant's medication intake data and side-effect reports. In case of alerts, the CRN informs the BCN from the respective hospital and they contact the patient to resolve medication non-adherence or manage SE, using a behavioural intervention.

Visit 2 – End of study

After 3 months, the participant fills out an end-of-study questionnaire and has a consultation (standard of care) with her oncologist at the respective hospital. During this consultation, the oncologist winds up the study while discussing the study process and counting the remaining pills.

6.3.5 Dosing and administration

The participant will take either Nolvadex-D 20 mg or Arimidex 1 mg per day as discussed with their oncologist. This treatment is the standard of care and the intake of this pill is through the oral route and does not change.

The CRN will explain the functionalities of the MEMS tool (helping hand or cap) and MEMS Mobile application to the BCS and dispatch their first medication blister in the MEMS helping hand or inserts the pills into the MEMS cap respectively. In case of questions, the patient can reach out to the CRN, her oncologist or the BCN.

6.3.6 Study Discontinuation

Participants will discontinue the study if:

- Hospitalized for longer than 7 days.
- Treatment changes, patients will be excluded from the study at the time of treatment change. Indeed, the MEMS Helping Hand are adapted to the blister size of Nolvadex and thus a new treatment would not fit the MEMS® Helping Hand.
- Any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the BCS.

The data collected up to the day of discontinuation will be kept and censored. Nevertheless, participants are free to leave the study at any time without justification.

6.3.7 Lost to Follow-up

Patients will receive questionnaires at baseline and at the end of the study. In addition, data is collected weekly throughout the three-month follow-up period. Lost to follow-up participants are those for whom no data could be collected after baseline.

6.3.8 Study Outcomes

All participants will fill out a baseline and end-of-study questionnaire through a REDCap login. During the study intervention, real-time data collection on medication adherence and side-effect occurrence is performed. Table 6.1 presents all assessments performed during the study. All questionnaires, as well as the Adherence application, are available in both French and German. Visit 1 takes about 30 minutes for the BCN and the patient to sign the informed consent, set up the intervention and log in to RedCap. The questionnaire at baseline and end of the study is estimated to take the patient about 50 minutes to answer.

Table 6.1: Study assessment timeline

Assessment	Time periods of the E-dherence Pilot Study		
	Visit 1 – Inclusion	3-Month Follow-up period	Visit 2 – end of study
Medical record - Disease and treatment history	x		
Adherence to study intervention		x	
Socio-demographic characteristics	x		
Quality of life (EORTC QLQ-C30)	x		x
Beliefs of medicine questionnaire (BMQ)	x		x
Medication adherence		x	

side-effect occurrence			
Behavioural intervention (frequency and nature)		x	
Technical support		x	
Intervention Quality and Satisfaction (uMARS)			x

Our primary goal is to determine whether the medication adherence enhancing eHealth intervention can be used to conduct a larger RCT evaluating its efficacy and thus be able to implement the medication adherence enhancing eHealth intervention into clinical practice. We defined feasibility as 1. medication adherence enhancing eHealth intervention acceptability, 2. medication adherence enhancing eHealth intervention quality and 3. medication adherence. Table 6.2 shows the definition and indicators of the feasibility outcomes used in this study.

Table 6.2: Medication adherence-enhancing eHealth intervention feasibility outcomes and indicator

Outcome	Definition	Indicator
Acceptability	Adherence to and frequency of use/ing the medication adherence enhancing eHealth intervention as per protocol.	The proportion of patients that adhere to the use of the eHealth intervention as described in the protocol. The proportion is based on the data transfers and side-effect reports done during the 3 months follow-up.

Quality	To rate the ease of use, how well it functions and if it does what it purports to do using quality subscales: (a) engagement, (b) functionality, (c) aesthetics and (d) information, subjective quality and perceived impact the medication adherence enhancing eHealth intervention has on medication adherence.	Mobile Application Rating Scale (uMARS)(Stoyanov et al., 2016). uMARS uses a 5-point scale. The Information (d) section has the possibility to declare 'not applicable' which thus excludes the question from the mean score calculation. The medication adherence enhancing eHealth intervention mean quality score is the average of a+b+c+d/4. The subjective quality scale is reported as individual items or mean scores. The Perceived impact items can be adjusted and used to obtain information on the perceived impact of the medication adherence enhancing eHealth intervention on the user's knowledge, attitudes and intentions related to the target health behaviour (medication adherence). The uMARS was translated and validated into French. The German version used within the present study was translated by the responsible research team in LIH. The questionnaire is filled out at the end of the study
Medication adherence	The process by which patients take their medications as prescribed using the MEMS helping hand/ cap and MEMS Mobile application.(Vrijens et al., 2012a)	The proportion of days covered by medication intake during three months of follow-up. Medication adherence will be measured through the MEMS® Helping Hand or MEMS® Cap, which is connected to the MEMS Mobile application.

6.3.9 Other study assessments

Medical record data Each participant's disease and treatment history data are retrieved from their medical record. CRN receive access to the participant's medical record from the respective hospitals once the informed consent is signed. CRN collect data on the participants' breast cancer

disease, treatment history (surgery, chemotherapy, radiotherapy) and information on concomitant medication (Appendix 6.1).

Socio-demographic data The socio-demographic characteristics are evaluated at baseline and entail information regarding; age, marital situation, nationality, children, education and professional status (Appendix 6.1).

Quality of life The EORTC QLQ-C30 (Quality of Life Group, n.d.) is a health-related quality of life questionnaire specific to cancer patients. It has been translated and validated into French and German among others. This 30-item questionnaire is divided into functional, symptom, global health, and quality of life scales. In addition, there are a number of single items assessing symptoms commonly reported by cancer patients. The functional scales, symptom scales, and single items assessing additional symptoms have a 4-point scale whereas the global health/ quality of life scale has a 7-point scale. A high score on the functional scale represents a healthy level of functioning. A high score on the global health/ quality of life scale represents a good quality of life. A high score on the symptom scale represents a high level of symptomatology. The EORTC QLQ-C30 is evaluated at baseline and end of the study.

BMQ – Beliefs about Medicines The BMQ is an 18-item tool that assesses the beliefs about treatment and has been translated and validated into French and German among others (Fall et al., 2014; Mahler et al., 2012). The items are divided into specific and general treatment beliefs and are assessed with a 5-point Likert scale, ranging from 1 “strongly agree” to 5 “strongly disagree”. Higher values represent stronger beliefs. The BMQ is evaluated at baseline and end of the study.

Behavioural intervention Each time a BCN calls a patient and performs a behavioural intervention (as presented in Figure 6.2) the data are registered within RedCap during the 3 months of follow-up.

Technical support During the 3 months follow-up BCS can reach out to the CRN, BCN or the AARDEX technical support team. Each time a technical occurrence is notified the responsible person registered the information within RedCap (Appendix 6.1).

6.3.10 Data management

Data will be collected through two different sources: Redcap and MEMS® Adherence Software. Self-reported questionnaires will be sent using the Redcap survey distribution function, each patient receives scheduled emails which contain a unique link to the survey form, and patients' responses will be registered within the RedCap database. ICF data will be entered by authorized staff into the "Patient Informed Consent" form within the RedCap clinical database. The data collected through the MEMS® Helping Hand, MEMS® cap and MEMS Mobile application are stored on an encrypted MEMS® Adherence Software. The solely authorized staff has access to these data.

Data quality, as well as data integrity, is assured through implementing edit checks which will be executed regularly to verify for possible inconsistencies.

Figure 6.4 illustrates the data flow and E-dherence architecture. All data collected in the framework of this study will be pseudonymized and centralized at LIH by the research team. LIH manages a unique and secure pseudonymization matrix, which enables the linkage of data coming from different sources.

At the end of the study, Aardex receives the medication adherence data of the 15 patients for the three months follow-up. A double pseudonymization principle is used to secure the patient's identity.

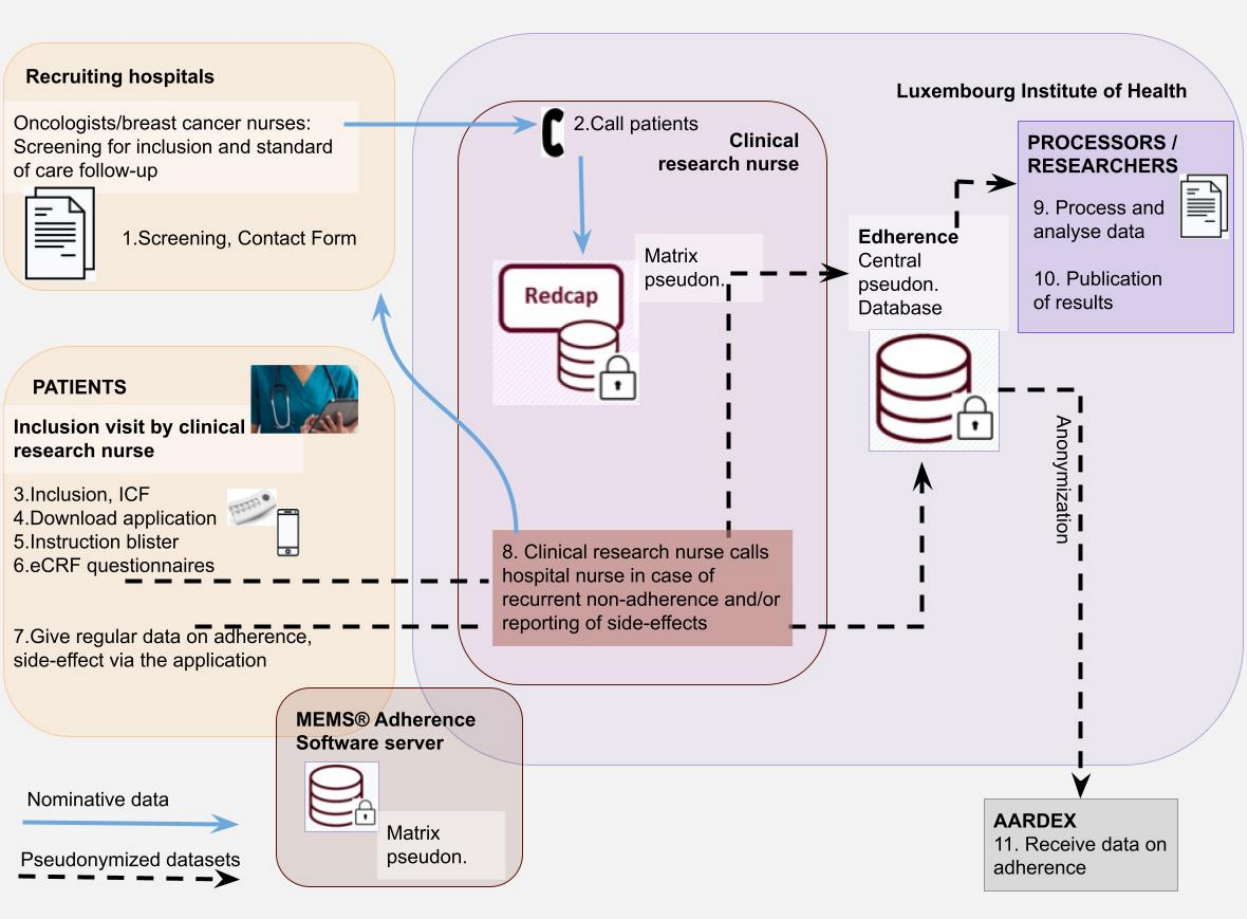


Figure 6.4: E-dherence Pilot study data flow architecture

6.3.11 Statistical analysis

Due to its pilot nature, the present study is not powered for statistical comparison. With regard to statistics, the pilot study aims to provide insightful information and figures to use later on for the planning of a larger randomized controlled trial.

Descriptive statistics will describe the study population as well as the primary and secondary endpoints from the questionnaires and the real-time data using the mean (+- SD) or frequencies (%).

The proportion of days covered by medication intake will be calculated for each patient to compare patterns of adherence between and within patients. Furthermore, a specific medication adherence analysis will be performed. We will calculate adherence using continuous medication availability. Using this method we can study both implementation (taking the AET as prescribed) and persistence (to continue taking the AET during the recommended time window).

Data will be available for analysis in a statistical program (e.g. R, SAS and SPSS).

6.3.12 Ethics approval

This study was approved by the national ethical committee (Comité national d'éthique de recherche (N◦201811/01 Version1.1) and the Luxembourgish Ministry of Health (82bxll634). The inclusion process began in March. The entire study is expected to be completed by early 2023. The study is registered on clinicaltrial.gov (NCT05324020).

6.4 Discussion

Cancer survivorship has been described as a specific transition period from cancer patient to survivor and is associated with anxiety and fear with patients claiming increased support during this period (Kantsiper et al., 2009). In addition, specific medical issues of medication management such as adherence and side-effects management are reported during this post-acute treatment period (Hurtado-de-Mendoza et al., 2018; Kantsiper et al., 2009). Hence the medication adherence enhancing eHealth intervention has the potential to support women during this period and more specifically foster personalized interaction between BCs and their healthcare provider (BCN and oncologist) in case of recurrent non-adherence and or side-effects occurrences. Due to the interactive nature of the medication adherence enhancing eHealth intervention, BCS might feel reassured and thus take their AET as prescribed and better manage their side-effects.

This study aims to evaluate the feasibility of the medication adherence enhancing eHealth intervention and serves as a preliminary trial (Phase 1) to provide information about feasibility, acceptability, and effect estimates for a larger RCT. This phase will advise which behavioural intervention components and MEMS tools should be retained for the medication adherence

enhancing eHealth intervention. The next phase (Phase 2) has the goal of refining and crafting a final medication adherence-enhancing eHealth intervention which then will test efficacy using an RCT in Phase 3. Not only does this feasibility study provide us with information for the medication adherence enhancing eHealth intervention but also for the full-scale RCT planning. Including patients and healthcare professionals from the beginning in the development of an intervention intended for them will facilitate the implementation of the intervention, in the healthcare setting (Aguayo et al., 2021). Also, it has the benefit to rule out biases that are related to technical and or logistical issues which could falsify the efficacy results in the RCT. Thus, this study allows us to identify the feasibility of an eHealth intervention to enhance medication adherence as well as technical occurrences, and limitations for the patients and can be taken into consideration for the larger RCT planning.

The medication adherence enhancing eHealth intervention has the potential to detect non-adherence early and might thus hinder long-term non-adherence or even discontinuation. Hence, the present study will give first insightful information on BCS initiation, implementation and persistence of their AET during the first 3 months. Results will be useful to develop more meaningful medication adherence-enhancing interventions subtyping support techniques relevant to the 3 phases of medication adherence, moving from 'one size fits all' to personalized interventions (Fagherazzi et al., 2021).

Nevertheless, the present study faces a few limitations. Within this study, only 2 molecules of the adjuvant treatment are tested thus limiting the potential benefits to BCS that take Nolvadex or Arimidex. The recording of medication adherence is triggered whenever the blister is removed and when it is inserted in the helping hand or when the cap is opened. Therefore, there is a certain risk that a patient takes the blister out of the helping hand or opens the cap without taking the pill. In this case, the patient would not be reminded and the study team would not notice the non-adherence to the treatment. This risk will be mitigated by clear explanations given by the CRN at the beginning of the study. Despite these limitations, this study has the potential to advance the medication adherence research to more personalized prevention strategies enhancing AET adherence in BCS and to lead to a large trial that will test a refined eHealth intervention to enhance medication adherence in BCS.

6.5 Acknowledgements

The E-dherence Pilot study is financed by LIH (Sponsor) in conjunction with the Ministry of Health. The authors thank the nurses and clinical research associates from the Clinical Investigation Center at LIH for their support and cooperation. In addition, we thank the data manager from the CCMS at LIH for their advice. Also, we would like to thank the oncologists to have helped us with the recruitment. Finally, we thank all the participants of the present study for having participated. Furthermore, we thank the Action LIONS Vaincre le Cancer as CG is funded by a PhD grant from them.

6.6 Authors' Contributions

CG and LH, conceived the original study idea. CG is the project manager and drafted the manuscript. GF and GB are the principal investigators and SR and CD are the clinical investigators of the present study. BV is the medication adherence and MEMS expert and advised on the eHealth measuring technology and outcome measures. MV provided statistical expertise and data management skills. All authors contributed to the review of the study protocol and approved the final manuscript.

Chapter 7

Discussion, conclusion and perspectives

7.1 General Discussion

The research presented in this thesis has focused on constructing a digital MAEI for BCS taking an AET. Despite various campaigns to raise medication awareness, such as U.S. Surgeon General C. Everett Koop's statement "Drugs don't work in patients who don't take them," adherence to treatment for chronic diseases remains suboptimal (Sabaté, 2003). Non-adherence is a major contributor to healthcare costs and poor health outcomes (mortality, quality of life).

Up to 73% of BCS discontinue taking their AET before the recommended 5-year treatment. Numerous technological advances (e.g. MEMS, or digital MAEI) showed the potential to support healthcare professionals and empower patients in detecting and managing non-adherence. However inconclusive results on which intervention components are more effective than others remain. It has been recognised that complex MAEI, sensitivity to the dynamic behaviour of medication adherence, and containing multiple components, especially patient-provider interaction are likely to be the answer to enhance AET in BCS.

Major challenges associated with developing and evaluating such interventions remain (Medical Research Council, 2008; Nieuwlaat et al. 2014).

The research in this thesis has therefore focused on developing a digital MAEI to support BCS with their AET while monitoring adherence electronically in real-time and to provide patient-provider interaction at the moment of need using behaviour techniques. To answer the needs of the literature gaps, the present thesis uses end-user co-design principles, involving both BCS and HCP (oncologists, BCN and pharmacists) to contextual analysis of AET management in Luxembourg and to establish usability patterns and acceptability of current MATech and MAEI for AET in BCS. In addition, this research project followed a behaviour theory-based framework to finally construct a digital MAEI for AET in BCS and test its feasibility.

7.1.1 Main findings and their implication

Breast cancer survivorship and AET management in Luxembourg - patient and HCP perspective

Even though AET management is challenging for BCS, they are also experiencing psychosocial difficulties, that make BCS often feel overwhelmed and isolated. This is mostly perceived as insufficient information and support from HCP. This study showed that the major barrier for HCP to answer to the needs of BCS during AET is the lack of an integrated post-acute treatment structure within the clinical setting. Due to the absence of a systematic follow-up, AET management remains often the patient's matter. The role and responsibilities of the different HCP are unclear on the one hand for the patient and on the other hand to the HCP themselves. Moreover, a lack of human resources to properly follow up on BCS was reported.

Digital MAEI for AET support in BCS

Digital technology as a BC survivorship companion could link the gap between BCS claimed needs and integrate the lack of a systematic post-acute treatment follow-up for AET management in a clinical setting. This research project found that although 1.2% currently use health-related apps over two-thirds would accept the use of a digital MAEI to support their AET management (adherence and side-effects).

Key components of this digital MAEI should be patient-provider interaction, support, information and remote AET monitoring while encouraging multidisciplinary teamwork. These findings resulting from a qualitative study were confirmed using the behaviour change wheel and COM-B model. The framework identified persistent AET taking and timing, side-effect management, and consistent AET pharmacy refill as target behaviours. Using the COM-B model the following components are necessary to enhance AET adherence; Capability (lack of knowledge, side-effects, size and texture of AET), Opportunity (social support, patient-physician communication) and Motivation (lack of routine, religion and beliefs). The following 6 intervention functions were chosen; education, persuasion, training, environmental restructuring, modelling and enablement.

Major barriers to using a digital MAEI to support AET intake in BCS are lack of data confidentiality, fear of data mistreatment and absence of reimbursement. Facilitators for such an MAEI usability are fast interaction with HCP, side-effect reporting and personalization aspect of such an intervention.

A digital MAEI to support AET in BCS - is it feasible?

Using a co-design approach and theory-based framework, led to an acceptable digital MAEI intervention to support AET in BCS. The present research project developed a digital MAEI for AET support in BCS including (1) a Medication Event Monitoring System (MEMS®) tool and (2) access to the MEMS Adherence Software. The MEMS tool consisted of an electronic blister or cap measuring the time and date of AET intake. An integrated microelectronic circuit records those data every time the blister is removed and/or inserted or when the cap is opened and closed.

The MEMS Adherence Software is a mobile app on the participant's smartphones (iOS or Android). The MEMS Mobile app entails an integrated calendar to remind BCS to take their AET as prescribed and to transfer their data from the MEMS tool to the MEMS Mobile app. Furthermore, the MEMS Mobile app includes questions on potential side-effects BCS could experience during the week and can be filled out if needed. For each side-effect, the BCS is asked to rate the severity from not severe at all to very severe.

The MEMS mobile app and MEMS tool were connected. The MEMS tools transferred its data using NFC to the MEMS mobile app.

Another aspect of the digital MAEI intervention to support AET in BCS was the digital monitoring by a Clinical Research Nurse (CRN) of data collected in real-time (weekly) of both AET adherence and reported adverse events using MEMS® Adherence Software. In the event of an alert, such as repeated non-adherence and/or reporting of adverse events and their severity, the HCP was notified and could contact the BCS by telephone. If no alerts were recorded, no further action was taken.

The interventions implemented by the BCN were behavioural and were developed based on the theory of the behaviour change wheel. The alert was triggered by 1. repeated AET non-adherence, 2. the occurrence of side effects and their severity, and 3. a combination of repeated AET non-

adherence and the occurrence of side effects. Behavioural interventions depended on the motive of the alert. Once the BCN determined the motive of the alert, it chose between the - or a combination of - intervention functions: 1. education - feedback about the behaviour and possible consequences, 2. training - demonstrations and instructions on how to perform/improve the behaviour, 3. encouragement - providing prompts and cues to improve the behaviour.

Thus the digital MAEI respects the needs and expectations of both BCS and HCP for enhancing AET intake. In summary, it includes the interactive approach allowing patient-HCP communication, support in terms of communication and AET management (adherence and side-effects). Also, it follows the intervention options and behaviour change techniques identified with the BCW.

The feasibility study, however, had to be stopped. The following are the potential reason why the feasibility of the above-mentioned digital MAEI failed.

1. Lack of fidelity - lack of patient recruitment

Although our contextual analysis showed that HCPs were willing to incorporate a MAEI into their clinical practice, this was only a snapshot of several HCPs. As part of the feasibility study, we asked all oncologists treating BC patients to participate. During recruitment for the study, only five patients were selected, three of whom were eligible for participation. All of these patients were from the same oncologist, so the lack of reliability of the digital MAEI to support AET in BCS may be one of the reasons for the failure of the study.

2. Lack of recognition that medication adherence is an issue

Medication awareness is very low in Luxembourg at all system levels. At the macro level, there are no dispensing or refill databases to assess adherence. There is also no systematic approach in clinical practice to record adherence using a self-completed questionnaire or electronic monitoring. Some HCPs indicated that they ask patients during the consultation if they are taking their treatment and/or if they have problems with it. Therefore, there are no publicly available estimates on medication adherence of patients in oncology and other pathologies in Luxembourg.

3. Lack of interprofessional approach

Contextual analysis revealed that there is no systematic approach to HCP collaboration. Oncologists are often reluctant to hand over responsibility to BCNs or pharmacists. In the Luxembourg context, the role of the pharmacist is underestimated and seen as a mere product seller. Nevertheless, they are highly motivated to get more involved in the patient's medication process. Oncologists complain of work overload and therefore often do not emphasize the importance of AET adherence and its impact. As a result, adherence is not an issue at every consultation.

The ugly truth regarding AET lack of adherence is that the consequences take years to come to light and are not reversible. Therefore, partnerships and interprofessional healthcare providers are paramount in the multifaceted journey toward treatment adherence (M. P. Schneider & Burnier, 2022). Thus, treatment management is an interplay between healthcare providers (e.g., physicians, pharmacists, nurses) and the patient. Smith et al. have shown that by using interprofessional healthcare providers and promoting patient-nurse partnership, the quality of care tends to improve (S. M. Smith et al., 2021).

Providing sufficient information about the AET adherence importance and improving health literacy enables patients to gain the autonomy they need to manage their medications and deal with symptoms and side effects associated with their disease and treatment (Zhang et al., 2014).

4. Lack of appropriate healthcare infrastructure

On the one hand, AET treatment is not part of a systematic follow-up. Depending on the hospital and physician, the frequency of visits and the importance of medication adherence vary. Without a systematic approach to AET management and follow-up, implementation of a MAEI into clinical practice is not possible.

On the other hand, each hospital employs 1-2 breast cancer nurses who are involved in both acute treatment and follow-up of the patient. The workload to monitor and provide intervention when needed is not manageable with current resources.

Finally, the clinical Internet infrastructure is not ready to integrate the digital MAEI described above. For this reason, the clinical research nurses at the research center took charge of monitoring compliance with AET and contacted the BCN at each hospital to implement the intervention.

7.1.2 Take-home message

1. BC survivors claimed increased support from healthcare professionals during the initiation and implementation phase of the adjuvant endocrine therapy
    - Initiation; AET beliefs, and habit creation
    - Implementation; side-effect coping strategies, patient-HCP interaction
2. MAEI to support BCS taking their AET:
    - BCS and HCP accept to use of a digital MAEI for AET
    - Be multifaceted; adjuvant endocrine therapy management (e.g adherence and side-effects), medical information, social support network, interaction with a healthcare provider
    - MAEIs' components changes over time depending on the adherence phase; initiation, implementation, persistence
3. The present research project collects insightful information regarding the content and acceptability of a digital MAEI for AET intake. However, its feasibility fails due to three major reasons
    - Methodology limitation of the research project. We did not involve the system level during the digital MAEI development.
    - Lack of MAEI fidelity mainly due to the lack of recognition of the scope of medication adherence at all three levels
    - Insufficient human resources for BC follow-up let alone AET monitoring (1-2 BCN per hospital)

i. For the moment pharmacists are not accepted by patients to take over the role of AET monitoring and nor interprofessional ecosystem in place to collaborate between HCP

4. Future MAEI research projects need to follow implementation research principles and involve the system level

5. Luxembourg specifically (Perspectives)

   - Raise medication adherence awareness across all levels; Micro, Meso, and Macro
   - Implement accessible medication adherence assessment databases
   - Restructure the follow-up care for BCS
   - Encourage an interprofessional healthcare ecosystem

7.2 Perspective

7.2.1 The future of real-world intervention development

Implementation of medication MAEI into routine care

The source of the following paragraph: Goetzinger, Schneider; Chapter 3.5.5 (Section 4) Interventions to improve medication adherence - Drug Utilization research book, 2023 (in external review)

> "The same way a medication only works in those that take them, medication adherence enhancing intervention only benefits patients if adequately implemented into the healthcare setting and daily practice for both patients and healthcare professionals." - Goetzinger, Schneider et al 2023

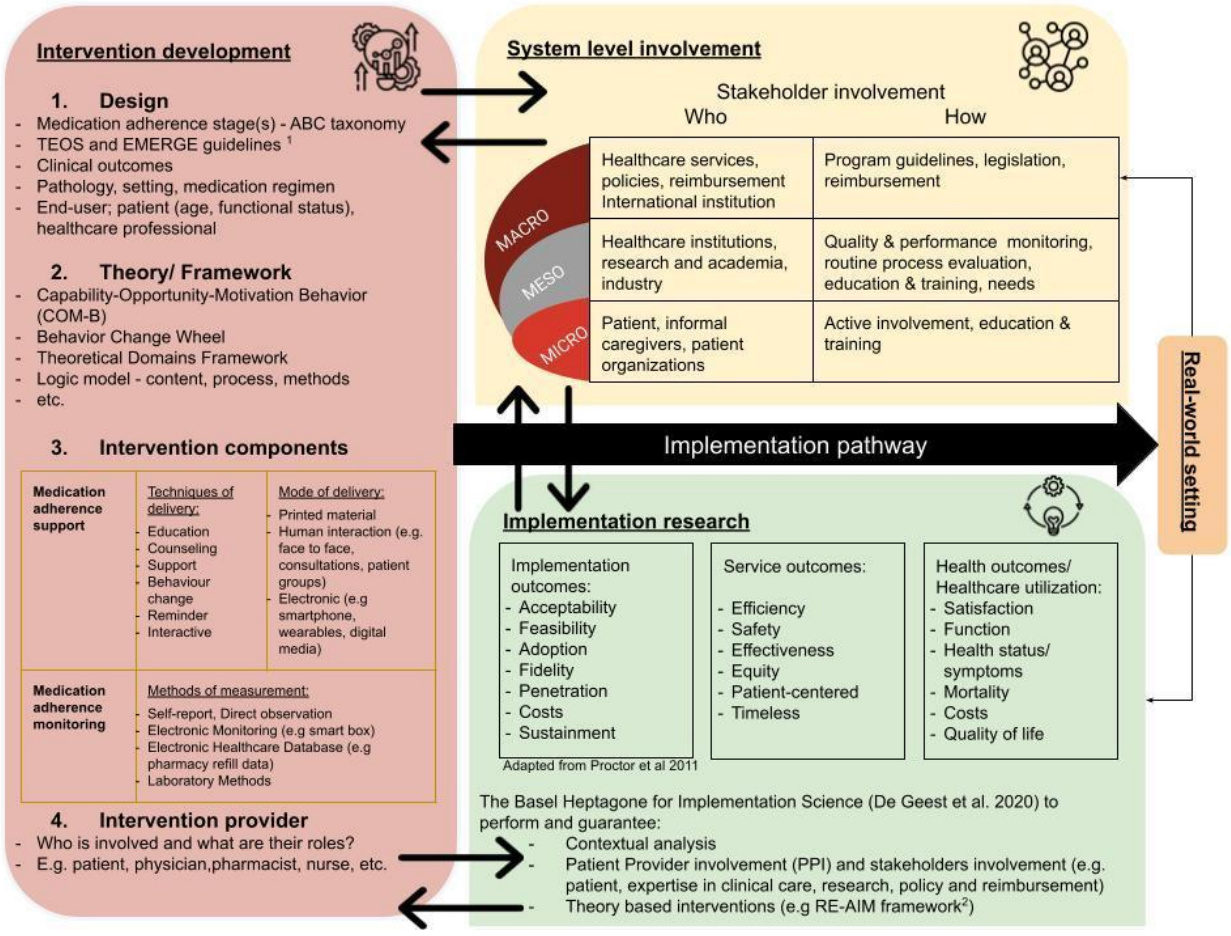
Health behaviour change interventions are complex. Thus, the UK Medical Research Council (MRC) revised their framework for developing and evaluating complex interventions (Skivington et al., 2021). As said by Araùjo et al. "developing real-world interventions is an opportunity to

create impact from behavioural science and to contribute to addressing some of the most pressing issues of our time" (Araújo-Soares et al., 2019). To avoid research waste and apply the best scientific practices, intervention developers and researchers should follow common standards. The Theoretical Domains Framework (TDF), which classifies health determinants into 26 categories (e.g. knowledge, skills, Social Role and Identity; Beliefs about Capabilities; Beliefs about Consequences of a Behaviour; Reinforcement; Intention; Goals; Memory, Attention and Decision Processes, Social Influences; Emotions etc.), is one example of such theory-based research to be used to classify medication adherence determinants (Carey et al., 2019). Moreover, the TIDieR checklist and guide, and the CHERRIES checklist (specific for digital interventions) were developed to improve the completeness of reporting of interventions and their replicability in other settings (Eysenbach, 2004; Hoffmann et al., 2014).

During the last years, implementation science grew popular in relation to medication adherence-enhancing interventions. 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" (Eccles & Mittman, 2006). This research should be undertaken from the early stages to build up contextually adapted interventions to increase feasibility, uptake and impact. Implementation science focuses on external validity and is sensitive to complex real-world contexts. De Geest et al. developed the 'Basel Heptagone of Implementation Science' representing the key components of implementation science (De Geest et al., 2020). Such theory-driven development of medication adherence interventions is particularly relevant for gathering evidence and allowing further sustainment and scaling up, for example in the field of digitally-delivered interventions (Ribaut et al., 2020).

Based on the existing evidence, Figure k depicts an illustration of how to develop real-world interventions that are implementable in the real-world (healthcare setting, daily routine of patients, healthcare pathway). In order to bridge the phase of development and the real-world implementation, it is essential to involve stakeholders from different system levels and to perform implementation research to guarantee the integration of the intervention into the real-world setting. Implementation of medication adherence-enhancing interventions can only succeed with an

interplay between the ‘co-designed intervention development’, the ‘system level involvement’, and ‘research implementation’. The intervention development focuses on the context into which the intervention is integrated and the content, form and interprofessional components of the intervention. In order to guarantee the implementation into the real world and thus the clinical practice and healthcare, multi-levelled stakeholders need to be involved in the implementation pathway. So as to achieve scientific, economical, technical and social validity implementation research will be used interchangeably during the intervention development and will work closely with the different stakeholders. Meaningful interventions serving the purpose of enhancing medication adherence while considering and respecting end-users needs will increase the usability of the intervention. End users (e.g. patients and the public, physicians, pharmacists, nurses, health psychologists, and social workers), multidisciplinary researchers and developers, policymakers, insurers and pharmaceutical/technology industries need to be involved throughout the process of medication adherence enhancing interventions. Engaging the health ecosystem is detrimental to guaranteeing the successful usability, acceptability and fidelity and effectiveness of the medication adherence intervention.



[1] TEOS - Timelines-Events-Objectives-sources framework (Dima et al., 2022)

EMERGE - ESPACOMP Medication Adherence Reporting Guideline (De Geest et al., 2018)

[2] RE-AIM framework (Glasgow et al., 2001)

Figure 7.1: Developing real-world interventions: intervention development, implementation science, system-level involvement, adapted from (De Geest et al., 2020; Proctor et al., 2011) Source: Goetzinger, Schneider; Chapter 3.5.5 Interventions to improve medication adherence - Drug Utilization research book, 2023 (in external review)

7.2.2 Medication adherence a new priority of public health for Luxembourg

For years, medication adherence has been a public health concern globally. Other European countries have worked continuously to assess medication adherence through dispensing and or other databases. The Netherlands and Poland have created national/regional medication adherence center. The Dutch center, MAECON (Medication Adherence Expertise Centre of the Northern Netherlands), fosters multidisciplinary collaboration and focuses on research, education, clinical practice and private-public partnerships (MAECON, 2023). MARC (Medication Adherence Research centre), is a polish centre aiming to further intensify research on medication adherence and perform educational l and disseminating activities.

In a study by Menditto et al. they point out the advantages of measuring persistence to treatment. They highlight the robustness of persistence as an indicator of medication adherence-related quality and performance of the healthcare system (Menditto et al., 2021).

The national health service in the UK introduced the largest-ever evidence-based medication adherence intervention called the New Medicine Service. They provide support to people who have newly prescribed medicine for a long-term condition, in order to enhance the patients' medication adherence and self-manage their condition (National Health Service, 2021).

Medication adherence experts in Switzerland developed a framework addressing medication adherence in a complex multilevel ecosystem. They divided the roles and responsibilities regarding medication adherence among stakeholders on the micro, meso and macro level for medication adherence research and development, education, policy and clinical practice (Bandiera et al., 2022).

It is time for Luxembourg to jump on the wagon and make medication adherence a public health priority; the following paragraphs highlight the different roadmaps Luxembourg can envisage to take medication adherence at all system levels.

Teaching communication skills to HCP to improve MA in patients

Communication is a skill that is not provided in the long curriculum of HCP (Moore et al., 2018). Nevertheless, the literature emphasizes the importance of communication skills related to health outcomes (Bestvina et al., 2014; A. J. Linn et al., 2012; Liu et al., 2013). Communicating the importance of medication adherence is key for the initiation of the treatment, correct implementation (timing, dosing) and persistence. There exist practical and perceptual barriers for patients to understand their disease and or treatment. Regarding the practical barriers, they can be either cognitive or routine. Perceptual barriers consist of needs and concerts. Specific communication techniques exist to overcome those barriers hence improving the understanding of comfort and quality of care for the patient (Riva et al., 2015; Wilkinson et al., 2002). Such communication techniques are: recall promoting techniques (repeating, teach-back method, actively engaging the patient in the conversation) exploring daily routines and engaging patients in solutions, providing information, involving the patient in conversation and decision, concerns: motivational interviews, effective communication

Raising awareness of medication non-adherence among all system levels

According to the World Health Organization report published in 2003, around 50% of patients deviate from their prescribed chronic treatments (Sabaté, 2003). Little improvement has been observed in the 20 years since and still leads to poor health outcomes, increased morbidity and mortality at the individual level. At the system level, it leads to increased use of health services and higher costs.

In the context of this research project, Luxembourg joined the joint forces of ENABLE (European Network to Advance Best practices & technoLogy on medication adherencE) to:

1. raise awareness of adherence enhancing technological solutions,

2. foster and extend multidisciplinary knowledge on medication adherence at the patient, treatment and system levels,

3. accelerate the translation of this knowledge to useful clinical application and

4. work collaboratively towards economically viable implementation of adherence-enhancing technology across European healthcare systems.

In line with the actions of ENABLE awareness was raised using a press publication explaining in lay language the importance of medication adherence and the work done at ENABLE (Goetzinger & Bella, 2022).

The OECD identified four enablers for improving medication adherence at the system level (Khan & Socha-Dietrich, 2018):

1. Acknowledge that medication non-adherence harms health and increases healthcare costs
2. Inform - systematically assess/monitor adherence
3. Incentivise - make changes in financial incentives for providers and patients
4. Steer and support - adherence begins with the patient and a prescribing physician and dispensing pharmacist should be supported by other health system stakeholders.

Healthcare systems, healthcare infrastructures and healthcare professionals have to acknowledge the scope of medication adherence and include it in their roadmaps of activities.

Most importantly the patient needs to be educated. Therefore patient organizations could be approached to work out an awareness program for patients in general or within pathologies to emphasize the importance of medication adherence and its implications.

Medication adherence centre (Luxembourg)

Monodisciplinarity and nonstandard approaches are major obstacles to medication adherence. Therefore it is crucial to join efforts focused on adherence research and stimulate the adoption of best practices in medication adherence-related research in a systematic way. More concretely, it means that there is a need for the establishment of national Medication Adherence Research Centers of Excellence (CoE). The Centers could not only conduct research but also serve the needs of patients, healthcare providers and systems, as well as economies. In addition, the centers have the potential to connect multidisciplinary stakeholders and develop national priorities and

strategies addressing medication non-adherence. Hence, a CoE has the potential to be local trendsetter and advocate for good practices and education regarding medication adherence.

In general, CoEs are organizations that aim for the highest attainable standards in their specific fields by synergies created through an exceptionally high concentration of expertise and related resources centred on a particular area (Elrod & Fortenberry, 2017). Various types of CoEs exist in the field of medicine. Based on the main area of their activity, the following major types may be distinguished: educational centres, clinical or healthcare centres, and research centres which usually provide some educational and/or clinical services (Damari et al., 2020).

As discussed in 7.2.2 current CoE exist in Poland and Netherlands merging local and international experts to pursue innovative research meeting the needs of patients and implement evidence-based strategies in the real-world setting.

7.3 Conclusion

The body of evidence regarding medication adherence interventions is increasing but progress in the science of intervention development is needed. Interventions to improve adherence require a systems-level change to alter healthcare practices and empower patients to self-manage. The transition from purely clinical care to clinical and behavioural interventions to effectively improve adherence has not yet been made in research and routine care.

More research is needed to show how best to help patients adhere to reasonably prescribed medications to make a positive contribution to health, i.e., to improve clinical outcomes and patient-reported outcomes (PROMs) such as quality of life. To improve the transfer of research findings into routine care, context-appropriate interventions must be developed, which requires the involvement of all stakeholders (patients, healthcare providers, pharmaceutical and technology engineers, researchers, data scientists, policy-makers, and insurers).

Research guidelines in the field of medication adherence (e.g. ABC taxonomy, EMERGE, TEOS) and theoretical frameworks in behavioural science (e.g. Behavioural change wheel) are needed to

improve the design and content of interventions, medication adherence measurement, the quality of intervention and to increase the reproducibility and comparability of results.

The digital transformation of healthcare, the use of eHealth and self-management apps, and data science are transforming adherence interventions, providing new opportunities to measure adherence, collect patient data, and deliver interventions directly to the patient. Digital health is reforming healthcare and represents a huge area of research and opportunity for adherence interventions while ensuring better care coordination and human collaboration between patients and interprofessional providers.

'Enhancing medication adherence is the effort of a multidisciplinary team' - Catherine Goetzinger

List of Publications

Goetzinger Catherine, Ben-Diane Marc-Karim, Rauh Stefan, Duhem Caroline, Jodocy Daniel, Préau Marie, Vrijens Bernard, Mancini Julien, Fagherazzi Guy, Huiart Laetitia. 2021 "eHealth technology to support breast cancer survivors during their adjuvant endocrine therapy: a qualitative study." *Patient Preference and Adherence. Dove Medical PressIn (In Peer-review)*

Goetzinger, Catherine, Caroline Alleaume, Anna Schritz, Bernard Vrijens, Marie Préau, Guy Fagherazzi, and Laetitia Huiart. 2022 "Analysing Breast Cancer Survivors' Acceptance Profiles for Using an Electronic Pillbox Connected to a Smartphone Application Using Seintinelles, a French Community-Based Research Tool." *Frontiers in Pharmacology* 13 (September). https://doi.org/10.3389/fphar.2022.889695. (slightly modified)

Goetzinger, Catherine, Caroline Alleaume, Anna Schritz, Bernard Vrijens, Marie Préau, Guy Fagherazzi, and Laetitia Huiart. 2022. " Barriers and Facilitators towards the acceptability and usability of an adjuvant endocrine therapy enhancing eHealth technology during breast cancer survivorship" (In co-author review and planned to be submitted to *Patient Preference and Adherence. Dove Medical PressIn)*

Goetzinger Catherine, Ribaut Janette, Jensen Milena, Diederich Celine, Backes Claudine, Vrijens Bernard, Huiart Laetitia, Schneider Marie-Paule, Fagherazzi Guy. 2023 "Developing a theory-driven eHealth intervention to support adjuvant endocrine therapy in breast cancer survivors" (In co-author review and planned to be submitted to BMC Implementation Science)

Goetzinger Catherine, Duhem Caroline, Rauh Stefan, Vrijens Bernard, Berchem Guy, Fagherazzi Guy, Huiart Laetitia. 2022 "Improving Adjuvant Endocrine Therapy Adherence in Breast Cancer Survivors using a Medication Event Monitoring System: Protocol for a Feasibility Study" *JMIR - Methods and feasibility Studies (In Peer-review)*

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Appendices

Appendix 1.1: Study characteristics of Included reviews (N=8)

Review (Year)	Patient Population	Sample size and study duration	Search strategies	Medication adherence -definition -measurement	Control for quality to lower risk of bias
(Kini and Ho 2018)	Disease with long-term treatment ≥18 years US only	49 trials included Total N=30183 Lowest sample size N=62 Highest sample size N=8517 Study duration 6-15months	MA primary outcome Use of objective measures for MA Studies from 1/1/2000-6/9/2018	Definition: 'The extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen.' - (Cramer et al. 2008).	Only included papers with low risk of bias based on the Methods Guide for Effectiveness and Comparative Effectiveness Reviews - Agency for Healthcare Research and Quality (Agency for Healthcare Research and Quality 2008)
(Rosenberg et al. 2020)	Cancer patients**	55 studies Total N=30183 Study duration 42 days - 2 years	Development, testing, or implementation of an intervention/ program related to oral anticancer medication Adherence as an outcome Through July 2019	No definition used for medication adherence	Mixed Methods Appraisal Tool v2018 (Hong, Gonzalez-Reyes, and Pluye 2018) - Overall study quality was mixed

(Smith et al. 2021)	Multimorbidity***	17 studies (19 papers) included 8 studies included on the meta-analysis Total N= 8217 Lowest sample size N= 50 Highest sample size N= 4023 Study duration; 8 weeks - 2 years	primary care and community settings based interventions Simple and multifaceted interventions Not specified date (included studies ranged from 1999-2015)	Medication use and adherence was defined as patient behaviour and needed to be measured with a validated scale	CochraneRisk of Bias tool (Higgins and Green 2011)- Reasonable quality with minimal risk of bias
(Wiecek et al. 2019)	Any clinical conditions****	69 meta-analyses extracted 468 primary studies Patient follow-up and results of adherence were reported in standardized periods of time: 0–3 months, 4–6 months, 7–9 months, and ≥10 months	Implementation adherence as an outcome using any measure (e.g. self-report, pill count, electronic monitoring) Adults; ≥ 18 years Up to 2019 (included studies range from 1971-2017)	NA	Cochrane Risk of Bias tool - most studies had an unclear risk of bias. The domains with a higher risk of bias were attrition bias and performance bias as studies lacked complete outcome data or were unable to blind participants due to the nature of the interventions

(Pouls et al. 2021)	Long-term medication use*****	22 studies (29 interventions) included Total N= 45293 Lowest sample size N= 70 Highest sample size N= 21752 Study duration; 4 weeks - 52 weeks	Control group had to be usual care Sample size at least 50 adult patients Medication adherence primary outcome Publication date ranged from 2014 to July 2019 Only eHealth interventions (interventions solely applied over a distance; e.g online portals, telephone calls,...) Blended care interventions, where face-to-face contact is combined with online components, were excluded	NA	Cochrane Risk of Bias tool - 15 studies had a positive score on at least 5 domains and thus regarded as high-quality studies

(Finitsis et al. 2019)	Breast cancer survivors taking an adjuvant endocrine therapy (AET)	7 studies (1 conference paper that provided supplementary information) included 8 interventions Total N= 4698 Lowest sample size N= 47 Highest sample size N=4844 Study duration; 8 weeks - 2 years	Interventions to promote AET adherence Report on at least one measure of medication adherence No time range as inclusion criteria. But included papers dated from 2002-2016	NA	Downs and Black's methodological quality scale, is a 27-item instrument that assesses five dimensions of research methodology (Downs and Black 1998).
(Cornelissen et al. 2020)	Patients taking osteoporosis medications	15 articles were included Total N= 162804 Lowest sample size N= 79 Highest sample size N= 147071 Study duration; 6-24 months	Interventions aimed at improving adherence or persistence of osteoporosis medications Published articles from July 1st 2012-December 31st 2018	Results on medication adherence measurements were organized using the ABC taxonomy, according to (Vrijens et al. 2012)l.	Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (J. A. C. Sterne et al. 2019) or the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) assessment tool (J. A. Sterne et al. 2016)

(Conn and Ruppar 2017)	Long-term medication prescription	771 articles were included for effect size 739 articles included in the meta-analysis	Adults Excluded studies of contraceptive/ sexual function medications, major psychiatric or substance abuse problems, and incarcerated/ institutionalized persons Small-sample and pre-experimental studies were included	Adherence refers to the extent to which patients' medication-taking behaviour is consistent with the prescribed regimen (Vrijens et al. 2012; Cramer et al. 2008; World Health Organization 2003) Common terms for adherence problems include inadequate adherence, poor adherence, lack of adherence, and non-adherence (World Health Organization 2003)	NA

*Dyslipidemia, venous thromboembolism, Osteoporosis, Coronary artery disease, Diabetes, Heart failure, Disease with long-term treatment, Myocardial infarction, Polypharmacy, Hypertension, Asthma, Kidney transplant, HIV, Stroke, COPD, Chronic disease, Chronic anticoagulation

** Breast cancer, Gastrointestinal cancer, chronic myeloid leukaemia, acute leukaemia and non-Hodgkin's lymphoma, Non-small cell lung cancer, Colorectal cancer, genitourinary cancer, Renal cell carcinoma

***Multimorbidity; co-existence of multiple chronic diseases and medical conditions in the same individual, usually defined as two or re conditions (Fortin et al. 2005). 9 of the 17 included studies focused on depression, diabetes and cardiovascular disease. The others on comorbid conditions in general.

**** 12 clinical conditions were found and the most common were cardiovascular diseases (N=206) followed by HIV (N=96)

**** The most common diseases were cardiovascular diseases and or diabetes

Appendix 1.2: In-depth information on main results and medication adherence enhancing intervention research recommendations from the included reviews

Review (N=9) (Year)	Main Results	Recommendations for future medication adherence enhancing intervention (MAEI) research
(Kini and Ho 2018) Long-term treatment in adults	Results on the effectiveness of MAEIs are inconclusive within the present review, however, the authors suggest the following identified intervention strategies to be clinically practical and successful to promote adherence: - combination pills to reduce daily pill burden - clinical pharmacist consultation for disease co-management - medication-taking reminders (e.g. to prompt refills)	Raise medication adherence awareness among all stakeholders. Interprofessional and implementation research approaches are required

(Rosenberg et al. 2020) Cancer	Most MAEIs were educational and counselling-based (e.g providing drug information, and strategies to manage side effects) Interventions were not tailored to the needs of the patient population, thus nonadherence to the intervention itself is the reason for non-effectiveness (e.g video game - 28% of patients playing the game each week for a full hour as intended (Kato et al. 2008)) Those interventions that reported statistically significant improvements in adherence were pharmacist-directed programs, particularly those that integrated monitoring or routine follow- up with a provider.	Future MAEIs need to: - Be tailored to the needs of the patient populations - Target intentional non-adherence - Consider interprofessional and implementation research approaches
(Smith et al. 2021) Multimorbidity	Most studies were organisational studies (changing the organisation of care delivery, usually through case management or enhanced multidisciplinary teamwork) Patient-oriented interventions that are not linked to healthcare delivery were revealed to be less effective.	Improving multimorbidity outcomes is challenging to be tackled effectively with a holistic approach, hence MAEIs need to be more targeted (e.g risk factor management, medicines management)
(Wiecek et al. 2019) Any clinical condition	Multicomponent MAEIs including educational, attitudinal and technical components are more effective than single-component MAEIs. The component(s) needed to support adherence may change over time The combination of educational + technical components consistently performed well.	Future MAEIs need to: - Find the best combination MAEI components considering the dynamic behaviour of medication adherence (timing) - Evaluate cost-effectiveness - Consider implementation research approaches

(Pouls et al. 2021) Long-term medication use	Most MAEI including interactivity as intervention components (17/29) had a statistically significant effect on medication adherence (P<.05). Interactive component was used to either inform and educate or to provide support through encouragement and assistance	Study methodology of future MAEIs should consider a continuous evaluation over a period of at least 6 months.
(Finitsis et al. 2019) Breast cancer survivors	Interventions with bi-directional communication showed statistically significant effects, whereas the ones using a one-way flow of communication failed.	Future MAEI studies need to improve and use standardized guidelines to construct a study methodology (Study sample, follow-up period) as well as use common guidelines to report on medication adherence. Consider theory-based approaches to construct MAEIs.
(Cornelissen et al. 2020) Osteoporosis	Multicomponent MAEIs based on patient education and counselling were the most effective interventions.	Future MAEIs should focus on: - Active patient involvement - Multicomponent interactive interventions - Differentiation of MAEI for initiation, implementation and discontinuation
(Conn and Ruppar 2017) Long-term medication prescription in adults	Habit-based and behavioural (vs. cognitive) interventions were more effective. Face-to-face and pharmacist-delivered interventions improved adherence.	More adherence research should report on outcomes of health, quality of life, and health care costs as they seek to fully evaluate the impact of adherence interventions. Methodology: control groups might often be biased as they also receive a sort of intervention.

Appendix 2.1: Overview of the interview questionnaire

Breast Cancer Survivor

How did you experience your breast cancer (BC)?
- When did you get sick?
- What are your experiences regarding the treatments?
- What impact does your disease have on your daily life?

What do you think about the care that was provided to you?
- Who was involved in your care?
- Was the care provided meeting your needs and expectations?
- How was adjuvant endocrine therapy (AET) introduced to you? And how did you feel about the treatment?
- How is your communication with your oncologist?
- Do you have a relationship with a BC nurse or a pharmacist and what do you think about it?

How do you manage your AET?
- Did your oncologist explain the usability of the treatment and did it help you to better understand it?
- How do you feel about the fact to take this treatment for several years?
- Was it challenging to initiate the treatment and why?
- Do you take your treatment regularly?
- Do you have challenges taking your treatment? And how do you manage those?

How do you feel about today's technology?

Do you use applications on your phone to manage or improve your health?
- Why do you use them?
- What do you like about those?
- When do you use them?
- What is important for you to continuously use an application?

In your opinion, what are acceptable tools that would help to manage your AET**?**
- What do you think about the 'Pill- reminder' application?
- Would you use this application to manage your treatment? Why?
- What would need to be improved to use such an application?
- Would you accept to be contacted by text messages or phone calls to support you in your AET management and by whom?

Healthcare professionals (Oncologists, Breast Cancer Nurses, Pharmacists)

How do you perceive your relationship with your patients?
- How do you make sure to support your patients?
- How do you present the AET to your patients?
- How do you communicate with your patients during the survivorship period?

Do you believe that it is challenging for your patients to manage their AET ?
- How do you manage or support those patients with challenges?

What do you think about today's technology and mobile applications?
- Do you yourself use health applications?

In your opinion, what are acceptable tools that would help to manage your AET ?
- Do you believe that applications could influence or even improve AET management?
- What would such an application need to entail in order to be useful?
- Would you accept an eHealth tool to communicate with your patients? And how?
- Do you believe that such a support tool could be integrated into the daily clinical practice? How?

Appendix 2.2: In-depth characteristics of each breast cancer survivor

No	Age (years)	OHT	OHT phase	OHT switch	Occupation status	Acute treatment	Nationality	Family history	Other chronic treatment
1	54	Tamoxifen	Persistence	2	Not working	S,R	Italian	No	Yes
2	65	AI	Implementation	0	Retired	S,R	Luxembourgish	Yes	Yes
3	52	unknown	Initiation	0	Sick leave	S,R	Portuguese	No	No
4	53	Tamoxifen	Persistence	1	unknown	S,R	Luxembourgish	No	No
5	57	AI	Persistence	1	Early retired	S,C,R	Portuguese	No	Yes
6	51	Tamoxifen	Persistence	0	Not working	S,C,R	Portuguese	No	No
7	50	Tamoxifen	Persistence	1	Not working	S,R	Italian	no	Yes
8	49	Tamoxifen	Implementation	0	Working	S	Luxembourgish	No	Yes

9	68	unknown	Persistence	0	Retired	S,C,R	Exjuguslavian	No	No
10	55	unknown	Implementation	0	Working	S,R	Luxembourgish	Yes	Yes
11	59	AI	Persistence	0	Working	S,C,R	Portuguese	No	Yes
12	42	Tamoxifen	Persistence	0	Working	S,C,R	Luxembourgish	No	no
13	60	Tamoxifen	Persistence	0	Retired	S,R	Luxembourgish	Yes	Yes
14	48	AI	Persistence	0	Working	S,R	French	No	No

AI; Aromatase inhibitor, S; Surgery, C; Chemotherapy, R; Radiotherapy, OHT; oral hormonal therapy, Initiation; the patient takes the first dose of their prescribed OHT, Implementation; the patient implements the treatment doses into daily routine, thus dosing corresponds to the prescribed dosing regimen, Persistence; the patient is persistently taking their OHT (the length of time between initiation and the last dose.

Appendix 2.3: Quotes from BCS and HCP interviews illustrating Topics, Categories, Themes and Subthemes

Breast Cancer Survivors

Topic	Category	Themes	Subtheme	Examples
OHT	BC – More than a medical treatment	Lifestyle change		'(...) I stopped smoking. (Participant 7) 'I took up running, I hated it before my disease. But now it kind of gives me peace of mind. And even when I am angry with what happened to me I run a little faster to get it all out of the system' (Participant 8)
		Support network	Social assistance	'I had social assistance helping me sort out financial matters because I was in a really bad situation' (Participant 6)
			Family & Friends	'I could not have done it without my family, my mum came with me to each chemotherapy and if she couldn't my husband did, this helped me a lot at the time' (Participant 11)
			Other patients' experience/ interaction	'I wish that sometimes I could have talked to someone in the same situation as I, I am glad I had my family and friends, they were very supportive. But sometimes I felt like they do not understand me..' (Participant 3)
		3 stages of emotions	Shock	'At the beginning it was a shock' (Participant 3)
			Fight modus	'After a few days of the announcement, it probably was the hardest time in my life. I told myself that I have to fight, I have a daughter and I will fight for her' (Participant 4)
			Feeling lost/empty	'During my treatment in the hospital I did not realize what I am going through, this happens during the treatment at home, where you are alone and you do not easily find your way back to your daily life, it would have been helpful to have support (...)' (Participant 5)

		Impact on private life	Family interaction	'My children were so scared of the disease, even if they are already older.' (Participant 1) 'No one in my family except for my husband and children knows about my disease. I don't want them to talk.' (Participant 9)
			Sexuality	'My intimate life with my husband was impacted. It feels like one breast is missing. (...) and I suffered from vaginal dryness' (Participant 14)
			Fertility	'I considered stopping treatment because I still wanted children. (...) Now I froze my eggs. But it is very difficult' (Participant 12)
		Professional life		'I had to change my job. I was no longer as resilient and also needed a part-time job' (Participant 8)
		BC perception in society	Lack of understanding	'My husband thinks that because I was operated, that it is gone and I should be fine' (Participant 3)
			Reintegration into society - Healthy vs sick	'The situation after [post acute phase] is really challenging. People are often confused as to whether you are healthy or still sick.'' (Participant 14)
	Medication adherence & management	Initiation	Trust in medical team/physician	'I told my oncologist I do what needs to be done. So he prescribed me the treatment. I started immediately, I completely trust him.' (Participant 2)
			Patient –survivor shift	'In the beginning, when I had my 1st prescription, I really doubted starting. I felt alone. I did not know if this treatment was worth the risk of side effects. I would really have needed some reassurance at that time.' (Participant 4)
			Fear of recurrence	'I told myself that if someday cancer comes back it will be my fault because I did not correctly follow my OHT. It is true, I have thought of not taking the pills, but I am too afraid of it to come back so I continue and I endure the side-effects' (Participant 5)

		Implementation	Creation of support tool	'I bought myself pillboxes, I fill them with my treatment and put them on my nightstand, that way I know that I have to take 1 pill every morning after waking up' (Participant 2)
			Integration into daily routine	'I get up, like every morning, I take my medication it is a habit like drinking a cup of coffee or eating dinner' (Participant 1)
		Discontinuation	Side-effect severity	'I usually get really bad migraines from my OHT, so I decided to take them before sleeping since they do not bother me as much as during the day. It is not ideal but it works now for me.' (Participant 4)
			Daily life & Forgetfulness	'I must admit I forget my medication from time to time, (…). I get up in the morning, (...) I take a shower, get dressed, feed the cats and dogs and then I drive to work. In the car I asked myself, did you take your pill?' (Participant 10)
			Treatment interaction	'I have taken a pill every single morning for my thyroid, already for years now. Well I know I cannot take both treatments [OHT and Thyroid treatment] at once but it would help me not to forget my hormone treatment.' (Patient 13)
		Perception	Medical procedure	'It is easy you know, you are sick you take your medicine' (Participant 6)
			Patient experiences	'I already went through the whole procedure with my mum, so yes it is scary to be affected yourself but also she had a good experience with the hormone therapy so for me I knew I do it it will be the same' (Participant 2)
		Side effect management techniques		'(...) If I have an important thing the following day it happens that I do not take my pill to avoid side effects.' (Participant 4)
HCP implication into medical follow-up	Patient – Physician (PP) communication	Bombardement of information	Overwhelmed patient	'After my consultation, I went home, and I noticed that half of the information I had already forgotten or couldn't really remember. I told myself that next time I need to write everything down' (Participant 2)

			Patient feels helpless	'He [oncologist] used so many terms I did not understand or I did not always follow, so I couldn't help myself but to follow his instructions. In the end, he is the medical doctor so he should know what he talks about.' (Participant 5)
		Means of communication	Medical language	'(...) my oncologist always says in your case in the American literature and he used words and statistics I don't even remember.' (Participant 7)
			Use of fear & miscommunication	'He [oncologist] told me to continue taking my treatment after 5 years so the cancer is not coming back' (Participant 5)
		Empathy		'She [oncologist] is very human (...) she is very close to her patients' (Participant 14) 'My oncologist called it ' your little cancer' I was shocked I had 5 tumours and mastectomy done (...) I don't know maybe he cannot put himself in my shoes as he is a man' (Participant 7)
	PP relationship	Dr is God / Medical professional		'If my doctor tells me to do something, I do it.' (Participant 5)
		Family member		'He [oncologist] is like a brother to me' (Participant 1)
		Patient as Partner		'I asked my oncologist for explicit information regarding the oral hormonal therapy, and why this treatment, I wanted to understand and also clarify the information I found online to be correct that you are healed, which is not the case, so it was good I asked' (Participant 14)
	PP interaction needs & expectations	Personalized interaction	Familiarization with patient treatment history	'Every time I come to the consultation I have to restart explaining my case. This annoys me. He should at least take 5 min before calling me in to familiarize himself with my history.' (Participant 7)
			Interaction at the moment of need	'At home, I sometimes think now it would be nice to ask him [oncologist] this or that but then I have to wait for the next consultation, mh it is ok but yeah sometimes it would be nice to have someone there directly when I have the need' (Participant 10)

		Multidisciplinary	HCP team involvement	'I accept MY group of healthcare providers that I know to be involved in my follow-up but not unknown people. That would not be so nice.' (Participant 11)
			See patient as a whole - Patient file	'To each physician, I go to, tell me something else [...] It is like if you go to a mechanic, he tells you to change the brakes, the other one tells you to change the filters and the next one wants you to do an oil change, so annoying.' (Participant 7)
			Shift of roles	'No no I don't talk to the pharmacist about my disease. No, not at all, I don't tell him about my life. He sells me my treatment' (Participant 6) 'It is difficult to talk to the pharmacist because often the pharmacy is full of people. I don't want everyone to know about my personal belongings. (...) I don't always go to the same pharmacy so it is also difficult to get a relationship with the pharmacist' (Participant 8) 'I remember that I asked the nurse during the radiotherapy to help me with the burning and she had to go ask the doctor. So I think they should be educated for the special needs of us and then I think BCN could actually take up parts of the follow-up but they need to take responsibility otherwise I can ask the physician myself' (Participant 10)
		Comfort and Reassurance		'I would have appreciated support, especially at the beginning. (...) I would have needed someone who reassured me that the treatment will be fine, as it is now, this reassurance would have been great, yes' (Participant 4)
		Accessibility and availability		'I know that I can call my physician all the time, I had really bad side effects and I fainted so my daughter called and he [the oncologist] said I can come immediately.' (Participant 1)
eHealth technology as support tool	Current practices	Internet – Source of Information		'Before my hormone therapy I did go on the Internet and read in a few forums, well I should not have done that' (Participant 4)

		Phone alarm as a reminder		'Every morning at 9 my phone rings, then I know that I have to take my pill. So I set this reminder on my phone myself' (Participant 1)
	Survivorship companion	Patient – survivor shift support	Comfort & Reassurance	'At the beginning of my treatment, I would have needed to be reassured more often because I was on my own. I was used to having all the clinicians around me so I felt alone and uncertain, maybe an application could potentially help to reassure us.' (Participant 6)
			OHT initiation support	'Now the app probably would not be so helpful anymore. Now I take my medication regularly. I have the habit. In the beginning, however, I did forget the pill from time to time or I couldn't remember if I took it, but now I have my pillboxes and it works fine. I would not like to change my habit now.' (Participant 5)
		Side effect management support		'Besides getting reminded to take my medication, I miss support with my side effects. Sometimes my joints ache really bad and I would just want someone to tell me what to do, to help me to get rid of this pain.' (Participant 10)
		Real-time PP interaction		'Having a discussion over a chat box, phone call (...) means I won't need to wait until my next consultation.' (Participant 14) 'I know my oncologist has a lot of work sometimes I hesitate to contact him, in that case, direct communication would help' (Participant 2)
		Informational		'It is difficult to know exactly what to eat and which physical activity is good. yes yes this I would definitely like to see in an app' (Participant 5) '(...) mh I only came across some support organizations like Europa Donna or Think Pink because I googled, I think have a place with all these relevant links would be good' (Participant 10)
		Motivational		'Five years is a looooong time, and I need to motivate myself to keep positive and not think the worst to come like cancer to come back.' (Participant 3)

		Interactivity & Automatization		'I believe it would really be beneficial to conceive a reminder system that works when I did not take my pill, I take my pill during lunchtime and imagine I did not take it, It would be great to have a reminder during the evening 'please take your pill'' (Participant 8)
	Barriers of usability	Inconvenience & inaccessibility		'It should not be too time-consuming, I work and I really do not have time to spend half my day filling out information on an application (Patient 8) 'I wouldn't use the application if it is not free.' (Participant 9) 'I stop using an app when it buffers, blocks, is slow, well I tell you this really annoys me. I also don't want to run through 37 steps to finally find the function I am looking for.' (Participant 10)
		Security and confidentiality		'If the security is not given I wouldn't like to use the application. It is really important. I do not want my bank, my insurance or my boss to get hold of my personal information. It is my liberty, (...)' (Participant 14)
		Replacement of standard of care		'An app is nice but I want to keep the contact and consultations with my physician, I think this is important' (Participant 8)
	Facilitators of usability	Personalized setting		'I would like to personalize (...) my application. I take the Nolvadex so I wish to only see information on the Nolvadex and my type of breast cancer. (...) I would imagine setting my reminders, having a different time during the week than the weekend.' (Participant 13)
		Approval of physician		'I would use this application only with the approval of my physician' (Participant 1)
		User-friendly	Easy – to use/simple navigation	'Using an application, I need to know directly what to expect when opening it. I do not want to go through one window to get to another window to finally find the window I looked for - so less is more.' (Participant 12)
			Lay language	'All these medical terms are so difficult to remember, or even to understand. Having a place with a 'normal' language would have helped me a lot' (Participant 7)

		Appearance	Colour code	'(...) using red or green could facilitate to know when I took my pill or not' (Participant 11)
			(Adjustable) Font-size	'(...)I am not capable to read small letters, this is especially hard nowadays with phones, I always have to zoom in' (Participant 13) 'I need the text and images to be large enough (...).' (Participant 12)
		Added value to daily life		'The application should fit into my daily routine.' (Participant 11) 'All the apps I use so far need to be helpful, have purpose and facilitate my everyday life. I use an app called Doctena, you have a list of physicians available. You select a speciality and BAM all the relevant physicians.' (Participant 14) 'If this app helps me to feel good, yes I'll use it' (Participant 3)

Healthcare Providers

Topic	Category	Themes	Subtheme	Examples
Post-acute treatment follow-up needs	Lack of post-acute treatment structure	Need for multidisciplinary teamwork		'I meet regularly with the other BCN, to exchange our experiences and help each other with certain patient matters.' (Nurse 2) 'Collaborating with other physicians would be great and is partially done but as we don't have a systematic structure of the BCS follow-up patients can see other physicians without me knowing. Another advantage would be to work closer with BCN, however, to date, we only have 1 per hospital and thus the workload would not be possible.' (Oncologist 1)

		A shift of responsibilities	Willingness	‘Breast cancer nurses could take over parts of the OHT follow-up in BCS. On the one hand, we got formed in psychology and social work, are aware of clinical matters regarding OHT and are in close contact with oncologists. On the other hand, we already get to know the patients during the acute phase of the treatment.‘ (Nurse 3) ‘I really think that the role of the pharmacist needs to shift, we need to be recognised as those responsible, in collaboration with the physician, for the follow-up of treatment. We are not only product sellers.’ (Pharmacist 1) ‘Of course, I would like to give BCN more responsibilities, (...).’ (Oncologist 1)
			Workload	‘We would most definitely be able to take over a good part of BCS follow-up, however, we are only one breast cancer nurse per hospital, so if we would need to follow up every single patient plus our daily work it would simply not be possible. In that case, we need to form more breast cancer nurses' (Nurse 2)
			Who does what?	‘(...)I believe that BCN are not taking up enough responsibilities, they ask us for our consent for every decision they have to take, probably because it is unclear in the distribution of what is my position and theirs. But then you also have oncologists that do not want to give up any responsibilities so I guess it is hard for them [BCN] to know all the time how to act…’ (Oncologist 1) ‘I rarely give up responsibilities to BCN because they are more actively intervening with patients during the acute phase. In my practice, I work closely with a gynecologist and we share information.’ (Oncologist 3) ‘I think we could follow other countries by introducing this model of integrating the pharmacist into the care model so that the pharmacist carries out the medication-related problems (....).’ (Pharmacist 1)
	OHT complexity	Challenges	Neglection of non-adherence issue	‘I don’t think my patients are non-adherent, I know them well and I have a good relationship with almost all of them.’ (Oncologist 4)
			More than medical treatment challenges	‘The oral hormonal therapy is more than just a treatment for those survivors, definitely more [...], it is linked to personal, financial and social challenges and these breast cancer survivors often just need someone that listens to them [...].’ (Nurse 1)

			Lack of OHT follow-up	'It is true that we do not follow-up, meaning we do not check their history, each time we see a patient. Even if we could do it and there are lack of refills it could be that they went to another pharmacy then we have no update on that.' (Pharmacist 3)
		OHT sensitisation	Lay language	'I try to use a schematic illustration to explain the mechanism of the oral hormonal therapy, I think using this schematic illustration helps the patient to understand better how the treatment works and also why it is important.' (Oncologist 3)
			Timing	'(…) I noticed that the timing of introducing the OHT is crucial. (…) some patients are not able to listen and capture all the OHT information. Therefore I started to introduce the OHT during the acute phase.' (Oncologist 2)
			Repetition	'In the pharmacy, we noticed that some participants did not know or maybe remember the use and importance of the OHT. We probably need to repeat this over and over again.' (Pharmacist 2) 'Often we share the task of informing the patient. So the oncologist tells the patient about the oral hormonal therapy during the consultation. Then we [breast cancer nurses] repeat it one more time when we see them.' (Nurse 1)
		OHT adherence monitoring		'Indeed monitoring adherence in real-time would definitely benefit my consultations because I could target patients that are non-adherent, this would improve the quality of the consultations and saves time. Patients often hesitate to tell the truth about whether they took their pill. (Oncologist 2)

Patient-provider communication	Personalized communication			'I go into further depth of explaining the disease and treatment when I know the patient is less educated or I get the feeling they do not understand.' (Oncologist 2) 'I notice that my patients differ in how they take up the information about their disease and treatment, so I have to adapt from my side how I communicate the information to that patient in order for her to understand it.' (Oncologist 1) 'I adapt my consultations with the breast cancer survivor regarding their needs and questions they bring along. After I try to do an understanding evaluation of the patient to see how much he understood and what he understood, and if needed I re-explain certain concepts.(Nurse 3)
	Lack of training			'The things we learned at school are so different to what actually happens in reality. I mean the whole therapeutic education is also quite new and is related to a lot of psychology so I had to educate and adapt myself slowly. Meaning you learn by experience but having regular workshops would definitely help.' (Pharmacist 1)
	Availability			'My patients call me and write emails while on vacation, there is a limit and I believe that such an eHealth tool could support me for example in this regard as the breast cancer nurse or my colleague could then handle patients needs' (Oncologist 4)
eHealth technology as support tool	Real-time remote monitoring	Personalized interface		'II rely on what my patients tell me, some are so nervous and scared that they forget their questions, so it is hard to intervene or support. (...) With a monitoring system of patients' health-related data as in this context, treatment adherence could ameliorate our consultations.' (Oncologist 1)
		Alert system		'I think that this monitoring system needs to work with an integrated alert system because I won't be able to individually follow up who took their treatment and who reported side effects (Nurse 3)
	Barriers of usability	Workload		'I fear that the main barrier for a real-time eHealth monitoring system is the workload. I think I do speak for my colleagues as well, we are already overloaded with work and we have inpatients to care about. The question really is how are we going to manage this system?' (Oncologist 1)

		Security & confidentiality		'Before implementing such a system I think we have to evaluate the data protection, who has access and how do we secure the access?' (Oncologist 4)
		Big brother is watching you/ blame the patient		'eHealth applications are awesome if they are a support and help the patient with taking their meds. However, I would not support these tools if their goal or intention is to control or even blame the patient when not taking the drugs, [...].' (Oncologist 3)
	Facilitators of usability	Real-time monitoring		'I think this application would make the most sense if we would be able to be connected remotely ' (Oncologist 2)
		User-friendly		'The system needs to be easy to use, with one click I should have my information.' (Nurse 1)
		Integration into the healthcare system		'Before implementing such an eHealth tool we would need to be trained. (...) the incentivisation of our service would need to be re-evaluated as the follow-up will be more time-consuming' (Pharmacist 1) 'I personally believe that the system must be integrated into our hospital in order to use it on a daily basis.' (Oncologist 3)

Appendix 3.1: Participant information sheet of the E-dherence survey

Madam,

The Edherence survey was developed by Prof. Huiart and Prof. Mancini. The study is conducted at Seintinelles under the responsibility of the Luxembourg Institute of Health.

This note is a written document to help you decide whether or not to participate in this study.

You are free to decide whether or not to participate in this complimentary study, regardless of your medical follow-up.

You can take time to think about your participation in this research, and discuss it with your doctor and your family.

Pr Laetitia HUIART, principal investigator (E-mail : laetitia.huiart@lih.lu) and Pr Julien MANCINI (julien.mancini@univ-amu.fr) are at your disposal to answer all your questions and to explain what you do not understand.

1. INFORMATION

The purpose of this document is to provide you with the written information necessary for your decision. We thank you for reading it carefully.

Purpose of the research: We would like to get your input on what could be done to support women who are on oral hormonal therapy (often-called hormone therapy) after breast cancer. We are particularly interested in your opinion on e-health applications.

Therefore, we invite you to take part in this survey:

→ Women,

→who have (had) breast cancer for the first time in the last ten years,

→for which they received (at least temporarily) an oral hormone therapy (Tamoxifen®, Tamofen®, Nolvadex®, Femara®, Letrozole, Arimidex®, Anastrozole, Aromasine®, Exemestane, Fareston®, Kessar®...)

For those who have had a recurrence or second cancer, please answer the questions based on your experience with your first breast cancer diagnosis.

2. CONDUCT OF THE RESEARCH

This is an online questionnaire survey. The questionnaire consists of about 30 questions and will require your attention for at least 20 minutes.

The questions will focus on characteristic elements of your personal situation, in order to know you better, as well as on your experience of the disease, of hormone therapy and finally, on your opinion concerning the use of new technologies to accompany patients in their medical follow-up.

If you were to interrupt the questionnaire, you can save your answers and continue later.

3. CONFIDENTIALITY AND DATA PROCESSING

The results of all participation to this questionnaire will be grouped together to be analyzed and all your answers will remain strictly anonymous. We, therefore, guarantee the confidentiality of the answers you provide.

These data will be kept for 5 years to allow their full exploitation.

The study will be conducted in accordance with the European and French laws in force concerning research involving the human person and the protection of personal data, in particular, Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 and the Data Protection Act No. 78-17 of 6 January 1978 as amended by Act No. 2018-1125 of 12 December 2018 on the protection of individuals with regard to the processing of data (RGPD)

At no time will your collected data be transmitted outside the European Union.

For more information, contact the data protection officers at the Seintinelles coordination center or the Luxembourg Institute of Health.

In accordance with articles L. 1121-1 and following the Public Health Code, this project has been studied by the Comité de Protection des Personnes Sud-Est III, which issued a favourable opinion.

The results of this research may be presented at conferences or in scientific publications. However, your personal data will not be identifiable in any way because no identifying data will be kept.

In application of the provisions of article L 1111-7 of the Public Health Code, you may, if you wish, be kept informed of the overall results of this research, by contacting directly Pr Laetitia Huiart (e-mail: laetitia.huiart@lih.lu) or Pr Julien Mancini (julien.mancini@univ-amu.fr). The people in charge of the research will then be able to explain to you the main results of the survey as well as the impact of the study.

If you are not satisfied despite the commitment to respect your rights and protect your data, you can lodge a complaint with the supervisory authority: the Commission Nationale de l'Informatique et des Libertés (https://www.cnil.fr/fr/cnil-direct/question/adresser-une-reclamation-plainte-la-cnil-quelles-conditions-et-comment).

4. ACCESS TO PERSONAL DATA

The French National Commission for Information Technology and Civil Liberties (CNIL) provides for the right to "data portability", which means that you have the right to access (for your personal use) your data collected and computerized in the framework of the survey. You also have the right to make or request a transfer of your personal data from one organization to another.

5. CONSENT

Your participation is voluntary: you are free to accept or refuse to participate in this research.

If you decide to participate, you may withdraw your consent to the research at any time without liability or prejudice. We will simply ask you to inform the person in charge of the research. You will not have to justify your decision.
For any questions concerning these rights, you can contact the researchers involved in this research.

Thank you in advance for your participation.
The research team of the study

The original document is in French, here is the English version translated with www.DeepL.com/Translator (free version)

Appendix 3.2: e-survey inclusion criteria & e-consent

Inclusion criteria

● Women,

● who have (had) breast cancer for the first time in the last ten years,

● for which they received (at least temporarily) an oral hormone therapy (Tamoxifen®, Tamofen®, Nolvadex®, Femara®, Letrozole, Arimidex®, Anastrozole, Aromasine®, Exemestane, Fareston®, Kessar®...)

E-consent

Before you begin, please confirm that you meet the following inclusion criteria:

You are a woman: ☐ Yes /☐ No

You have been treated for breast cancer in the past 10 years: ☐Yes / ☐No

You have been treated at least temporarily with oral hormone therapy: ☐Yes /☐ No

If at least 1 No:

To ensure consistency in the responses collected, this survey is addressed exclusively to women who have had breast cancer in the past 10 years and have been treated with hormone therapy. We are therefore unable to continue the survey, thank you for your attention and understanding.

If yes: Please confirm your consent to participate in the E-dherence survey:

☐Yes

☐No

The original version is in French, here is the English version translated with www.DeepL.com/Translator (free version)

Appendix 3.3: Structure and definition used in the e-survey

E-survey structure of sections	Variables asked within sections
I. Sociodemographic characteristics	• Age • Marital status • Children • Educational level • Professional status • Financial situation
II. Health status and disease experience	• General health status • Medication intake for other chronic diseases • Quality of Life • Year of diagnosis • Disease impact on life • Power to control disease • Disease knowledge • Disease recurrence

III. Medication adherence	• OHT adherence
	• Motivation for OHT adherence/non-adherence
	• Side effect management
	• OHT management
	• The implication of physicians in OHT adherence
	• Satisfaction of information given by physician regarding
	  ○ The nature of the treatment
	  ○ Potential health benefits
	  ○ Side-effects

IV. eHealth utilisation	• Possession of wearables/ health applications • Utilisation frequency • Reasons for use • Important solutions for OHT management
Medication adherence enhancing eHealth technology	• Barrier to usability and acceptability • Fascilitatiors of usability and acceptability

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Appendix 4.1: Case-Scenario

Case scenario of a breast cancer survivor taking adjuvant endocrine therapy and being proposed an eHealth intervention to support her adjuvant endocrine therapy intake.

The case scenario is a fictitious experience of Louise, who is offered to test an electronic pillbox* and a mobile application (see Figure 1) to support her with oral adjuvant endocrine therapy management.

**Note: The blister is a compartment where the medication blister can be stored in order to facilitate the taking of medication. The electronic pillbox record the doses taken (and not taken) of the medication.*

Setting the scene

Louise was diagnosed with breast cancer at the age of 43. After a lumpectomy, chemotherapy and radiotherapy, she is currently undergoing oral adjuvant endocrine therapy, Tamoxifen. She has to take one tablet a day. During an appointment with her doctor, Louise tells him about her difficulties in taking her hormone therapy every day. He suggested that she uses the E-dherence system, an electronic pillbox connected directly to an application downloaded to her smartphone, to monitor her AET intake behaviour.

e-Questionnaire

The questionnaire involves the participants by asking their opinion on the acceptance and preferences towards the proposed electronic pillbox connected to a mobile application on a smartphone (eHealth intervention). Throughout the questionnaire, the participants are introduced to new aspects of Louise's journey and experience with AET and the proposed eHealth intervention to collect input on what participants find acceptable to use in their daily journey of BC survivorship taking AET.

Q 1 If you were Louise, would you be willing to use a pillbox connected to an app to help you monitor your adjuvant endocrine therapy?

1. Yes, I would accept to use it
2. Yes, if my doctor asks me to use it
3. Yes, maybe depending on the explanation I get
4. No, I don't trust connected health devices
5. No, because I don't know how to use new technologies
6. No, because I do not have and do not want a smartphone
7. No, for other reasons.

Louise downloads the application on her smartphone and uses the electronic pillbox on a daily basis. The information stored in the electronic pillbox regarding her AET intake is transmitted daily to the connected application on her smartphone. In the application, she can now follow her medication intake history. With Louise's consent, the information can also be transmitted to a referral hospital to ensure personalized support.

Q 2 How often do you think the medication data recorded on the app should be transmitted to the referral hospital?

1. Daily
2. Several times a week
3. Once a week
4. 1 or 2 times a month
5. Less often
6. ever, you would not allow the hospital to have access to your medication data

On the application, Louise can also report, in real-time about her health status and inconveniences associated with the treatment (undesirable side effects, constraints in the renewal, etc.), have targeted information on the disease and on the medication, and get in touch directly with the nursing staff.

Q 3 In your opinion, the information on Louise's health status should be given in the form of:

Multiple answers possible

1. A short questionnaire (about 5 questions) filled out regularly by Louise
2. Emoji/smiley pictures selected regularly by Louise and representing her health status
3. A free field where Louise can describe her health status at any time
4. Other: specify...

Q 4 How often should Louise fill out this form?

1. Several times a day
2. Once a day
3. Not every day but at least once a week
4. Not every week but at least once a fortnight
5. Not every 15 days but at least once a month
6. Less often

Louise accepted the transfer of her health information to the hospital. There, they can follow in real-time her AET take and her reported health status and side effects. If necessary, they contact Louise to assist her in her AET management.

Q 5 If it were you, who would you prefer to be contacted by?

Several answers are possible

1. My general practitioner
2. A professional already involved in my medical care (doctor or nurse at the hospital)
3. Any health professional (doctor, nurse, pharmacist, etc.) even if I do not know them personally
4. Someone close to me, to whom I give access to my AET data
5. No matter what the status of the person who contacts me
6. Nobody, I do not wish to be contacted

Q 6 In your opinion, this initial contact should be made in the form of:

1. A reminder phone call
2. A reminder message or notification on the phone
3. An e-mail
4. A request for an appointment
5. A questionnaire to fill out on the application
6. Other: please specify...
7. Don't know

Q 7 In your opinion, the best time to make first contact is from...

1. One day without taking the medication
2. Two days without taking the medication
3. Three days in the same week without taking the medication
4. One full week without taking the medication
5. 10 or more days in a month without taking the medication, even if not consecutive
6. Other: specify...
7. Don't know

Louise suffers from side effects that impact her daily life. After reporting them on the application, she is invited to make an appointment with her doctor, who suggests her to change treatment. However, in the weeks that followed the side effects did not diminish an Louise starts taking her treatment irregularly. The hospital that has access to her data thus wishes to continue supporting Louise with her daily AET management.

Q 8 What kind of follow-up support would you prefer?

Several possible answers

1. A reminder by phone call
2. A reminder by message, notification or e-mail
3. Access to a forum - sharing space - to interact with other patients on AET
4. Videos and articles explaining the disease, AET and side effects
5. Other: please specify...

Thereafter, the side effects diminished significantly. For two years following the diagnosis, Louise then takes her medication daily.

Q 9 In your opinion, should Louise stop using the connected pillbox?

1. Yes, she no longer needs it
2. Yes, it could now actually decrease her motivation
3. No, it is still an important support
4. No, it could be useful again

Louise decides to continue using the connected electronic pillbox. However, Louise goes on vacation for a week in another region, and forgets her connected electronic pillbox, which records thereafter a week without taking medication.

Q 10 In your opinion, Louise should...

1. Call the hospital to inform them of her forgetfulness and ask for advice
2. Momentarily check the option "do not send my information to the center" on the application
3. Permanently check the option "do not send my information to the center" on the application
4. Nothing, she will be able to explain the situation to the center if it contacts her

Later, her doctor proposes her a new innovation of the connected application, that is supposed to be more fun. The application is still connected to the electronic pillbox, and makes use of Avatares. The avatar needs to be feed every day (by taking her hormone therapy) and take (virtually) to the doctor in case of pain by providing her vitals and by indicating directly on the avatar the painful areas. Moreover, the adoption of good health behaviors (taking hormone therapy every day, practicing physical activity, etc.) would allow the character to evolve.

Q 11 Would you be more favorable to the use of this new avatar application?

1. Yes, more favorable than the previous application (described above)
2. Neither more nor less favorable
3. No, less favorable than E-dherence

If '1. Yes, …'

Q 11a For what reason(s)?

Multiple answers possible

1. Because taking care of an avatar gives me a more active role in my treatment
2. Because the "game" aspect of the application makes it easier for me to use the applicaiton
3. Because the evolution of the character gives a concrete aspect to the effect of the antihormonal treatment
4. Other : specify ...

The following questions are specific on barriers and facilitators of an AET-enhancing eHealth intervention.

Q 12 From the following objectives, select the ones that you feel are important in using a connected device and app as part of your medication taking:

1. To self-monitor
2. To have information about your disease and treatment
3. Report in real time any inconvenience (e.g side effects) related to your treatment
4. Remote monitoring by health professionals
5. To communicate more easily with the medical profession (through dematerialized contact)
6. Being reminded to go to the pharmacy to get the refill of the medication
7. Reduce the number of visits to the doctor when it is not necessary

8. To have a personalized support in the post-acute follow-up
9. Help to respect the medical prescription of the hormone therapy medication
10. Exchange with other patients who have the same treatment
11. None

Q 13 For each of the following statements, please indicate whether it is a facilitating factor for using the electronic pillbox connected to a phone application (eHealth intervention)?

Please answer by checking the box that best corresponds to you on the scale from 1 to 5, 1 representing "not at all important", 5 "very important" and the intermediate numbers allowing you to qualify your answer.

	1 ‘not important at all’	2	3	4	5 ‘very important’
The eHealth intervention was recommended by your doctor					
The eHealth intervention serves as a reminder to take your AET every day.					
The eHelath intervention provides the possibility to report on side effects					
The playfulness of the eHelath intervention (e.g avatar)					
The simplicity of the eHealth intervention use: selection of smiley faces to describe the health status for example					

The eHealth intervention gives its end-user a challenge through incentivisation (e.g. gaining point for taking treatment)					
The comfort of knowing to have a personalized and continuous follow-up					
The remote contact with healthcare providers					
The fact to deny (at any time) data sharing of medical information to the referring hospital					
The physical appearance of the eHealth intervention: small and silent					
The speed of reaction from healthcare providers in case of need					

Q 14 For each of the following propositions, please specify if it is a barrier for using the electronic pillbox connected to a phone application (eHealth intervention)?

Please answer by checking the box that best corresponds to you on the scale from 1 to 5, 1 representing "not at all important", 5 "very important" and the intermediate numbers allowing you to qualify your answer.

	1 'not important at all'	2	3	4	5 'very important'
To not possess a smartphone					

The fear of not knowing how to use the eHealth intervention					
The fear of not knowing how to interpret the medication intake data					
Having to pay for the eHealth intervention					
Your doctors reservations about the eHealth intervention					
Fear of my medical data misuse					
The lack of information on eHealth intervention functionality					
The fear of lack of data confidentiality					
The fear of a malfunctioning of the eHEalth intervention (e.g. bug)					
The fear of feeling observed by the medical team					
An additional application on my phone					

Q 15 How much would you be willing to pay to use the above mentioned electronic pillbox connected to the phone?

1. 0€, I would only use it if it were free (or 100% reimbursed)
2. Less than 5€ per month
3. Between 5€ and 9€ per month
4. 10€ to 19€ per month
5. 20€ to 30€ per month
7. More than 30€ per month
8. Not interested

Appendix 6.1: Data collection in RedCap (other study assessment)

1. Medical Record

MEDICAL RECORD – Breast cancer disease and treatment history/ Information concomitant medication	
Subject ID	Date of data retrieval:_ _/_ _/_ _
Date of diagnosis: _ _/ _ _/ _ _	
Tumor location: _ _ _ _ _ _ _ _ _ _	
Code: _ _ _ _ _ _ _ _ _ _ _ _	
Prescribed Oral hormonal therapy: Nolvadex, Arimidex	
Surgery: YES, NO	If yes: Date of surgery:_ _/_ _/_ _
Chemotherapy: YES, NO	If yes: Name of the drug: _ _ _ _ _ _ _ _ _ _ _ _ Start date:_ _/_ _/_ _ End date: _ _/_ _/_ _ Nr of cycles: _ _ _ _ _ _ Dose for 1 cycle: _ _ _ _ _ _

<table>
<tr><td>Radiotherapy: YES, NO</td><td>If yes:
Start date:_ _/_ _/_ _
End date:_ _/_ _/_ _
Dose: _ _ _ _ _</td></tr>
<tr><td>Concomitant medication: YES, NO</td><td><table><tr><td>Medication name</td><td>Frequency</td><td>Reason for use</td><td>Dose</td></tr><tr><td></td><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td><td></td></tr></table></td></tr>
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2. Sociodemographic characteristics

Q1 How old are you?

Q2 What is your nationality?

- □ Luxembourg
- □ Portuguese
- □ French
- □ German

□ Other:

Q3 What is your marital status?

□ Single

□ Married or living in a registered partnership (PACS)

□ Widowed

□ Divorced

Q4 Do you have any children?

□ Yes

□ No

Q5 What is your highest level of education (ORISCAV).

□ Early childhood development, pre-primary education, early childhood education.

□ Elementary education

□ Lower secondary education (e.g., 5th general secondary, 9th technical, 9th modular preparatory, 9th of the 2nd qualification track)

□ Upper secondary education (e.g., high school diploma, technical high school diploma, technician diploma, apprenticeship completion diploma (CCP, DAP, CITP, CCM, CATP))

□ Non-tertiary postsecondary education (e.g., Master's degree)

□ Higher education; short course of higher education with a practical, technical, or vocational orientation after completion of secondary education (e.g., BTS)

□ Higher education; bachelor's degree level or equivalent (e.g., Bachelor's degree)

□ Higher education; Master's level or equivalent (e.g., Master's degree, former Bachelor's degree, or university degree of at least 4 years)

□ Higher education; PhD level or equivalent

Q6 What is your professional status?

□ Employed

□ Independent

□ Looking for a job

□ In training (student, intern)

□ Not working due to disability

□ Retired

□ Other inactivity (at home, on sick leave without compensation, on availability, on sabbatical ...)

If Q6 = 1 or 2:

Q6a Are you currently working? (*If you are on leave, rest or short-term sick leave (less than or equal to 30 days), please position yourself on one of the first two following propositions)*

□ Yes, full-time,

□ Yes, part-time,

□ No, you are on long-term sick leave (more than 30 days)

3. TECHNICAL SUPPORT

TECHNICAL SUPPORT – Technical support given by CRN, BNC or AARDEX, to help with MEMS tools or MEMS application or redcap login and questionnaire conduction

Subject ID:

Date of technical support given	Who? (indicate initials)	Reason (MEMS cap, MEMS helping hand, MEMS adherence app, REDCap)	Indication (login, adherence transfer,….)