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ePROMs in Clinical Oncology: What is the Evidence?

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Abstract

There is no denying fact that digital therapeutics (DTx) such as electronic patient monitoring outcome measures (ePROMs) will play a decisive role in the future of clinics especially as efficient tools for addressing some unmet needs in the management of chronic conditions such as cancers. While many conventional pharmacotherapies have undergone multistage stringent verification and safety measurements well over a substantial period of time, barriers to the application and adoption of DTx such in clinics have been dramatically low (Kim, H. S. 2020). One of the major barriers to adoptions of DTx into clinical practice remains unavailability of adequate data quality and robustness of clinical evidence.

The aim of the current thesis was to examine the robustness of scientific evidence for effectiveness and utility of ePROMs in oncological settings. As per the hierarchy of evidence for the evaluation of health care outcomes randomized control trials (RCTs) are considered as the gold standard since they not only deliver the highest level of evidence but are also limited in all kinds of study bias and control confounding variables Therefore to realized our aims we took an approach that focused on studying methodology and design integrity of RCTs using several critical appraisal tools such as our modified Critical Appraisal Skill Programme (mCASP) checklist (primary analysis tool) comprising of 23 items that also incorporated items from additional RCT appraisal tools such Joanna Briggs Institute Critical Appraisal tools for RCT, BMJ pest practice and John Hopkins RCT appraisal checklist. To check the authenticity of mCASP checklist we also employed a battery of some other other well-known critical appraisal tools such as modified Jadad scale (mJadad scale), van Tulden scale and Cochrane Tool Effective Practice and Organisation of Care (EPOC) Risk of Bias Tool that served as a secondary analysis tools.

Using specific keywords, we screened about 4751 RCTs on MEDLINE and with our inclusion and exclusion criteria we were finally able to narrow down on 7 ePROM RCTs from the last 10 years.

Abstract

Examination of selected RCTs using our primary appraisal tool mCASP checklist showed that >50% of the studies lacked critical components of a RCT such as allocation concealment, blinding, true intention to treat (ITT) analysis, similarity at baseline. Precisely about 70-85% of studies(n=6-7) scored negatively on the items related to blinding with only a single study recording a score above zero. Similarly scores of true ITT Analysis were negative to zero for about 85% of studies (n=6) and only single study was able to score maximum points for ITT analysis. Internal validity total scores as per mCASP checklist showed that more than 50% of studies had total score values below average score value of 9. Based on grading criteria for mCASP checklist roughly about 60% (N=4) of studies were graded as Low quality, about 25% (n=2) as medium quality and only a single study could meet the criteria for a high-quality study.

Although tools for secondary analysis like mJadad Scale and van Tulder scale were not as elaborative as the mCASP checklist, in scrutinizing the internal validity of the RCTs we did find a good correlation between different the appraisal tools. Comparative analysis of the four critical appraisal tools categorized n=3 studies as medium-high quality (with mCASP, mJadad scale and van Tulder scale), n=2 studies were categorized as low quality (mCASP and mJadad scale). Comparative analysis further revealed a trend for a low risk of bias with higher quality score for a study

We conclude that majority of the RCTs that were examined had a number of serious methodological flaws that could compromise the quality of ePROMs RCTs and as such raise a question mark of the internal and external validity of these studies. Apparently, the foundation of empirical evidence advocating clinical utility of ePROMs for the management of cancer patients could be somewhat shaky. Due to lack of high-quality evidence, and because of limited generalizability for a major portion of RCTs we recommend a more in-depth scrutiny for the clinical evidence generated by ePROM RCTs in oncological settings and excising caution while prescribing these DTx to patients.

Keywords	"Electronic patient reported outcome measures", “ePROM" "Patient Reported Outcome Measures", "symptom monitor", "web-mediated follow up"

Contents

1 BACKGROUND

The treatment scenario for several diseases including some of the most formidable ones such as cancers have changed rapidly during the last decade. While targeted therapies, immune checkpoint inhibitors have already revolutionized how we treat cancer patients, the emergence of digital therapeutics has ushered in a new horizon that promises to improve our current standards of cancer treatments and patient management-engagement. One such approach electronic patient reported outcome measures (ePROMs) has been implemented to delivering cancer care in form of longitudinal monitoring of therapeutic adverse effects, functional status, understanding symptomatic complications and psychological states, and even generation of real time alters and prediction of disease prognosis throughout the cancer therapy. Furthermore, more and more ePROs are being increasingly incorporated into clinical trials, where it is anticipated that they could provide a better comprehensive outlook of the therapeutic adverse events than conventional methods.

In current times when healthcare institutions face budget and resource constrains as well as global challenges like coronavirus disease 2019 (COVID-19) pandemic, digital health tools like ePROMs seem to offer invaluable tool for optimizing cancer care delivery by improving patient-healthcare team communication and engagement, increasing muti-professional interactions and patient empowerment for e.g. by shared decision making.

Despite these promises the effects of ePROMs on vital primary clinical outcomes in cancer care such as survival, quality of Life (QOL)and improvement of symptom distress remains somewhat ambiguous which should be perceived as a substantial barrier towards integration of these digital tools into routine cancer care practices. As such, as multiple ePRO systems begun to be widely deployed and accepted at several cancer care institutions there is need to ascertain that these platforms should be clinically validated, reliable and meaningful especially for clinical parameters that are of vital importance in oncology and cancer patient care.

In the race for optimizing cancer care delivery by digitalization tools especially under constrains of healthcare resources optimism should not shadow logic, reasoning and evidence. This warrants examining the evidence robustness for clinical utility of ePROMs

that could exhort clinicians and cancer healthcare team to take a more balanced approach when scrutinizing ePROMs as cancer care and delivery tools.

We first start by summarizing the literature from digital health tool and ePROMs as we dive deeper into the direction of clinal evidence and robustness for ePROMs in clinical oncology in the alter part of the thesis.

1.1 Digital health

In today´s world our every aspect of life is becoming digitalized and so are medicine and patient management.

According to Digital Technology alliance (DTA), the term “digital health” refers to all technologies that may engage with patients for various health-related purposes. Digital health encompasses a wide spectrum of products that are used across the wellness and healthcare industries (Digital Therapeutics Alliance 2018). These array of technologies (Figure 1) that assist patients through different phases of their healthcare include:

1. Mobile Health (e.g., Fitness Trackers, Nutrition Apps)
2. Health Information Technology (e.g., Electronic Medical Records Systems, Electronic Prescribing and Order Entry)
3. Devices, Sensors, and Wearables (e.g., Wearable and Wireless Devices, Biometric Sensors.)
4. Personalized Healthcare (e.g., Patient-Reported Outcomes, Predictive Analytics, Clinical Decision Support)
5. Telehealth (e.g., Telemedicine, Virtual Visits, Remote Patient Monitoring, Remote Care Programs)

Digital therapeutics (discussed below in detail). Table 1 highlights some examples from digital therapeutics on the market or that are currently under development.

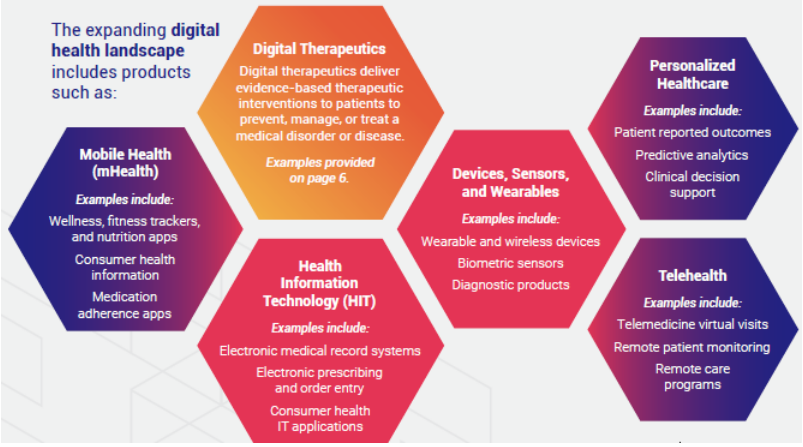

Fig. 1 Highlights the wide spectrum of digital health landscape. **Adapted from DTA website** (Digital Therapeutics Alliance 2018)

1.2 Digital therapeutics

Extrapolated from the digital health the concept of “digital therapeutics” may have sounded a bit futuristic a couple of years ago. With the rising levels of digital literacy and increasing popularity of internet and smartphone use these therapies have begun to being witnessed as omnipresent. With the current emphasis on personalized medicine and patient centricity it is beyond doubt that such digitalization tools will converge with medical science and have a decisive impact on the way healthcare be defined and consumed globally within the next 5 years.

1.3 Definition of Digital therapeutics

The term “digital therapeutics” was first mentioned by Sepah *et al.* in a peer-reviewed publication and defined as “evidence-based behavioral treatments delivered online that can increase accessibility and effectiveness of healthcare.” (Sepah, Jiang et al. 2015).

Furthermore, DTA elaborates “Digital therapeutics (DTx) deliver evidence-based therapeutic interventions to patients that are driven by high quality software programs to prevent, manage, or treat a medical disorder or disease. They are used independently or in concert with medications, devices, or other therapies to optimize patient care and health outcomes” (Digital Therapeutics Alliance 2018).

DTA further elaborates that DTX products involve use of advance technology with best practices relating to design, clinical validation, usability, and data security. DTX products are reviewed cleared/approved by regulatory bodies to supplement product claims of efficacy, risks and intended use. Furthermore, DTx empower patients, healthcare providers and payers with smart tools. DTx products incorporate the best advanced technologies that can address a wide variety of conditions safely and effectively (Digital Therapeutics Alliance 2018). Digital therapeutics can be distinguished from other co-existing digital health categories by the fact that they involve mediation of software based tools to deliver direct therapeutic interventions to patients with a wide range of functions such as prevention, management, or treatment of a certain medical disorder or disease (Chung 2019). Fig. XX highlight examples of DTx currently in the market or under development. DTx can be easily confused with digital medicine or “smart pills” where a prescription medication is combined with an ingestible sensor to monitor or communicate patient adherence compliance to mobile and/or web-based applications. These could be critical in certain conditions where routine adherence may be decisive factor in deciding the patient outcome for e.g., HIV and neuropsychiatric disorders. A good example from digital medicine comes from ABILIFY MYCITE® which is a prescription medicine of an aripiprazole tablet with an Ingestible Event Marker (IEM) sensor inside it for treatment of certain neuropsychiatric disorders such as schizophrenia, bipolar I and major depressive disorder (MDD) (Otsuka America Pharmaceutical 2021) . Furthermore some DTx interventions can also combine software with hardware such as external sensors or virtual reality (VR) goggles.

Table 1: Some examples of digital therapeutics in the market or under development. Table adapted from (Digital Therapeutics Alliance 2018)

AI-based digital diagnostics and personalized therapeutics for pediatric behavioral healthcare
Digital therapeutic used as an adjunct to standard, outpatient treatment for substance use disorder (SUD)
Digital therapeutic engaging individuals with Type 2 diabetes, hypertension, and obesity, and their providers, to improve self-management and outcomes
Combined software and hardware program to improve asthma and COPD control and optimize healthcare utilization

1.4 Categories of Digital therapeutics

The DTx products across the industry that aim to serve patients are as diverse as the diseases itself. The advancement of DTx over the years will further widen the comprehensive network of therapy options that could be available for various ailments. As per DTA, DTx have been classified into 4 categories and each digital therapeutic corresponds to one of four categories based on its intended use and official product claims (Kaiku Health White Paper 2017). Table 2 highlights the primary purpose of a DTx and its intended use for a medical condition as to:

1. Address a medical condition.
2. Manage or prevent a medical disorder or disease.
3. Optimize medication.
4. Treat a medical disease or disorder.

The requirements for each of the 4 categories of DTx product vary according to it primary purpose which may include : supporting the product claim, clinical evidence generation, patient access to product, and relationship to concurrent therapies (Digital Therapeutics Alliance 2018).

Table 2: DTx product categories and their regulatory requirement for each category. Adapted from DTA website (Digital Therapeutics Alliance 2018).

PRIMARY PURPOSE OF THE PRODUCT:	ADDRESS A MEDICAL CONDITION	MANAGE OR PREVENT A MEDICAL DISORDER OR DISEASE	OPTIMIZE MEDICATION	TREAT A MEDICAL DISEASE OR DISORDER
To support product claims of risk, efficacy, and intended use:	Regulatory enforcement discretion (without explicit oversight)	Third-party validation of efficacy and safety claims by regulatory or equivalent national body	Third-party validation of efficacy and safety claims by regulatory or equivalent national body	Third-party validation of efficacy and safety claims by regulatory or equivalent national body
Product claims related to a medical disorder or disease:	No efficacy claims regarding a medical disorder or disease	Low to medium risk claims *(e.g., reduce rate of disease progression)*	Medium to high risk claims *(e.g., improve efficacy of adjunctive therapies)*	Medium to high risk claims *(e.g., direct efficacy claims on clinical outcomes)*
Clinical evidence generation:	Clinical trials and ongoing evidence generation required	Clinical trials and ongoing evidence generation required	Clinical trials and ongoing evidence generation required	Clinical trials and ongoing evidence generation required
Patient access to product:	Direct-to-Consumer (Prescription not required)	Over-the-Counter OR Prescription required	Over-the-Counter OR Prescription required	Prescription required
Relationship to concurrent therapies:	Works independently OR Indirectly supports another therapy	Monotherapy OR Directly supports a concurrent treatment	Directly supports a concurrent treatment	Monotherapy OR Directly supports a concurrent treatment

1.5 Benefits of DTx

DTx promise highly meaningful benefits across a wide spectrum of stakeholders. As per DTA the beneficial outcomes of DTx can be broadly targeted across three main categories of stakeholders: patient & caregivers, healthcare providers and health care systems and public and private payers (Digital Therapeutics Alliance 2018):

1.5.1 Patient & caregivers

The pros related with the use of DTx for this category of stakeholders include:

1. Can be personalized based on individual patients' needs and abilities.
2. Adress a problem independent of patient´s schedule and environment (i.e., can be administered from anywhere and anytime without any privacy concerns)
3. Secure updates on real time status of disease/treatment progression can be obtained.
4. Since DTx take into consideration patients security and privacy concerns they could reduce certain stigmas associated with the treatment and management of certain conditions such as mental disorder, AIDS, venereal diseases, leprosy, and certain skin diseases.
5. Eventually empower patients with self-management therapeutic options.

1.5.2 Healthcare providers and health care systems

The pros related of DTx for this category of stakeholders include:

1. Patient with unmet medical needs or patients with difficult diseases have an increased access to novel treatments.
2. Facilitate intelligent data-driven patient management (irrespective of time and space) and more effective clinical decision making.
3. Patient data is delivered securely into healthcare providers portals and clinical data warehouses which eventually can not only be utilized for patient's personalized therapy and management but also to predicts course of disease, relapse and generate alerts for the healthcare teams using AI.
4. Improve patient adherence.
5. Improve patient engagement with healthcare team.
6. Expand access to therapies from local to global levels.

1.5.3 Public and private payers

The main benefits under this category include:

1. Provide a great and an unlimited opportunity for treatment of difficult conditions especially those which have been untreated or undertreated by conventional medications for e.g., for a large range of physical, behavioural, and mental disorders
2. Increase access of patient population to therapies without the need for corresponding increase for an equivalent workforce expansion
3. Generation of real-world evidence (RWE) for treatment efficacy may help payers/ insurance companies in making a better or value-based reimbursement decisions.
4. Bring down the overall cost of treatment of medical conditions.

1.6 PROs and PROMs

The fundamental goal of patient visits to the doctor's clinic is to collect all the relevant information of patients health, treatment and symptoms. Besides patient visit should also reflect their psychosocial physical and social functioning status. Current demanding times have strained the healthcare system as witnessed by ever increasing patient volumes, lack of specialists furthermore a surge of documentation requirements, stringent privacy requirements, lack of reimbursements and ease of information available on the net have greatly burdened the clinicians which eventually threatens the very nature of the patient-provider relationship (Schwartzberg 2016).

To address these challenges a record of PROs, which are quantitative, validated, standardized, easily captured, and recorded in the electronic health record, offer a huge potential. All of the above emphasised patient care parameters are achievable via variety of electronic systems that have been developed to enhance the interaction between the patient and their clinical care teams (Schwartzberg 2016)**.**

A patient-reported outcome is defined as a "measurement of the patient's condition, reported directly by the patient himself/herself without interpretation by a clinician or any other individual" (World Health Organisation 2022). These measures include qualities such as pain quality of life or functional status. Such data are usually collected in the form of standardised questionnaires, so-called Patient-Reported Outcome Measures (PROMs), which have been validated in numerous studies (World Health Organisation 2022).

PROs can be used for longitudinally monitoring of a response to therapies, tolerance/side effects to a particular therapy and symptoms resulting from the underlying disease or treatment. Furthermore, psychological, and functional status of a patient can also be assessed. Table 3 highlights the examples of current utility of PROs. This real-time data can complement the clinical data and support the clinical care team in identifying and tracking disease /symptom progression and incorporating patient-specific intervention opportunities into routine clinical care (Bennett, Jensen et al. 2012).

Table3. Highlights the examples of current utility of PROs (Locklear 2014, Bennett, Jensen et al. 2012)

Symptoms (pain, fatigue, nausea etc.)
Physical functioning
Mental health (stress, anxiety, fear)
Adhere to medication/treatment
Health Related Quality of Life

As tools to measure PROs, PROMs are usually validated questionnaires that patients complete by self-assessing their health status (Weldring, Smith 2013). Williams has pointed out “PROMs are tools used to capture a patient's perspective of their own treatments and care.” (Williams 2016). Traditionally, PROMs have been used for clinical trials where they are routinely used for measuring secondary outcomes, audits and for registries, but with the advancing digital therapeutics they are now becoming part of routine clinical practice.

A number of disease-specific validated questionnaires have been developed for a wide variety of conditions including difficult diseases such as cancers. The task of standardizing these questionnaires and promoting the global use of health outcomes data is currently held by International Consortium for Health Outcomes Measurement (ICHOM)(International Consortium for Health Outcomes Measurement (ICHOM) 2022).

Based on utility PROMs can be categorised into different categories for e.g. generic (targeting health status and common QOL measures), disease-specific (e.g., cancer) or condition-specific (for e.g. related to rehabilitation, mental health and geriatric care) (Morelle Menezes 2020).

As emphasized in the definition, PROs represent only patient experiences that is totally independent of the interpretation by anyone (e.g., family member, caretaker or clinical care team). It is therefore imperative that the methods used for collecting these data points via questionnaires must provide an unbiased perspective of the patient's condition.

Until couple of years ago PROMs were being collected from the patients via traditional paper and pen method, however in today´s digital age these have been replaced with electronically devices such as with tablets, smartphones, PC, laptops, wearable devices, web-based portals etc. replacing the traditional PROMs with ePROMS. ePROMs can be administered in clinics, with/without clinical supervision, or alternatively remotely in patients home under unsupervised settings. A growing body of evidence suggests that data collected with ePROMs are valid and of comparable quality to paper administered PROMs (Gwaltney, Shields et al. 2008, Bliven, Kaufman et al. 2001). Furthermore, ePROMs are less time consuming, efficient and the data points are more reliable, scalable, and adaptable (Velikova, Wright et al. 1999)

PROMs provide a patient-focused, clinically relevant, and reliable perspective on the patient journey during a course of a disease or a therapy. From a clinical perspective there are two ways of utilizing data provided by PROMs.

Firstly, as a part of clinical care following patient treatment and its symptoms. These prompts following treatment specific symptoms, initiating or changing treatment options in case of any adverse effects or low drug efficacies, timely intervention by clinical care team when any red flags are raised that could further prompt additional investigational appointments and even lowering of hospital visits whenever deemed necessary. Secondly, as a part of real-world data (RWD) at the population level PROs can be used for analytical and strategic purposes. For e.g., PROMs can be used by relevant authorities for health performance management, benchmark patients' outcomes against other services, formulation of policies, comparative effectiveness analysis, and improvement of quality and safety of healthcare measures. Furthermore these may be used for monitoring and identifying gaps in the health care system (Canadian Institute for Health Information 2022, Kaiku Health White Paper 2019).

1.7 PROMS in Cancers

e-PRO system development and implementation have occurred in a wide range of "early adopter" cancer clinical care settings, however there are very few scientific studies that have tried to identify these systems and their features.

A review by Jensen et al. identified systems implemented over the past 12 years and also evaluated their administration, data collection, and reporting features (Jensen, Snyder et al. 2014). Jensen et al. identified 33 e-PRO systems vast majority of which (about 70%) were based in US. About one third of these systems were implemented in a single academic institutions and majority were used in medical oncology clinics at the point of care, mostly as web-based systems. The primary focus of these systems was treatment and follow-up care, for cancer therapies. (Jensen, Snyder et al. 2014). Several studies and meta-analyses have also concluded that scores derived from ePROMs are equivalent to their original paper versions (Campbell, Ali et al. 2015, Gwaltney, Shields et al. 2008)

1.8 Benefits of ePROMs

1.8.1 Patient Empowering

It has been well documented that patients with cancer are often reluctant to discuss important toxicities with healthcare providers for a variety of reasons including beliefs that such symptoms are simply a part of the cancer experience that must be tolerated (Patrick, Ferketich et al. 2003). Participation by patients in electronic survey might help in reducing that reluctance (Gwaltney, Shields et al. 2008).

Due to complex nature of cancer and their therapies clinicians may often miss sub-clinical symptoms or symptoms that may emerge in the later course of treatment. Furthermore, symptoms may also go unreported because of inadequate patient communication between clinical visits and follow ups. Basch et al. (Basch, Jia et al. 2009) reported that there were significant differences between the incidence of symptoms reported by patients vs. clinicians, with symptoms underreported by clinicians compared with ePROs based on touch screen tablet computer interface. As such ePROs could be a great opportunity to catch symptoms early enough and improve the patient experience and potentially avoid downstream complications. Patient monitoring becomes even

more important with the advent of many new cancer drugs like immunotherapies, that have a high potential for novel toxicities, possibility of missing unusual but important adverse effects that not are not familiar to the clinician. In conclusion novel cancer therapies may pose a big challenge for patient management in the absence of poor symptom communication.

1.8.2 Adverse Event Monitoring (AEM) and alarms

One of the most impressive advantages of using ePROMs and their algorithms have the provisions for PRO-based warning systems during systemic therapies and follow ups. Here, real time alerts can be generated for the patient care teams when certain pre-defined thresholds are overwhelmed (Basch, Deal et al. 2016a). These alters can initiate timely intervention and further treatment steps wherever necessary. Some treatment side effects also known as adverse events can be quite severe and even life threatening in some circumstances, however careful monitoring and in time early interventions, can offset most of them. ePROMs can not only facilitate early detection of AEs and demonstrate improved safety of the treatment but also facilitate a better QOL.

1.8.3 Early detection and prediction of symptoms

As AI based analytics are gaining moment in the diagnosis and treatment of cancers these tools can be utilized to capture vast real time data pools for generating value-based healthcare assets via predictive and prognostic analytics. A recent data showed that machine learning based algorithms could help identify cancer patients who were at a high risk of short term mortality of 6 months , suggesting that such predictive models could have the potential to trigger more timely actions between patients and their health care teams (Parikh, Manz et al. 2019)

A study by Ivanainen et al. suggests that machine learning based prediction models using ePRO and electronic health record as input points could predict the presence and onset of immune related adverse events (irAEs) with a high accuracy in patients with advanced cancers receiving immune checkpoint inhibitors (Iivanainen, Ekstrom et al. 2021).

1.8.4 Patient management and follow-up

During the last decade novel cancer therapies have evolved that have already transformed some cancer types from an acute disease to a chronic condition. As the number of cancer patients continue to rise symptom management has evolved into a key cornerstone of current healthcare system. Furthermore due to rapid development of novel therapies and changes in the treatment scenarios the needs of cancer patients and the evaluation criteria are also changing at such a pace such that now the focus of current clinical care has been tilting towards the QOL and solutions that prompt a productive and functional existence in the long term (Warrington, Absolom et al. 2015).To serve this purpose, a long-term follow-up of cancer patients is warranted and integration of ePROMs into clinical practice seems to be the need of the hour.

A web-mediated algorithm-based follow-up on self-reported symptoms for lung cancer patients improved overall survival due to early relapse detection and better performance status at relapse. This study shows that critical parameters like overall survival in cancer patients could be improved by using a web-mediated follow-up than traditional scheduled follow-up to the doctor´s clinic. (Denis, Lethrosne et al. 2017) Furthermore follow up studies on cancer patients have suggested that that real-world symptom data collected through the ePRO application on patients receiving immune checkpoint inhibitor therapy aligns with the data from clinical trials (Iivanainen, Alanko et al. 2019), which supports the fact that ePROMs could be suitable tools for monitoring side effects and QOL during and after cancer therapies (Basch, Deal et al. 2016a)

1.9 Improving communication

Current oncology practices warrant that patient care teams monitor effects of cancer therapies on patients' physical and psychosocial well-being, and also incorporate these into clinical decision making. As many cancer symptoms may remain underreported in routine clinical visits and in addition different physicians might differ in their ability to recognize patient physical or psychosocial information, as such good communication between health care teams and cancer patients, have been recognized to be central for the management of cancer patients (Department of Health (UK) 2000). Patients may have a number of concerns related to the disease and treatment, with electronic tools like ePROMs patients can freely ask questions with the healthcare team anytime and this helps in reducing their anxiety that may promote better treatment outcomes.

To this end utilization of patients' health-related quality of life (HRQOL) which is a multidomain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life offers a vast potential to improve the process of care treatment course. Previous studies including studies from oncology, have suggested that individual HRQOL reports provide useful information to physicians as well as facilitate communication (Rubenstein, McCoy et al. 1995, Taenzer, Bultz et al. 2000, Detmar, Muller et al. 2002). Furthermore, a randomized trial on cancer patients involving HRQOL measurement using a touch screen-based tool for European Organization for Research and Treatment of Cancer-Core Quality of Life Questionnaire (EORTC QLQ C33) and Hospital Anxiety and Depression Scale (HADS) reported an impact on patient-physician communication with better HRQOL and a positive effect on emotional well-being than in the control group. (Velikova, Booth et al. 2004)

1.9.1 Enhanced Patient experience

A good patient experience is associated with better clinical outcomes (Doyle, Lennox et al. 2013).Patients tend to cope better when patients feel they can affect the outcomes of treatment (Livneh 2000)

Patient experience starts already before the initiation of care and continues beyond clinical visits, and throughout the whole recovery process. Patient experience is affected by several factors such as culture, behaviour of people of the organization and even by the patient's perceptions and expectations (Howell, Molloy et al. 2015). As part of patient centricity ePROMS increases awareness of patients' functioning and wellbeing and facilitates shared medical decision-making by enhancing patient participation in the treatment course (Wintner, Sztankay et al. 2016, Velikova, Booth et al. 2004).

Digital Health tools like ePROMs allows cancer patients to remain connected with their health care team, get updates on the status of their health, receive educational materials and tailored self-care instructions for disease management, and irrespective of physical location have a day-night access to customized care information while remaining connected with their near and dear ones and cancer communities. It is thus easy to conceive why such tools may result in a better patient satisfaction and experience that has a positive effect on disease/treatment outcome.

1.9.2 Efficient utilization of healthcare resources and Cost Effectivity:

Since patients can be monitored remotely with ePROMs and hospital appointments made as per need, the use of ePROMs in the routine clinics could offer a more efficient utilisation of limited healthcare resources especially for several chronic conditions. For e.g., a generic ePROM system, from Nordics Ambuflex, is being used routinely to manage and facilitate clinical decision making for patients across nine chronic conditions such as different cancer types, epilepsy, sleep apnoea, asthma etc. Interestingly it demonstrated a decrease of 48% and 57% in hospital follow-up visits for epilepsy and sleep apnoea groups respectively (Schougaard, Larsen et al. 2016). Further study by Bash et al. that used STAR ePROM system has also reported benefits related to healthcare resource utilisation where patients in the STAR arm had significantly fewer emergency department (ED) visits compared with those who received routine care (34% *versus* 41%).(Basch, Deal et al. 2016a). Further ePROMs may also help in bringing down reimbursement cost related to patient transportation and need to destroy chemotherapy drugs due to better patient adherence (Aiyegbusi, Nair et al. 2021).

Human resource costs which included time spent by an employee preparing, receiving, and handling data, were compared between web-based and paper-based questionnaires. The mean human resource cost for the web version was 9.5 minutes versus 24 minutes for the paper version (Engan, Hilmarsen et al. 2016). In a cohort study of 500,00 subjects the total financial costs for paper-based questionnaire were €4,965,833 (€9.94/subject) when compared to the development of a web-based tool that estimated to cost just 3% of the amount of the paper version (only €150,000 (€0.3/subject) (Touvier, Méjean et al. 2010). Further in chemotherapy patients monitored with a tablet based ePRO (intervention arm) were less frequently admitted to the emergency room (34% *v* 41%) or hospitalized (45% *v* 49%) when compared to non-intervention arm that received usual care consisting of symptom monitoring at the discretion of clinicians (Basch, Deal et al. 2016a).

These results suggest that not only are the developmental costs of digital tools like ePROMs less expensive, but they could also offer long term cost effectivity for institutional health budgets.

1.9.3 Improved data quality

Several studies have indicated that electronic methods are associated with less missing data and data error mistakes in the form of missing, inconsistent, or abnormal values could even be minimized to even zero with electronic methods (Meirte, Hellemans et al. 2020)

1.9.4 Adherence and Compliance

Studies have suggested that the use of ePROMs in routine clinical practice is both acceptable and feasible and patients have reported better satisfaction with preferential attitude towards ePROMs (Dumais, Dias et al. 2019, Schick-Makaroff, Molzahn 2014). On the other hand there is somewhat conflicting evidence as to if electronic data collection tools like ePROs improved patient adherence and compliance (Meirte, Hellemans et al. 2020). Studies have indicated that although adherence to ePROM declines over time (Andikyan, Rezk et al. 2012) however the opportunity to send time bound automated reminders for example with email or notification may improve patient response rates and compliance.(Andikyan, Rezk et al. 2012, Kongsved, Basnov et al. 2007).

1.9.5 Reduced risk of disease transmission during disease outbreaks

It has been suggested that the incidence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) transmission in patients with cancer could be greater than in the general population (Yu, Ouyang et al. 2020). Reports from China suggest that cancer patients have a higher than threefold risk for admission to intensive care unit, mechanical ventilation, or death, compared to patients without cancer (Liang, Guan et al. 2020).

Cancer therapies such as chemotherapy and radiotherapy promote immune suppression that might increase the susceptibility of cancer patients to the virus. The present corona virus disease 19 (COVID-19) pandemic has changed the treatment scenario for cancer patients mainly due to two reasons:

1. Clinical care teams and resources have been diverted to fight the pandemic and prioritising acute COVID-19 patients over other chronic conditions.
2. Since cancer patients are more susceptible to infections as such their hospital visits for treatments must be delayed (until acutely necessary)

These scenarios have necessitated that providing medical care and health monitoring with digital tools like ePROMs outside hospital settings might go on a long way not only in reducing the risk of exposure and transmission of, COVID-19 both for patients and clinicians but also for remote symptom monitoring that might facilitate the identification of early life-threatening complications in cancer patients.

1.10 Limitations of ePROMs

1.10.1 Survey Fatigue

It has been shown that use of ePROMs may lead to a steady decline in survey completion over time. This may be precipitated by several factors such as older age, disease severity, the presence of comorbidities, questionnaire length, item relevance, and perceptions of response burden. Low compliance rates could result in missing data points from patient reported data and compromise the clinical utility of ePROMs. (Buergy, Siefert et al. 2020, Atkinson 2018)

While traditional method of clinical diagnosis may result in “underreporting of symptoms”, as symptoms reported from PROs are very individual this may increase the risk of misunderstandings among the healthcare staff especially they may “threshold” patients for any future actions. This may even result in ignoring the daily PRO reports as some kind of medical “spam.” Therefore, it is important to introduce some kind of validation tolls such as sensors, temperature probes and gyroscopes etc. in parallel to ePRO instruments. (Giordano, Welzel et al. 2020).

1.10.2 Integration of ePROMs into existing health systems

The successful integration of ePROM into existing health systems and workflows could be complex, resource-intensive, requiring a co-ordinated multistakeholder involvement. Furthermore, this may require training of HCPs and medical staff in order to facilitate integration of these systems with existing clinical workflows (Aiyegbusi, Nair et al. 2021). This may prompt changes to healthcare team workflows and increase their work burden by onslaught of data and its required interpretation. Technical difficulties may adversely impacted compliance rate for example one study reported that patient technical difficulties resulted in fewer daily symptom entries (41.0%) than counterparts who

did not (76.0%) with Sickle Cell Disease Mobile Application to Record Symptoms via Technology (SMART) tool (Jonassaint, Shah et al. 2015). Another major limitation of ePROM is the potential of a ‘digital divide’ especially people with lack of computer literacy and old age. Study by Giordano et al. reported inability to complete the electronic version for Cancer-Specific Geriatric Assessment (CSGA) tool without assistance for about that more than half of >70-year-olds (Giordano, Welzel et al. 2020). A second study also reported significant difficulties in completing electronic tools with older ages (Richter, Becker et al. 2008).

1.11 Barriers to Adoption

All DTx including ePROMs aim to provide solutions to ailments that have been left unaddressed with the traditional medicinal system however until now DTx have not been able to penetrate the core of health care system. There are certainly a number of factors that might support reluctance of physician prescribing them or more and more patients adopting them. As per a report by McKinsey & Company,(Joyce 2018) proposes two main obstacles that impediment wider adoption of DTx. Firstly, difficulty in distinguishing DTx from the more general health and well-being offerings in the overall digital health market. Secondly, misaligned incentives in the healthcare ecosystem comprising of stakeholders such as health care services, insurers and pharma companies (Rastegayeva 2019).

1.12 Security and data breach

Since ePROMs involve transfer personal information over the internet this could pose a potential for high risks of data breach in form of unauthorized access and manipulation of personal patient data that could dangerously compromise both trust in the software products and patient care security. Regulatory bodies like the food and drug association (FDA) have defined two tiers for software-as-a-medical-devices (SaMD): Tier 1 (higher cybersecurity risk) and Tier 2 (standard cybersecurity risk). FDA has also issued guidance regarding cybersecurity measures for SaMD devices including design, labelling, and documentation for example for premarket submissions, and device manufacturers must comply with these regulations to address cybersecurity nonetheless these regulations still seem to be somewhat slack. For example a study found that between 2002 to 2016, out of 13.79% identified regulatory devices only 2.13% of software-enabled device had product summaries that included cybersecurity content over

the period studied (Stern, Gordon et al. 2019). With the concepts of patient centricity and data protection legislations, providing safe and fast data storage, handling and analysis tools may be a challenge and consequently patients and clinicians may be unable to make informed decisions about potential product risks (Patel, Butte 2020). A study published in BMJ reported that out of 20,000 apps studied over one-third had third part services embedded in them. A majority of these apps could access and potentially share user date. Although this was more with health and fitness apps (36%) compared with medical apps (17%) (Tangari, Ikram et al. 2021).

1.13 Lack of Standarisation

One of the key issues for implements DTx including ePROMs remains lack of dedicated pathways to assess the value proposition of these technologies. In today's COVID-19 situation more than 300,000 health apps are currently available for the customers (Bini 2021). This shows that possibly anyone can post an app in the various online app stores, even though their claims about the majority of app's effectiveness are neither validated nor regulated in the absence of a single system for vetting these health-related apps.

Additionally, this situation may vary from country to country with different payers having different guidelines for digital health technology adoption. For e.g., Germany's Digital Healthcare Act, approved in December 2019, permits physicians to prescribe health apps to patients (self-determined access). After the evidence from clinical trials is reviewed the apps are included in a public list and conditional reimbursement is available for apps where trials still need to be carried out (German Fedral Ministry of Health 2020).

In the UK, meanwhile, National Institute for Health & Care Excellence (NICE) Medtech Innovation Briefings aims to support National Health Service (NHS) and social care staffs who plan to use new medical devices and novel diagnostic technologies such as digital health for patient treatment, review of evidence and likely financial impacts (Wiederhold 2021). Although these briefings facilitate local decision-making by providing a rational overview nonetheless currently, they do not recommend anything. In contrast to Germany this approach basically mimics medical device approach where software is considered a secondary aspect (National Institute for Health & Care Excellence 2022) . In the US, regulations had lagged until now and but with the introduction of the

FDA's digital software pre-certification program there seems to be a light at the end of tunnel. Although this program has been heavily criticized for ambiguity in evaluation criteria and setting less stringent standards for evaluation as compared to traditional pharmaceuticals (Wiederhold 2021).

To add on for patient cantered mobile health apps there could be a number of discrepancies for example with comparable data collection and analysis system leading to variations in outcomes even if they aim to address a similar disease condition.

1.14 Pricing and reimbursement challanges

Besides regulatory challenges, the DTx also faces hurdles for pricing and reimbursement as the traditional pricing and payer reimbursement models, are not well suited for them. Currently, direct-to-consumer (DTC) approaches and business-to-business-to-consumer (B2B2C) approach has been the main channel for reimbursement in the DTx industry which inarguably is not the most sustainable long-term market strategy. The first and most obvious driver of adoption is price. If the reimbursement model relies on patients to pay too much for DTx, this will obviously hinder usage and adoption among patients (Evidera 2020).

In practise, a value-based healthcare delivery model where service providers are paid based on the values and merits delivered to patient health outcomes is a viable path for reimbursement, however this is highly dependent on the level of clinical evidence and robust RWE generated by DTx products to support claims and demonstrate values. Unfortunately payers still need to see robust clinical evidence and economic benefits that these technologies have promised and which also happens to be a key factor for enforcing the trust especially among health care communities which in turn promises a successful market access for them (Evidera 2020).

1.15 The evidence

All products claiming to be a digital therapeutic must adhere to 10 foundational principles: out of which one of the core issues remains demonstration of a robust evidence generation as emphasized by Digital Technology Alliance “publish trial results inclusive of clinically-meaningful outcomes in peer-reviewed journals”(Digital Therapeutics

Alliance 2019). Although studies that aim to show the evidence-based effectiveness of DTx such as ePROMs have begun to rise, there seems to be a long way ahead before the benefits of the digital revolution in health care could be realized in practice from a clinical validation perspective.

A systemic review by Boyce and Browne investigated the impact of PROMs feedback to healthcare professionals both at the individual patient and their group-level on the patient-reported outcome concluded that the evidence regarding the impact of PROMs feedback on patient outcomes was weak, with frequent methodological issues (Boyce, Browne 2013). Furthermore, authors concluded that there was weak evidence supporting with the use of PROMs as a screening tool. The studies which had reported a positive effect had primarily used PROMs as a management tool in outpatient settings on a specialised patient population with a lower quality score on average that according to authors warranted additional qualitative research for providing a deeper understanding of the PROMs (Boyce, Browne 2013). In conclusion PROMs were primarily a management tool on a specialized patient population rather than an effective screening tool. Despite pointing some weakness with PROMs one of the drawbacks of this review was that majority of the studies examined were primarily cross-sectional, feasibility or pilot in nature, which may not be necessarily capture the real impact of PROMs on patient outcomes. In addition, many of these studies were conducted much before PRO specific clinical trial guidelines and standards were established that could form the guidelines for reporting PROM data (Aiyegbusi, Nair et al. 2021).

A systematic review by Kotronoulas et al. examining the inclusion of PROMs in routine cancer clinical practice found only marginal effects for symptom reduction and the effects on QOL, supportive care needs, and effects on psychological symptoms were equivocal (Kotronoulas, Kearney et al. 2014). Similarly, a phase III RCT with eRAPID- an online eHealth system for patients to self-report symptoms during cancer treatment reported a non-significant effect on symptom control, patient self-efficacy, improving symptom management and QOL for patients with metastatic disease (Absolom, Warrington et al. 2021). This was in stark contrast to other contemporary studies reporting improving symptom management, QOL, and survival in patients with advanced cancer (Denis, Basch et al. 2019, Denis, Yossi et al. 2017, Basch, Deal et al. 2016b). Furthermore, the study reported no differences for hospital admissions, chemotherapy delivery and utilization of healthcare resources between the intervention (eRAPID) and control

(usual care) arms. A clinical trial with 102 chemotherapy patients from the Showa University Hospital (Tokyo, Japan) reported no significant improvement in common cancer treatment symptoms such as anxiety, depression on symptom monitoring with hospital anxiety and depression scale (HADS) between intervention (breast cancer patient support system app) and non-intervention arms. Kroenke et al. have critically commented on the results from Symptom Tracking and Reporting (STAR) interface that has been used by cancer patients in the clinical studies by Bash et al., which has been considered as one of the pioneering studies for generating positive clinical evidence in support of ePROMs for the management of cancer patients. Kronke et al. (Kroenke, Cheville 2016) have suggested that self-symptom monitoring/screening alone does not result in clinical benefits but rather coupling of additional components such as patient engagement and care management. Further the concept that symptom monitoring alone can affect clinical patient outcomes is not clearly supported by scientific evidence as shown by a meta-analysis from depression studies (Gilbody, Sheldon et al. 2008) and a randomised clinical trial from lung cancer study (Cleeland, Wang et al. 2011). In addition, Kroenke has also expressed their speculations on cost or utilization differentials between the STAR and control arms in the absence of key methodologic elements such as accurate and comprehensive collection of costs with a validation strategy. (Kroenke, Cheville 2016).

While digital health solutions are scalable, convenient and efficient the success of these products invariably rests on the quality of evidence generated to meet the needs and expectations of the patients. Studies that aim to show the evidence-based effectiveness of DTx have begun to rise and there is already a substantial data supporting this. Nonetheless the journey has just begun and there seems to be a long journey ahead before the benefits of the digital revolution in health care could be realized in practice from a clinical validation perspective.

While digital health solutions are scalable, convenient and efficient the success of these products invariably rests on the quality of evidence generated to meet the needs and expectations of masses. In the absence standardisation, stringent regulatory environment and dedicated value assessment methods for these therapeutics many clinicians could be reluctant to incorporate digital therapeutics in routine clinical care despite the tremendous potential of these technologies to influence quality of care and outcomes of their patients. While many conventional pharmacotherapies have undergone multistage stringent verification and safety measurements well over a substantial

period of time, barriers to the application and adoption of DTx such in clinics have been dramatically low (Kim, H. S. 2020). Furthermore, another consistent challenge for DTx remains ensuring adequate data quality and robustness (Sharma, Harrington et al. 2018)

In light of these apprehensions it seems plausible that from a healthcare practitioner's point of view, DTx need to be approached more conservatively, emphasizing this concern Dr. Andrew Krystal from Weill Institute for Neurosciences has suggested the need for digital therapeutics companies to demand the gold standard of research i.e. randomized placebo-/sham-controlled trials that would promote more confidence among researchers and health care practitioners towards these technologies supporting the fact that improvements in the patient measured outcomes are truly due to the digital interventions and not because of some other compounding factors (Big Health 2022).

In conclusion there is no denying fact that DTx such as ePROMs will play a decisive role in the future of clinics especially as efficient tools for addressing some unmet needs in the management of chronic conditions such as cancers. Despite these optimistic indications it appear that these digital tools still have a long way to go and their vast potential in healthcare industry can only be realized If they prove to be accurate, reproducible and above all present a strong scientific evidence basis which would eventually clear off the apprehensions that are usually associated with use and adoption of these promising tools (Duffy, S. 2021).

2 AIMS OF THE STUDY

In the past decade a lot of scientific literature had been published on the utility of digital health tools for healthcare. As reviewed in the previous sections a growing body of evidence suggests the utility of such digital therapeutic tools like ePROMs in the management and treatment of a number of complex chronic diseases such as cancer. On the contrary a number of studies have also disputed the true effectiveness of these tools. As per our own observation majority of the published material in form of pilot studies, feasibility studies, proof of concept studies and reports advocating the positive outcomes for ePROMS in oncology already exists, unfortunately this data is suboptimal from a clinical applicability perspective and scientific strength. To add on, there are some published clinical trials supporting the clinical utility ePROMs in oncology however to the best of our knowledge no studies have so far examined the robustness and the strength of evidence presented in these studies that supports the outcomes these digital therapeutic tools in clinicals settings.

As per the hierarchy of evidence for the evaluation of health care outcomes randomized control trials (RCTs) are considered as the gold standard since they not only deliver the highest level of evidence but are also limited in all kinds of study bias and control confounding variables (Bondemark, Ruf 2015). Therefore, RCTs can be considered a reliable means to examine the clinical utility as well as robustness of scientific evidence for studies with a clinical outcome including ePROMs. As ePROMs constitute a part of DTx therefore RCTs are also the best way to examine the true “effects” of a “cause” (therapy).

Despite considered as one of the highest levels of evidence in clinical practice, RCTs are not free of internal pitfalls and the quality of the evidence produced by these clinical studies is dependent on the methodological rigor employed at every stage of their execution. In our quest for examining the robustness of scientific evidence for effectiveness of ePROMs in oncology we took an approach that focused on studying methodology and design integrity of RCT that categorize it as “High quality” trial. High quality RCTs not fulfil the conditions of methodological consistency and design but are also instrumental in the production of a reliable evidence favouring clinical decision making that facilitates best health care for the patient. Therefore, the current thesis aimed to:

- Firstly identify “high quality” RCTs for clinical utility of ePROMs in oncology

- Secondly, Examine the methodological robustness and design integrity of these RCTs
- Thirdly based on methodological and design of RCTs evaluable if the strength of data and scientific evidence was sufficient to support the outcome of these ePROM RCTs in oncology?

3 METHODS:

3.1 Reserch question

In light of our aims, we first started by framing a primary research question for our study. We used PICOT model (Riva, Malik et al. 2012) to frame our research question as under:

P - Patient or population/disease: We asked the question which relevant population should be included in the study and what would be the characters of this population type? (disease type age, gender, ethnicity etc.)

In the present study we were keen to study all cancer patients on various cancer therapies (chemotherapy, radiotherapy, immune checkpoint inhibitors and targeted therapies) irrespective of age, gender and ethnicity but only restricted to developed countries. Our selection criteria were limited to developed countries since we assumed that developed countries might have the best clinical experiences from digital health tools like ePROMs

I - Intervention, prognostic factor, or exposure: What next asked what would be the intervention/therapy or exposure?

In the present study our aim was to focus on ePROMs as intervention tools

C - Comparison or control: We next asked who/what could be a good comparator or control groups for the intervention?

In the present study we focused on control groups without ePROMs on traditional follow ups or usual care follow up for oncology patients on therapies.

O - Outcome: We next asked what should be patient-relevant consequences of the intervention?

In the present study we wanted to focus on clinical outcomes that have a direct relevance to a cancer patient for e.g., survival, QOL, relief from pain and symptom distress.

T- Time We finally asked what should be a valid time frame for the study?

We wanted to look for studies where patients were exposed to interventions for at least 12 weeks.

We famed our research question as: In cancer patients on therapies (Population) how effective are ePROMs (Intervention) when compared to subjects without ePROs or usual care (control) in improving primary clinical parameters such survival, QOL, symptom distress (for e.g. pain) or any other clinically relevant patient centric metrics (outcomes) during an exposure period of at least 12 weeks (Time).

3.2 Screening Process

3.2.1 Electronic database searches, keywords, and search strategy

A number of databases such as CINAHL (EBSCO), MEDLINE (OVID), PubMed @ UM (MEDLINE), PsycINFO (EBSCO) etc. are available for evidence based medical literature search. In the current thesis we utilised PubMed @ UM (MEDLINE) and PubMedCentral as the primary search engines for the articles of interest. We decided to set the time limit of the search for past 10 years. The cut-off date of past 10 years was chosen as it approximately coincides with onset of the digital revolution for clinical use with smartphones/tablets capable of running third-party apps and opening of major app stores. Our search included a number keywords such as " electronic patient reported outcome/measures" "ePRO"/"ePROM" "patient reported outcome measures, "symptom monitor", "web-mediated follow up" "automated symptom monitoring" , "web application", "mobile app", "mHealth", "telemedicine" in combination with the keywords "cancer treatment" "cancer" "neoplasm". Our search strategy utilised combination of different keywords, MeSH, with Boolean operators, truncation and field tags to ensure that all relevant and recent articles were captured. Finally, a combination resulting in a search for the most optimal articles was adopted on 9th February 2020 as illustrated in table 4.

3.2.2 Inclusion criteria:

Since we aimed to include only highly quality RCTs in our analysis we therefore set relatively high thresholds for screening in form of stringent inclusion and exclusion criteria. Our inclusion criteria for RCTs were:

1. RCT with a PROMs tools in digital format and could include assessment from any web, tablet, computer, or mobile app sources
2. RCTs not older than last 10 years.
3. RCTs were included if they focused on clinical outcomes that had s direct impact on a cancer patient´s health (for e.g. patient survival, QOL, symptom management, treatment adherence, hospitalization)
4. All cancer types with no bar on age, gender, ethnicity, and cancer therapy

3.2.3 Exclusion criteria

1. Systematic reviews, non-randomized control trials, observational studies, case studies and case reports and expert opinions.
2. RCTs deviating from direct and meaningful clinical outcomes for the cancer patient (excluded topics included patient-clinician communication, financial needs, weight loss, decision aid, self-esteem, genetic counselling, acceptability of ePROs, fear of recurrence, physical inactivity, engagement with app, vegetable consumption, psychoeducation, cognitive therapy, patient education, exercise as therapy, tobacco cessation.
3. Studies relating to PROMs administered in paper form (PROs with “e” component).
4. Pilot studies., feasibility studies, proof of concept studies, design of RCT, cost effectiveness studies.
5. Total study N <100 and duration of intervention follow up< 12 weeks.
6. RCT with secondary analysis.
7. RCTs populations outside the developed countries.
8. RCTs involving telephonic intervention/monitoring.

Table 4. Highlight the search strategy on PubMed search engine

#1	"Electronic patient reported outcome measures" [tw] OR "ePROM" [tw] OR "Patient Reported Outcome Measures"[Mesh] OR "symptom monitor*"[tw] OR "web-mediated follow up"[tiab] OR "mobile app" OR "Telemedicine"[Mesh]
#2	" cancer treatment" [tiab] OR "cancer" [tw] OR "Neoplasms"[Mesh]
#3	#1 AND #2
#4	4751 hits

3.3 Search Results

Our search resulted in total of 4751 hits. To narrow down the number of articles we applied filters such as Randomised Clinal Trial, language as English which a time frame of 10 years that eventually resulted in 439 items. We next applied additional filters of Associated Data that narrowed down our results to 312 searches. Out of 312 articles 218 article were opted out since they did not had electronic(digital) component in the PROs The remaining 95 articles were screened with our inclusion and exclusion criteria and we were finally able to narrow down to 7 RCTs. The entire screening process and results are elaborated by PRISMA flow diagram in figure 2 below.

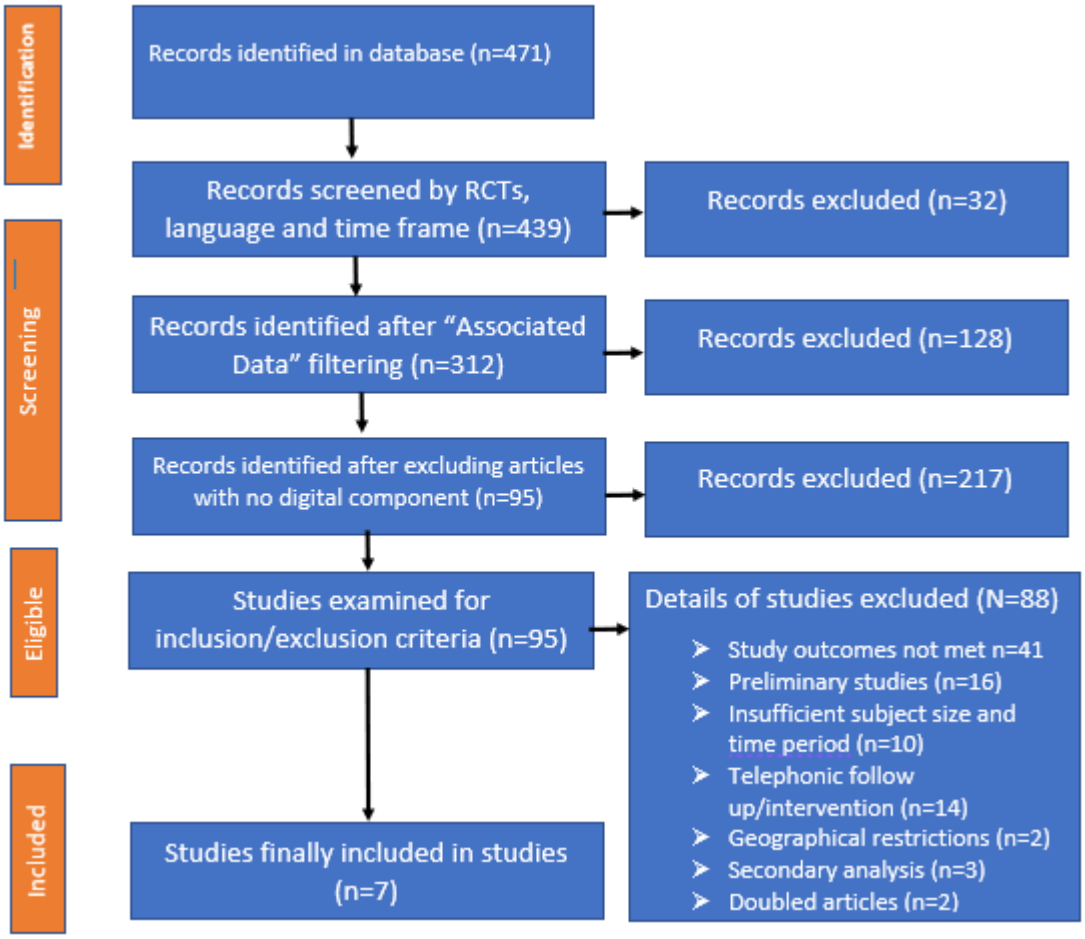

Figure 2. PRISMA flow diagram of screening process

3.3.1 Critical appraisal and mCASP checklist

Critical appraisal, as defined by Duffy (Duffy, J. R. 2005) comprises "an objective, structured approach that results in a better understanding of a study's strengths and weaknesses". It facilitates identification of evidence that comes from rigorous, reliable, unbiased, and methodologically appropriate research which can be used to inform synthesis and interpretation of the study results (Melnyk, B. M., & Fineout-Overholt, E. 2015) There are number of tools available for critique or appraisal of the research evidence from RCTs. However, these tools do not offer one-size-fits-all resource and compounding the problem is the lack of a "gold standard" critical appraisal tools with sheer volume of available tools. In order to check the methodological integrity and validity of the selected RCTs we used a conglomerate of critical appraisal checklist tool derived primarily from Critical Appraisal Skill Programme RCT checklist. as well as

other checklists from the Joanna Briggs Institute Critical Appraisal tools for RCT (The Joanna Briggs Institute 2019), BMJ pest practice (BMJ Best Practise 2022) and Johns Hopkins (Dang, D., Dearholt, S., Bissett, K., Ascenzi, J., & Whalen, M 2022) that offer one of the best tools or guideline for meeting evidence-based practice (EBP) competencies. We called this tool as modified CASP checklist (mCASP checklist). mCASP checklist resulted in a set of 23 questions. As per CASP guidelines these questions tried to judge a RCT based on its four aspects ((Critical Appraisal Skills Programme (CASP) 2022):

1. Study Design (Section A): This section attempted to ask: Is the basic study design valid for a randomised controlled trial?
2. Methodology (Section B): This section attempted to ask: Was the study methodologically sound?
3. Results (Section C): This section attempted to ask: What are the results?
4. Applicability of results (Section D): This section attempts to ask: If the results help locally and be of any application for the population in question?

3.4 Quality rating with mCASP checklist

mCASP checklist had a total of 23 questions. Each questions had 4 options with predesignated score points as below:

1. Yes (score points= 1)
2. No (score points= -1)
3. Somewhat (score point = 0.5)
4. Cant's say (score point =0).

Each question carried a maximum score of 1 and minimum score of -1. The maximum score attainable was 23 points. Studies with score points ≥17.25 (75% of maximum score) were classified as high quality (H) while those between 11.5-17 as of medium quality (M) and studies with a score of <11.5 (scores less than 50% of maximum score) were qualified as low-quality studies (L). Further the checklist was demarcated into internal validity (total 17 questions) and external validity questions (a total of 3 questions). Refer to item template in appendix

3.5 Additional tools for critical appraisal

Since critical appraisal checklists are designed to be used as educational pedagogic tools and scoring could be highly subjective (Kim, K. S., Jo et al. 2017) we further decided to cross check the methodological quality and validity of RCT separately using the modified Jadad scale, the van Tulder scale and the Cochrane Effective Practice and Organization of Care (EPOC) Risk of Bias Tool.

3.5.1 Modified Jadad scale

The Jadad scale is also known as the Oxford quality scoring system. It is one of the standard methods for evaluating the methodological quality of RCTs and it focuses on three items: randomization, blinding and patient withdrawals/dropouts. It is scored on a scale of 0-5. The main advantages of this scale are that it is quite handy to use, it contains many essential elements that have scientifically correlated with study bias. Besides it has been known to be reliable and externally valid (Stephen H. Halpern, M. Joanne Douglas 2005). However, in the current study we used modified Jadad scale (mJadad scale) which is an 8-item based tool which besides traditional randomization and blinding also incorporates withdraw/dropout rates, inclusion/exclusion criteria, adverse effects and statistical methods. The total score for each article ranged from 0 to 8 and was calculated by adding the individual scores of each item. Low quality studies yielded scores of 0 to 3, and high-quality studies achieved scores of 4 to 8 (Oremus, Wolfson et al. 2001). We exclude item 7 (Was the method used to assess adverse effects described?) since it had less relevance to current selected studies. Refer to item template in the appendix

3.6 van Tulder scale

The van Tulder scale consists of 11 components: adequacy of the randomization method, treatment allocation concealment, similarity of groups at baseline , proper blinding, presence of co-interventions, compliance, drop-out rate, timing of outcome assessment and intention to treat analysis (ITT). Each item is scored using the options 'Yes,' 'No' and 'Don't know' (answer to question insufficient). A rating of ‘1’ is allocated for any affirmative response, or ‘0’ for ‘no’, or ‘don’t know. When ≥5 items are satisfied (≥5 points), the quality of the report is deemed high ‘.(van Tulder, Furlan et al. 2003) Refer to item template in appendix

3.6.1 Cochrane EPOC Risk of Bias Tool

Cochrane EPOC modified tool was used for assessing risk of bias for methodological quality of randomised trials with a separate control group. It addresses 8 domains and judges them as “Low risk” “high risk” and “unclear risk” when something is unspecified in the paper. Refer to item template in appendix

4 RESULTS

4.1 General Characteristics of the selected studies

Out of 95 studies that were screened for inclusion and exclusion criteria 7 RCTs were finally included for this thesis. These all studies involved an ePROM intervention (IV) that was used to study cancer patients on a certain anti-cancer therapy or medication. Table 5 list the characters of these studies chosen. None of the included studies were older than 2014 and 2 studies were from 2021. The study subjects included ranges between 33 (lowest) to 83 highest) with a variable spectrum for every individual study. Out of 7 included studies majority of them were multicentred except 2. The study subjects were cancer patients based in US (2 studies) and Europe (5 studies). Nealy all of the studies had cancer patients on CTx however some of the studies also had patients on targeted therapies (n=1), radiation therapy (n=1), surgery (n=2) hormonal therapy (n=1) or their combinations of therapies (n=3). The cancer under treatment included breast cancers (n=5), lymphoma (n=1), genitourinary cancers (n=1), lung Ca (n=2), gynaecological cancer (n=2), any type of Ca (n=1), colorectal cancer (n=1).The primary outcomes of the studies focused on QOL (n=1), ER visits+hospitalization (n=1), symptom control/distress (n=4), Overall survival (n=1) and treatment adjustment (n=1). Disease severity ranged from early cancers (n=2) advanced/metastatic cancer (n=2) to any stage cancers (n=2). The secondary outcomes mainly addressed overall survival (n=1), QOL (n=1), hospitalization (n=1), febrile neutropenia (n=1) and self-efficacy (n=1). The Interventions were mainly web based that could be accessed by PC, tablet, mobile app and touchscreens at clinics. Out of 7 studies selected five were able to provide real time monitoring of patients with alters generated for health care teams that often generated an action by clinical care team. Table 5 highlights the features of selected RCTs and table 6 showcases the characters of IV used in the studies.

Table 5 : Highlights the general characters of the 7 selected RCTs

ID	Study	Characters of population	Tumor type	Intervention	PROMs used	Outcomes	Study duration	Study Findings (IV vs UC/CTR)
1	Basch et al. 2016	N=766, Age (26-91), F=58%	GU, GY,Lung, Breast	STAR	EuroQol EQ-5D Index	HRQOL (primary outcome) emergency room (ER) visits, hospitalizations, and survival (secondary end point)		HRQL ↑, < hospitalisation, remained on ChT ↑ period
2	Absolom et al. 2021	N=782, Age(18-86), M~20%, F~80%	CRC,Breast, GY	eRAPID	FACT-PWB, EQ5D-VAS, and EORTC QLQ-C30,FACT-G , EQ-5D-5L,Patient Activation Measure,CBI-B	Primary outcome was symptom control, Secondary outcomes patient self-efficacy, and global QoL	18 weeks	showed ↑ physical well-being at 6 and 12 wks, no difference at 18 wks, few clinically meaningful physical well-being deterioration, better self-efficacy and better health and patient compliance
3	Denis et al. 2017	N=133, Age (35-77), M=66.9%, F=33.1%, multicentre trial	Lung	e-FAP	FACT-L score	primary outcome was OS.	upto 24 months	OS was ↑ signficantly, QoL to six-month score↑ number of imaging events ↓ in the IV arm
4	Maguire et al.2021	N=829, Mean age52.4 years, F= 81.8% , multicentred	breast cancer, CRC, Hodgkin's disease, NHL	ASyMS	MSAS, FACT-G, STAI-R, SCNS-SF34, CASE-Cancer, WLQ	Primary outcome was symptom burden. Secondary outcomes were HRQoL care needs, anxiety, communication and attitudinal self-efficacy and work limitations	about 36 months	symptom burden remained unchanged, Significant ↓ in MSAS sub-domains, ↑ FACT-G scores CASE-Cancer scores and no changes in, WLQ.
5	Pappot et al. 2016	N=682, Age (21–82),	breast Ca	PRO-CTCAE on tablet	PRO-CTCAE	Primary outcome was fewer treatment adjustment for better symtom cintrol, secodary outcomes frequency of hospitalisation, febrile neutropenia	about 24 months	No effect observed for treatment adjustment, hospitalisations and frebile neurtopenia

6	Berry et al. 2015	N=752,Age range?, gender ?	any type of Ca	ESRA-C	SxQOL,SDS-15, EORTC QLQ-C30, EORTC-CPIN20, PHQ-9, depression scale, pain intensity numerical scale, and a skin problems questionnaire	Symptom distress and frequency of intervention use by participants	about 36 months	The SDS-15 score was ↓ in IV group
7	Børøsund et al. 2014	N=167,18 Years and older F	BCa	WebChoice	SCQ-19, MSAS,HADS,CBI	Primary: symptom distress, anxiety, depression, Secondary:Self-efficacy	6 months follow up	WebChoice group had significantly ↓ symptom distress , anxiety , and depression

ASyMS: Advanced Symptom Management System; BPI: Brief Pain Inventory-Short Form; CBI**:**Cancer ; CBI-B: Cancer Behavior Inventory–Brief Version**;** Behavioral Inventory,CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group;e-FAP: e-follow-up application;EORTC QLQ-C30 :European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Quality of Life Core Questionnaire C30;EORTC QLQ-CR29: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Quality of Life Core Questionnaire Colorectal Cancer Module;EORTC-CPIN20:European Organization for the Research and Treatment of Cancer-Chemotherapy-induced peripheral neuropathy;EORTC QLQ-H&N43: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module ;EORTC-QLQ-NHL-HG29: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire: On Hodgkins Lymphoma-High Grade; ER:Emergency Rooms;ESRA-C:Electronic Self Report Assessment-Cancer ;EQ-5D-VAS:European Quality of Life 5-Dimensions*Visual Analogue Scale*;EQ-5D-5L: European Quality of Life 5-Dimensions 5-Levels questionnaire ;FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-G: Functional Assessment of Cancer Therapy – General;FACT-L : Functional Assessment of Cancer Therapy – Lung;FACT-PWB: Functional Assessment of Cancer Therapy – Physical Well being; HDAS: Hospital Anxiety and Depression Scale ; HRQOL:Health Related Quality of Life;PAM:Patient Activation Measure ;PRO-CTCAE:Patient Reported Outcome Common Terminology Criteria for Adverse Events;PHQ-9:Patient Health Questionnaire;MAAS: Mindful Attention Awareness Scale ;MSAS:Memorial Symptom Assessment Scale;STAR :Symptom Tracking and Reporting;SDS-15:Symptom Distress Scale;SCQ-19 Stress of Conscience Questionnaire

Table 6. Characters of ePROMs in the selected studies

Intervention	Delivery/interface	Description	Real time patient monitoring with alerts for care team	Recommendations provided for HCT for action plan
STAR	A web-based interface with self-reporting either via wireless touchscreen, tablet computers or freestanding computer kiosks	Questions adapted from NCI-CTCAE pertaining to 12 common symptoms experienced during chemotherapy with levels of grading.	yes	No
eRAPID	An online interface based on use of own PC or mobile device,	Online monitoring for treatment-related symptoms with severity levels, and a clinical algorithm for patient advice and e-mail alerts. Also included weekly reminders via text or e-mail.	yes	no
e-FAP	Web based app	12 items (symptoms) reported weekly by patients in an electronic form and sent immediately to the medical team after completion	Not real time monitoring but alerts generated	yes
(ASyMS)	Tablet or secure weblink based	Completion of validated self-reported questionnaire (DCTAQ) that assesses 10 symptoms related with CTx side effects. Patients also collected body temperature	yes	yes
PRO-CTCAE reporting	**Tablet computer based**	42 PRO-CTCAE questions on 25 symptoms of chemotherapy	yes	Not mentioned
ESRA-C	**Internet or a tablet at the clinic**	Self-report symptom and quality of life questions and also patient educational material	no	no
WebChoice	**Web based tool**	Contains components for treatment symptom monitoring, tailored information and self-management support, a diary, and communication with other patients.	no	yes

ASyMS: Advanced Symptom Management System; ESRA-C: Electronic Self Report Assessment-Cancer; e-FAP: e-follow-up application; PRO-CTCAE:Patient Reported Outcome Common Terminology Criteria for Adverse Events; STAR :Symptom Tracking and Reporting;

4.2 mCASP Checklist Scores

Based on our scoring the average score for the mCASP checklist questions from the 7 selected studies was 12.21. The lowest score was 6 and highest 19 out of maximum score of 23.

4.2.1 Section A (Study Design)

All studies scored well for Study design (Section A) ad were able to gain maximum score points (3 points).

4.2.2 Section B (Methodology)

Majority of the studies were able to obtain a satisfactory score for randomization with roughly 70% (n=5) of the studies hitting a score of 1 (Q4-Q4a). On the contrary, majority of the studies scored poorly for blinding (Q5-Q5b). About 70-85% of studies (n=6-7) scored negatively on the items related to blinding with only a single study recording a score above zero (Q5a, Q5b). Furthermore, the study scores seemed to be variable on items related to baseline similarity and sample size with score ranges from -1 to 1 or 0-1. Majority of the studies were able to score maximum points for description of data collection methods, validity of instruments for outcome measures and adherence (Q8-Q10). The adhere rate in the studies ranged between 57-87% which was well over than the required ≥ 25%.

4.2.3 Section C (Results)

All studies fared well for first 4 items related to result presentation, comprehensive reporting, precision and accounting of study participants (Q11-Q14) with a maximum score of 1. However scores of ITT Analysis were 0 to negative for about 85% of studies (n=6) and only single study was able to score maximum points for ITT analysis. In addition majority of studies (n=5) were able to score satisfactorily for items related to attrition and identification of study limitations (Q15-Q17).

4.2.4 Internal validity Scores

The average scores for the internal validity comprising methodology (section B) and results (section C) ranged between 3-14.5 (max. score 20) with average score of 9. Results showed that more than 50% of studies had total score values below average score value of 9.

4.2.5 Part D (External validity)

Par D (External validity) attempted to address 3 items related to practical applicability of the study results and its value in real world scenarios (Q18-Q20). The score range for the studies was between 0-1.5 with an average value of 0.21. Majority of the studies (n=6) scored 0 in each of these items except single study by Maguire et al. which scored 50% of the maximum points. Results from external validity are in contrast to internal validity scores where most of the studies were able to score maximum points allocated for majority of the items.

4.2.6 Total Scores:

The total score range for the entire 7 studies was between 6-19 with an average value of 12.21. About 60% studies (=4) scored below the average total score. Total scoring further revealed that based on grading criteria for mCASP checklist about roughly 60% (n=4) of studies were graded as Low quality, about 25% (N=2) as medium quality and only a single study could meet the criteria for a high-quality study. Table 7 highlights the results as individual scores from the 23 items in the mCASP checklist and overall scores for internal validity, external validity and quality scores.

Table 7. Highlights the results from mCASP checklist as individual scores for all 23 items

Selected Study								
Checklist question		Basch et al. 2016	Abslom et al. 2021	Denis et al. 2017	Maguire et al. 2021	Pappot et al. 2016	Berry at al. 2015	Borosund et al. 2016
Part A :Study Design								
Q1	**Did the study address a clearly focused research question?**	1	1	1	1	1	1	1
Q2	Does the researcher identify what is known and not known about the problem?	1	1	1	1	1	1	1
Q3	Does the researcher identify how the study will address any gaps in knowledge?	1	1	1	1	1	1	1
Part B: Methodology (Internal Validity)								
Q4	**Was the assignment of participants to interventions randomised?**	1	1	1	1	1	1	1
Q4a	**Was Randomisation process appropriate?**	1	1	1	1	0	0	1
Q5	**Was blinding performed?**	-1	0	-1	1	-1	-1	0.5
Q5a	**Were the investigators 'blind' to the intervention they were giving to participants?**	-1	-1	-1	-1	-1	-1	0.5
Q5b	**Were the people assessing/analysing outcome/s 'blinded'?**	-1	-1	-1	1	-1	-1	-1
Q6	**Were the study groups similar(baseline) at the start of the randomised controlled trial?**	0.5	1	-1	1	0	1	1
Q7	**Was sample size sufficient based on study design and rationale?**	1	1	0.5	1	0	0	0
Q8	**Are data collection methods described clearly ?**	1	1	1	1	0	1	1

Q9	**Were instruments used to measure the outcomes valid and reliable?**	1	1	1	1	1	1	1
Q10	**If surveys or questionnaires were used, was the response rate > 25%?**	1	1	1	1	1	1	1
Part C: Results (Internal Validity)								
Q11	**Were the results presented clearly?**	1	1	1	1	1	1	1
Q12	**Were the effects of intervention reported comprehensively?**	1	1	1	1	1	1	1
Q13	**Was the precision of the estimate of the intervention or treatment effect reported (P values, CI, SD)?**	1	1	1	1	1	1	1
Q14	**Were all participants who entered the study accounted for at its conclusion?**	1	1	1	1	1	1	1
Q15	**Did the RCT analyse in groups to which people were randomised to (intention-to-treat analysis)?**	0.5	-1	0.5	0.5	-1	-1	1
Q16	**Was there any loss of follow up** (a**ttrition bias)? If yes was it** < 20% **?**	-1	1	1	1	0	1	1
Q17	**Were study limitations identified and addressed**	1	1	1	1	0	0.5	1
Internal validity score		**8**	**10**	**8**	**14.5**	**3**	**6.5**	**13**
Part D: Applicability of Results (External Validity)								
Q18	**Do the benefits of the experimental intervention outweigh the harms and costs?**	0	0	0	0.5	0	0	0
Q19	**Can the results be applied to your local population/in your context?**	0	0	0	0.5	0	0	0
Q20	**Would the experimental intervention provide greater value**	0	0	0	0.5	0	0	0

	to the people in your care than any of the existing interventions?							
External Validity score		**0**	**0**	**0**	**1.5**	**0**	**0**	**0**
Internal+ External Validity Score		8	10	8	16	3	6.5	13
Total Score		**11**	**13**	**11**	**19**	**6**	**9.5**	**16**
Quality		**L**	**M**	**L**	**H**	**L**	**L**	**M**

L Low Quality, **M** Medium Quality **H** High Quality

4.2.7 Strength vs. Drawbacks for the studies investigated

The major strength of the selected studies included good study design, more than 70% (N=5) of the studies had sufficiently large number of participants which was in the range of 133-829 with an average value of 587.28 Furthermore most of the studies address clinically meaningful and important outcomes for the cancer patients such as QOL, survival, symptom distress, symptom control etc. The adherence rate was quite impressive with an average 72.75 with a range of 62-87.

On the contrary major drawback backs of the studies included failure of allocation concealment (n=6), proper binding (n=5), lack of blinding for outcome assessors (n=6), randomization process not specified (n=2), not true ITT (n=6), High attrition (n=2) lack of similarity at baseline among participants (n=2), missing data (n=2), gender imbalance in studies (n=2), small participant group size (n=2), short follow up periods (n=2), not multicentred (n=2), low precision in result reporting (n=2). Other drawbacks of the studies include lack of identification of study limitations by the authors (n=1), lack of aged populations (n=1), no metastatic population included (n=1) and only single type of cancer addressed (n=1).

Despite good study design many of the shortcoming highlighted above may contributed to several biases such as selection bias, performance bias, detection bias attrition bias and reporting bias that tend to limit the internal and external validity of the study. Table 8 highlights the strength and weaknesses of the seven studies included in the analysis.

Table 8. Summary of strength and limitations of the selected studies.

Article	Strength	Weakness
Bash et al. 2016 (Basch, Deal et al. 2016a)	-Good number of subjected investigated with different age groups and cancer types (n=766) -QOL as primary outcomes -Sufficient follow up time (6 months) -Good patient adherence	-No allocation concealment could lead to selection bias -No mention of blinding, could arise suspicion of performance bias -Outcome assessors were not blinded which could lead to detection bias -Hight attrition rate (> 20%) could lead to attrition bias -- Missing primary outcome data (HRQOL) upto 15% at 6 months could lead to reporting bias -Not multicentered -Variability in baseline characters for some groups -About 60% females in trials as such not gender balanced - Less number of participants in computer inexperienced group -No ITT for HRQOL
Absolom et al. 2021 (Absolom, Warrington et al. 2021)	-Good number of subjected investigated with different age groups and cancer types (n=782) -Wide variety of instruments used -Good patient adherence	-No allocation concealment could lead to selection bias -No mention of blinding, could arise suspicion of performance bias -Outcome assessors were not blinded which could lead to detection bias -Not multicentered -No mention how blinding was carried -No ITT -Results show a weak impact of IV probably that might fade up with longer follow up period - 95% CI values highly variable -Short follow up periods - No benefit for metastatic patients reported -Authors claim IV decreases hospitalization but most patients were treated with curative intent and as such they did not need to go to emergency room visits -Cancer types mainly relate to females as such cannot be generalized to other cancer types
Denis et al. 2017 (Denis, Lethrosne et al. 2017)	-Survival as primary outcome -M & F ratio fairly balanced with variable age group -Multicentered trial -Good follow up period (upto 24 months)	- No allocation concealment could lead to selection bias -No mention of blinding, could arise suspicion of performance bias -Outcome assessors were not blinded which could lead to detection bias -Not true ITT but modified ITT -Overall patient number are somewhat small -Early trial stoppage due to the large survival benefit -Baseline QOL data showed a statistically significant difference in QOL favoring the intervention arm. -Only single cancer type studied as such result may not be generalized to other cancer types.
Maguire et al.2021 (Maguire, McCann et al. 2021)	- Good number of subjected investigated with different age	-No allocation concealment could lead to selection bias -Outcome assessors were not blinded which could lead to detection bias

	groups and wide cancer types (n=829) -Multicentered trial -Blinding attempted for patients (hypothesis) and the outcome evaluators were also blinded -Well planned study where high attrition rate was already taken into account -Good patient adherence	-Some data points missing from control group which could lead to reporting bias. -With 80% females in the trial the results may be more restricted in gender applicability. - Lack of strong evidence for what is clinically meaningful difference in MSAS score -Not true ITT but modified ITT
Pappot et al. 2016 (Pappot, Baeksted et al. 2021)	- Good number of subjected investigated with different age groups (n=682) -Multicentred trial --Good patient adherence	- No proper clarification of randomization process and allocation concealment could lead to selection bias -Outcome assessors were not blinded which could lead to detection bias -Weak clinical primary outcomes targeted -Few validated tools used -Data collection methods and other sections not described clearly in the article - Relatively few contact points of patients with IV -No ITT performed -Some limitations of study not identified - Single cancer targeted as such results may not be generalized to other cancer types
Berry et al. 2015 (Berry, Blonquist et al. 2015)	- Good number of subjected investigated with different age groups (n=752) -Multicentered trial --Good patient adherence -Good number of validated tools used	- No proper clarification of randomization process and allocation concealment could lead to selection bias - Outcome assessors were not blinded which could lead to detection bias - Several patients in IV arm could not be exposed to study materials due to software glitch which could lead to reporting bias -Participant sample was less diverse with regards to race and ethnicity -No ITT performed - Results calculated from 3-4 time points after a short follow up period (12 weeks) -Low precision in results (high SD). -A third of the intervention group participants never received pushed teaching tips in the assessment
Børøsund et al. 2014 (Børøsund, Cvancarova et al. 2014)	-Multicentered trail -Good study design, instruments and statistical tools used -Results reported prudently	- high attrition rate (>20%) could lead to attrition bias -True ITT performed -No old, aged patients included -No metastatic patients included -Low precision in results (highly variable CI)

	-Sufficient follow up time (6 months) -Investigators possibly blinded - Blinding and hurdles in blinding addressed prudently	

4.3 Modified Jadad scale

Based on the 8 items of the modified Jadad scale the score range for all of the seven studies was 2-5.5 with an average value of 3.6. Results from modifies Jadad scale Jadad scale suggest that most of the studies addressed randomization items. Additionally, 70%-100% studies (n=5-7) able to obtain maximum score of 1. However, majority of the studies failed to address blinding with almost 85% of studies (n=6) reporting minimal scores of -1 to 0. Further all studies were able to obtain a maximum score (1) for items related to withdraw/dropouts, inclusion/exclusion criteria and description of statistical methods.

Out of total 7 studies about 70 % of studies (n=4) were able to obtain a total score of ≥ 4 which categorised them into high quality studies as per modified Jadad scale quality criteria. Based on the quality scoring criteria about 85% of studies (n=5) could be categorized as High Quality. Only n=2 studies were categorized as Low-quality studies. Table 9 (below) highlights the findings from the mJadad scale for the selected studies.

Table 9. Highlights the scoring results from mJadal scale

Item	**Article**						
	Basch et al. 2017	Absolom et al. 2021	Denis et al. 2017	Maguire et al.2021	Pappot et al. 2016	Berry et al. 2015	Børøsund et al. 2014
1.Was the study described as randomized?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
2. Was the method of randomization appropriate?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Not described(-1)	Not described(-1)	Yes (1)
3. Was the study described as blinded (Were both the patient and the assessor	No (0)	No (0)	No (0)	No (0)	No (0)	No (0)	Yes possibly single blinded (0.5)

appropriately blinded)?							
4.Was the method of blinding appropriate?	Not described(-1)	Not described(-1)	Not described(-1)	Not described(-1)	Not described(-1)	Not described(-1)	No(0)
5.Was there a description of withdrawals and dropouts?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
6.Was there a clear description of the inclusion/exclusion criteria?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
7.Was the method used to assess adverse effects described?	NA	NA	NA	NA	NA	NA	NA
8.Was the methods of statistical analysis described?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
Total Score	4	4	4	4	2	2	5.5
Quality	High	High	High	High	Low	Low	High

4.4 van Tulder scale

For randomization about 70% of studies (n=5) were allocated a maximum score of 1. Further allocation concealment resulted in a non-affirmative response for 85% of studies (n=6). Scores from baseline similarity were somewhat variable however for majority of the studies (n=6) scores for the blinding items were largely non -affirmative (“NO” as the most common response). All studies had an affirmative response (“Yes”) for items pertaining to acceptability of compliance and timing of the outcome assessment. Despite having an affirmative response for ITT majority of the studies (n=7) could not be awarded maximum points since it was a modified ITT which carried a maximum of 0.5 points. Based on the 10 items considered in the analysis the score range for all of the seven studies was 2-7 with an average value of 4.5. Based on the quality scoring criteria only 45% of studies (n=3) could be categorized as High Quality. Table 10 highlights the findings from the van Tulder tool for the selected studies.

Table 10. Highlights the scoring results from van Tulden Scale

Item		Study						
		Basch et al. 2017	Absolom et al. 2021	Denis et al. 2017	Maguire et al.2021	Pappot et al. 2016	Berry et al. 2015	Børøsund et al. 2014
A	Was Method of Randomisation Adequate?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Don´t know (0)	Don´t know (0)	Yes (1)
B	Was treatment allocation concealed?	No (0)	No (0)	No (0)	No (0)	No (0)	No (0)	Yes(partially) (0.5)
C	Were the groups similar at baseline regarding the most important prognostic indicators?	Somewhat No (0.5)	Yes (1)	No (0)	Yes (1)	No (0)	Yes (1)	Yes (1)
D	Was the patient blinded to the intervention?	No (0)	No (0)	No (0)	Yes (1)	No (0)	No (0)	No (0)
E	Was the care provider blinded to the intervention?	No (0)	No (0)	No (0)	No (0)	No (0)	No (0)	Somewhat YES (0.5)
F	Was the outcome assessor blinded to the intervention?	No (0)	No (0)	No (0)	Yes (1)	No (0)	No (0)	No (0)
G	Were co-interventions avoided or similar	Don´t know (0)	Don´t know (0)	Don´t know (0)	Don´t know (0)	Don´t know (0)	Don´t know (0)	Don´t know (0)
H	Was the compliance acceptable in all group?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
I	Was the drop-out described and acceptable?	No (0)	Yes (1)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)
J	Was the timing of the outcome assessment in all groups similar?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
K	Did the analysis include an intention-to-treat analysis?	Modified ITT (0.5)	No (0)	Modified ITT (0.5)	Modified ITT (0.5)	No (0)	No (0)	Yes (1)
	Total score	4	5	4.5	7.5	2	4	7
	Quality		High		High			High

4.5 Cochrane EPOC Risk of Bias

Based on the scores from Cochrane EPOC Risk of Bias Tool it was apparent that most of the studies carried a “low risk” for a number of domains such as random sequence generation (n=5), protection against contamination (n=7), selective outcome reporting

(n=7), Baseline outcome measurements similarity (n=7). However the domains with highest frequency for “High Risk” were allocation concealment (n=6), similarity of baseline characteristics (n=3) and incomplete outcome data (n=2). Table 11 highlights the findings from the for Cochrane EPOC Risk of Bias Tool the selected studies.

Table 11. Highlights the scoring results from Cochrane EPOC Risk of Bias Tool

Cochrane Effective Practice and Organisation of Care (EPOC) Risk of Bias Tool – *EPOC modified tool for assessing risk of bias for randomised trials.* EPOC Quality Assessment Form /Risk of Bias Tool –							
Domain	**Risk of Bias**						
	Basch et al. 2017	Absolom et al. 2021	Denis et al. 2017	Maguire et al.2021	Pappot et al. 2016	Berry et al. 2015	Børøsund et al. 2014
1. Random sequence generation	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
2. Allocation concealment	High risk	High risk	High risk	High risk	High risk	High risk	Unclear risk
3. Baseline characteristics similar	High risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk
4. Knowledge of the allocated interventions adequately prevented during the study [1,2]	High risk	. High risk	High risk	Low risk	High risk	High risk	High risk
5. Other risks of bias due to problems not covered elsewhere in the table.	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
6. Protection against contamination	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
7. Selective outcome reporting	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
8. Baseline outcome measurements similar [1,3]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

9. Incomplete outcome data[1]	High risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk

[1]If some primary outcomes were imbalanced at baseline, assessed blindly or affected by missing data and others were not, each primary outcome can be scored separately.
[2]This refers to blinding of participants and personnel and blinding of outcome assessment.
[3]If "Unclear risk" or "High risk", but there is sufficient data in the paper to do an adjusted analysis (e.g. Baseline adjustment analysis or Intention to treat analysis) the criteria should be re scored as "Low risk".

[1]If some primary outcomes were imbalanced at baseline, assessed blindly or affected by missing data and others were not, each primary outcome can be scored separately

4.6 Comparison of critical appraisal tools

We first analysed the selected studies with mCASP checklist tool and to corroborate our findings the selected RCTs were later cross checked by other well-known tools for accessing methodological quality of RCTs such as modified Jadad scale, van Tulder scale and Cochrane EPOC Risk of Bias tool.

Although the different tools that were utilised in this study to assess the quality of RCTs have their own strength and weaknesses, the comparative analysis suggests that majority of the studies had several common strengths such as use of appropriate randomization methods, high rate of adherence, good follow up and fairly low attrition. However, these tools also pointed out some serious common drawbacks for e.g., majority of studies (upto n=6) scored poorly for items related to blinding (patients, health care team not being blinded), allocation concealment, outcome assessors not being blinded. Another common drawback pointed out by all tools was baseline variation in few studies (n=3) and above all lack of true ITT analysis except for 1 study.

On comparison the trends showed that higher is the quality of a study lower is the risk of bias. N=3 studies were categorized as Medium-High quality with mCASP mJadad scale and van Tulder scale and majority of the items (6-7) falling in low risk of bias for these studies. Further n=2 studies were categorized as low quality by mCASP and mJadad scale with fairly high number of items (2-4) falling in the risk of bias category. Although tools like mJadad Scale and van Tulder scale were not as elaborative as the mCASP checklist for assessing methodological robustness of a RCT, in conclusion there was a good correlation between the appraisal tools. Table 12 summaries the findings for overall score and quality ratings for the seven selected studies based on

mCASP checklist, mJadal scale, van Tulder scale and Cochrane EPOC Risk of Bias tool.

Table 12. Comparison of the scores of RCT quality assessment tools used in the study

	CASP composite cheklist		**Modified Jadad scale**		***Van Tulder scale***		***Cochrane EPOC Risk of Bias Tool***		
Article	***Score***	***Quality***	***Score***	***Quality***	***Score***	***Quality***	***High****	***Low****	***Uncertain****
Basch et al. 2016	14.25	Low	4	High	4		4	4	1
Absolom et al.	16	Medium	4	High	5	High	2	6	1
Denis et al. 2017	14.25	Low	4	High	4.5		3	5	1
Maguire et al. 2021	18.5	High	4	High	7.5	High	1	7	1
Pappot et al. 2016	11	Low	2	Low	2		4	3	2
Berry et al. 2016	13.25	Low	2	Low	4		2	5	2
Borosund et al. 2014	16.5	Medium	5.5	High	7	High	1	6	2
Average Score	12.21		3.64		4.85				
*no. of items (frequency) with high risk									

5 DISCUSSION

During the past decade several scientific materials had been published that advocates the use of digital health technologies such as ePROMs in routine cancer care. This scientific evidence includes pilot studies, feasibility studies, proof of concept studies, reports and RCTs. Although majority of this form of scientific data presents a freak picture of the quality and standard of evidence available for the utility of ePROMs in clinics, RCTs remain the fountain head of level of clinical evidence. The aim of the current thesis was to examine the quality of evidence generated by RCTs employing use of ePROMs as IV tools for patients with oncology therapy settings by examining the study design methodical robustness as well as external validity using critical appraisal tools as mCASP checklist, mJadad scale, van Tulden scale and Cochrane EPOC Risk of Bias tool. Our primary assessment tool was the mCASP checklist however other addition tools (mJadad scale, van Tulden scale and Cochrane EPOC Risk of Bias Tool were employed to double check the validity and co-relation of the primary assessment tool.

Out of the 95 articles that were screened for inclusion/extrusion criteria about 38% (n=36) of the articles addressed a topic that did not focus on meaningful clinical outcome for a cancer patient, or the outcomes of the study were not of any direct relevance for the cancer patients. These outcomes included cancer treatment-related financial assistance, cognitive style and mobile e-learning in medical students, motivate use of genetic counselling among cancer patients, obesity/overweigh/weight loss among cancer patients, reducing fear of recurrence, promoting physical activity , studying effects on moderate physical activity and vegetable consumption among cancer survivors, psychoeducation (anxiety and self-esteem)lifestyle-related effects, promoting tobacco cessation etc.

Further about 15% (n=14) of the studies were feasibility studies, protocols, plan for future studies or reports. With over 50% of studies either addressing a low threshold or a “soft” outcome for a cancer patient itself demonstrates that the current quality of studies related to ePROMs in oncological settings remains highly deplorable.

Our results also showed that about 9.5% (n=9) of clinical trials had a small number of study participants (n<100 even up to n=40) and very short follow up durations (upto 3

weeks). This data further points out to lack of reliability of data for the applicability of many ePROMs in clinical practice.

Out of the 4751 hits generated in our search we were finally able to screen 7 RCTs from the last 10 years that matched our study and analysis criteria. Our result from mCASP checklist showed that strengths of the selected RCTs included good study design (section A of checklist) where scores were 100% for all studies. Besides majority of the studies had common strengths such as use of appropriate randomization methods, high rate of adherence, good follow up and fairly low attrition that also formed components of methodology (part B) and result (part C) sections of the checklist.

On the contrary a number of shortcomings were also observed in the examined studies. However the major drawback of majority of the studies included ignoring any form of blinding and studies performing modified ITT analysis rather than true ITT analysis.

In clinical trials, blinding refers to keeping study subjects, health care team, and those assessing outcomes unaware of the assigned intervention. The aim of blinding is to reduce any potential bias and confounding factors that would minimize the likelihood of prognostic differences between the study groups. 85% of the selected RCTs (n=6) were either non blinded or unable to mention if the study subjects, health care teams, outcome assessors and data collectors/analysers were blinded or not.

Quantitative evidence demonstrates that blinding in clinical trials influence the outcomes reported. For e.g., data from meta-epidemiological studies from 250 RCTs showed that studies that did not report double blinding***** showed on an average odds ratio that were 17% higher than the double blinded studies (Schulz, Chalmers et al. 1995). Another study reported about 13% exaggeration of odds ratios in non-blinded trials and even higher bias (22%) when outcomes measured were subjective in nature (Hróbjartsson, Emanuelsson et al. 2014).

Hróbjartsson et al. observed an exaggerated effect size and higher rate of attrition in controls groups when compared to treated groups in non-blinded studies. (Hróbjartsson, Emanuelsson et al. 2014). Studies show that non-blinded assessors may also significantly favour control, rather than experimental arms, thereby underestimating the effects of an intervention(Hróbjartsson, Thomsen et al. 2013).

Furthermore, the average bias of non-binding appears to be greatest in trials with subjective outcomes. Subjective outcome such as pain scores present a great opportunity for bias (Schulz, Chalmers et al. 1995). A meta-analysis from 24 epidemiological studies reported that the average bias was observed to be greater in trials with inadequate/unclear (versus adequate) sequence generation and allocation concealment. For these characteristics, lack of/unclear double blinding (versus double blinding where both participants and personnel/assessors were blinded) showed a 23% exaggeration of intervention effects in studies with subjective outcomes. On the contrary, there was somewhat weaker evidence of such a bias in trials with objective outcomes such as mortality (Schulz, Chalmers et al. 1995). However, this finding may be inconsistent as few other meta-epidemiological studies have reported no significant differences for anticipated treatment effects based on outcomes subjectivity (Moustgaard, Clayton et al. 2020, Hróbjartsson, Thomsen et al. 2012). As for PROMs whether paper or electronic based most of the reported outcomes are subjective measures therefore it cannot be ruled out that some of the studies may have had the potential to present exaggerated results in absence of proper blinding. Our study found a number of methodological shortcomings in evaluation of the selected ePROM RCTs. These included high risk of bias in the outcomes reported due to lack of blinding. Similar anomalies have also been reported in a review by Byambasuren et al.(Kolachalama, Garg 2018). In the absence of proper blinding, we could not rule out performance bias (lack of blinding), ascertainment bias (lack of blinding), detection bias (outcome assessors not blinded) and selection bias (lack of allocation concealment) form majority of the selected studies.

Although blinding can be challenging for studies with DTx component, it is important to tacked this in a good clinical trial because of the digital placebo effect-which may arise in many mobile health interventions because patients may have a high level of affinity for their digital devices, and as such tag them with certain expectations. (Torous, Firth 2016). A good option for creating a control group could be creating a sham app that could help in counteracting digital placebo effect and facilitate gauging true efficacy of the interventions. Similarly allocation concealment in the trials could have been addressed along the similar lines as for RCTs with pharmaceutical interventions where members of the intervention team would not have any contact with the patients for app installation purposes and unfortunately no studies tried to ensure this.

Another issue with these trials especially with a small number of participants could be that treatment or control groups may been susceptible to sort of “contamination” with

other similar apps since the internet is flooding with hundreds of such freely available apps outside of the controlled conditions of the trial (Kolachalama, Garg 2018). Additionally, many trials compared outcomes to baseline values rather than the control group which again doesn't establish the true value of interventions. Many studies showed positive outcomes however these outcome measures were marginal which questions the clinical applicability of these results. Such marginal benefits or changes detected can only be re-established by rigorous testing. Another major drawback of selected ePROM studies included possibility of differential treatment of patients which again has its origins due to lack of/improper blinding among the members of the investigator team. Trial investigators includes a broad team such as trial designers, participant enrollers, randomization implementors, health-care providers, intervention counsellors, and routine data collectors and outcome assessors(Schulz, Chalmers et al. 2002). If members of investigator teams such as attending physicians, nurses or interventional counsellors are not blinded, there is a high probability that their prejudices and inclinations for or against an intervention could be directly transferred to participants (WOLF 1950). These prejudices or inclination could manifest as preferential prescription of supplementary care/treatment, participant withdrawal decisions from a trial, cross over or biased dose adjustments. Most importantly lack of blinding among the outcome assessors could precipitate as information or ascertainment bias due to differential assessment of outcomes. In a randomized, placebo-controlled multiple sclerosis trail where all patients were examined by both a blinded and an unblinded neurologist unblinded neurologists' scores demonstrated an apparent treatment benefit for certain patients however this bias was not reflected in a blinded neurologists scores. Which supports that physician blinding prevented an erroneous conclusion about treatment efficacy (Noseworthy, Ebers et al. 1994).

In light of above discussions clinical trials should endeavour to incorporate blinding into their trial designs as an essential component. Wherever possible, clinical trials should endeavour to blind 5 groups of individuals which include: participants, clinicians, data collectors, outcome adjudicators and data analysts.

When critically appraising a RCT one needs to check both its internal and external validity. Our mCASP checklist average scores for the internal validity ranged between 3-14.5 with average score of 9. In practice more than 50% of studies had total score values below average score value of 9. This showed that for >50% of the studies the inter-

nal validity represented by methodological robustness and reliability of results was below average. Weak internal validity affected the sores for external validity with a score range 0-1.5 (max. score 3) and an average value of 0.21. This implies that for >50% chosen RCTs the result represents somewhat inconclusive evidence that spell suspicion on clinical applicability of ePROMs applicability in oncology treatment and patient management settings. Supporting this interpretation roughly 60% (n=4) of studies were graded as Low quality, about 25% (n=2) as medium quality and only a single study could meet the criteria for a high-quality study with mCASP checklist scores.

Our findings from mCASP checklist tool are also supported by similar interpretations from mJalad scale, van Tulden scale and Cochrane EPOC Risk of Bias Tool that were also employed to assess the quality of RCTs. These tools also point out to already observed drawbacks with our selected RCTs such as non-blinding, lack of true ITT and variation in baselines among groups. Although mJalad scale, van Tulden scale and Cochrane EPOC Risk of Bias Tool may not be as elaborative as mCASP checklist (due to lack of many internally validity and external validity items) they do show a relatively high degree of similarly and correlation for the RCT quality parameters with about 45% of studies (N=3) being categorized as Medium-High quality and 30% (n=2) studies categorized as low quality studies.

5.1 Drawbacks of the current study

Most of the studies ePROM studies included did not report blinding the reason for this could be that sparse reporting on blinding, is common for trials. Literature shows that many investigators neglect to report whether or not their trial was blinded. For e.g. 51% trials for cystic fibrosis (total 506),33% of trials in rheumatoid arthritis (total 196), and 38% of trials in dermatology (total 68) did not report blinding status (Schulz, Chalmers et al. 2002). Thus, there is probability that blinding may have been overlooked in these trials as well.

Another drawback of the current study includes that statistics that are not only a critical part of RCTs but also influences its full spectrum right from its design, protocol development, data monitoring conduct, data management, analyses, and reporting. Statistical concepts can be difficult for non-statisticians to understand, and studies have suggested a marked increase in the complexity of statistical methods in the medical literature (Horton, Switzer 2005). We acknowledge that despite our familiarity with basic

statistical methods, our current level training in complex medical biostatistics may have been inadequate and this might have created certain biases when examining the robustness of statistical methods for the RCTs.

Although due to qualitative nature of the study it may have a limited impact on the generalizability of the findings with mere 7 RCTs being considered. However our study had already a very stringent inclusion and exclusion criteria quality that resulted in 7 RCTs do represent one of the most widely cited and popular scientific materials available till date in the field and despite its qualitative nature it does.

5.2 Ethical Considerations

The study was based exclusively on published literature in form of reviews, systemic reviews, editorials and original clinical trials articles available from PubMed and various open-source materials freely available from the internet. All data sources used in the study have been listed precisely in the reference section and to the best of the authors knowledge the intext references have been correct and precise. Furthermore, the entire thesis was run through Turnitin software to check for plagiarism. The study protocol and structure of thesis was reviewed and approved with thesis supervisor Dr. Marianne Pitkäjärvi (PhD) in accordance with Master thesis guidelines from Helsinki Metropolia University of Applied Sciences. The author declares no conflicts of interests. The author did not receive any funding from any academic institution or business establishment for completing the manuscript. In the current study YS had a role in in study design, data collection and analysis, and preparation of the manuscript.

6 CONCLUSION

It can be assumed unequivocally that DTx like ePROMs will play an important role in the management of cancer patients eventually. However, at present several barriers may significantly impede its broad clinical implementation such as lack of robust and quality data. Most of the current scientific evidence regarding the utility of ePROMs in oncology exists in form of pilot studies, feasibility studies, proof of concept studies, reports rather than RCTs which form the golden standard of a clinical evidence. Furthermore, a large on the well-being of a cancer patient.

Among the seven RCTs that were examined with the 4 critical appraisal tools about > 50% were found to have a number of serious methodological flaws such as lack of allocation concealment, difference at baseline similarity, lack of true ITT and above all overlooking of any form of blinding. These flaws may compromise the methodical quality of ePROMs RCTs and put a question mark of the internal and external validity of these RCTs.

We therefore conclude that at present the foundation of empirical evidence advocating clinical utility of ePROMs in the management of cancer patients could be somewhat shaky. Given the fact that a large portion of oncology ePROM trials conducted may not be of high quality, and of limited generalizability we recommend a more in-depth scrutiny of the clinical evidence generated by RCTs and excising caution while prescribing ePROM based DTx to patients (Duffy, J. R. 2005).

DTx products such as ePROMs having different characteristics than the traditional pharmacological components may need a diffident clinical trial design and regulatory yardsticks. The need of the hour is that regulatory agencies like European Medical Agency (EMA), FDA and profession organizations like the DTA should work together to remove the distrust and hurdles around the clinical implementation of these products so as to realize their full potential.

7 REFERENCES

ABSOLOM, K., WARRINGTON, L., HUDSON, E., HEWISON, J., MORRIS, C., HOLCH, P., CARTER, R., GIBSON, A., HOLMES, M., CLAYTON, B., ROGERS, Z., MCPARLAND, L., CONNER, M., GLIDEWELL, L., WORONCOW, B., DAWKINS, B., DICKINSON, S., HULME, C., BROWN, J. and VELIKOVA, G., 2021. Phase III Randomized Controlled Trial of eRAPID: eHealth Intervention During Chemotherapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* **39**(7), pp. 734-747.

AIYEGBUSI, O.L., NAIR, D., PEIPERT, J.D., SCHICK-MAKAROFF, K. and MUCSI, I., 2021. A narrative review of current evidence supporting the implementation of electronic patient-reported outcome measures in the management of chronic diseases. *Therapeutic advances in chronic disease,* **12**, pp. 20406223211015958.

ANDIKYAN, V., REZK, Y., EINSTEIN, M.H., GUALTIERE, G., LEITAO, M.M.,Jr, SONODA, Y., ABU-RUSTUM, N.R., BARAKAT, R.R., BASCH, E.M. and CHI, D.S., 2012. A prospective study of the feasibility and acceptability of a Web-based, electronic patient-reported outcome system in assessing patient recovery after major gynecologic cancer surgery. *Gynecologic oncology,* **127**(2), pp. 273-277.

ATKINSON, T.M., 2018. **Perceptions of Response Burden Associated with Completion of Patient-Reported Outcome Assessments in Oncology** *Values in Health,* **22**(2), pp. 225-230.

BASCH, E., DEAL, A.M., KRIS, M.G., SCHER, H.I., HUDIS, C.A., SABBATINI, P., ROGAK, L., BENNETT, A.V., DUECK, A.C., ATKINSON, T.M., CHOU, J.F., DULKO, D., SIT, L., BARZ, A., NOVOTNY, P., FRUSCIONE, M., SLOAN, J.A. and SCHRAG, D., 2016a. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* **34**(6), pp. 557-565.

BASCH, E., DEAL, A.M., KRIS, M.G., SCHER, H.I., HUDIS, C.A., SABBATINI, P., ROGAK, L., BENNETT, A.V., DUECK, A.C., ATKINSON, T.M., CHOU, J.F., DULKO, D., SIT, L., BARZ, A., NOVOTNY, P., FRUSCIONE, M., SLOAN, J.A. and SCHRAG, D., 2016b. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* **34**(6), pp. 557-565.

BASCH, E., JIA, X., HELLER, G., BARZ, A., SIT, L., FRUSCIONE, M., APPAWU, M., IASONOS, A., ATKINSON, T., GOLDFARB, S., CULKIN, A., KRIS, M.G. and SCHRAG, D., 2009. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. *Journal of the National Cancer Institute,* **101**(23), pp. 1624-1632.

BENNETT, A.V., JENSEN, R.E. and BASCH, E., 2012. Electronic patient-reported outcome systems in oncology clinical practice. *CA: a cancer journal for clinicians,* **62**(5), pp. 337-347.

BERRY, D.L., BLONQUIST, T.M., PATEL, R.A., HALPENNY, B. and MCREYNOLDS, J., 2015. Exposure to a patient-centered, Web-based intervention for managing cancer symptom and quality of life issues: impact on symptom distress. *Journal of medical Internet research,* **17**(6), pp. e136.

BIG HEALTH, 2022-last update, **Are digital therapeutics (DTx) the future of mental health care?**. Available: https://www.bighealth.com/blog/are-dtx-the-future-of-mental-health-care/ [November, 2021].

BINI, M., 2021-last update, **Health Care Trend: Digital Health in the World of COVID-19** . Available: https://www.express-scripts.com/corporate/articles/health-care-trend-digital-health-world-covid-19 [January 15, 2022].

BLIVEN, B.D., KAUFMAN, S.E. and SPERTUS, J.A., 2001. Electronic collection of health-related quality of life data: validity, time benefits, and patient preference. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation,* **10**(1), pp. 15-22.

BMJ BEST PRACTISE, 2022-last update, Appraise the evidence. Available: https://bestpractice.bmj.com/info/toolkit/learn-ebm/appraise-the-evidence/ [January 16th, 2022].

BONDEMARK, L. and RUF, S., 2015. Randomized controlled trial: the gold standard or an unobtainable fallacy? *European journal of orthodontics,* **37**(5), pp. 457-461.

BØRØSUND, E., CVANCAROVA, M., MOORE, S.M., EKSTEDT, M. and RULAND, C.M., 2014. Comparing effects in regular practice of e-communication and Web-based self-management support among breast cancer patients: preliminary results from a randomized controlled trial. *Journal of medical Internet research,* **16**(12), pp. e295.

BOYCE, M.B. and BROWNE, J.P., 2013. Does providing feedback on patient-reported outcomes to healthcare professionals result in better outcomes for patients? A systematic review. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation,* **22**(9), pp. 2265-2278.

BUERGY, D., SIEFERT, V., NEUMAIER, C., GANSLANDT, T., SPERK, E., BLESSING, M., HESSER, J., WELZEL, G., WENZ, F. and GIORDANO, F.A., 2020. Prospective trial on telemonitoring of geriatric cancer patients using handheld devices. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft ...[et al],* **196**(3), pp. 205-212.

CAMPBELL, N., ALI, F., FINLAY, A.Y. and SALEK, S.S., 2015. Equivalence of electronic and paper-based patient-reported outcome measures. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation,* **24**(8), pp. 1949-1961.

CANADIAN INSTITUTE FOR HEALTH INFORMATION, 2022-last update, Patient Reported Outcome Measures(PROMs). Available: https://www.cihi.ca/en/patient-reported-outcome-measures-proms [15th October, 2021].

CHUNG, J.Y., 2019. Digital therapeutics and clinical pharmacology. *Translational and clinical pharmacology,* **27**(1), pp. 6-11.

CLEELAND, C.S., WANG, X.S., SHI, Q., MENDOZA, T.R., WRIGHT, S.L., BERRY, M.D., MALVEAUX, D., SHAH, P.K., GNING, I., HOFSTETTER, W.L., PUTNAM, J.B.,Jr and VAPORCIYAN, A.A., 2011. Automated symptom alerts reduce postoperative symptom severity after cancer surgery: a randomized controlled clinical trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* **29**(8), pp. 994-1000.

CRITICAL APPRAISAL SKILLS PROGRAMME (CASP), 2022-last update, CASP Randomisd Controlled Trial Checklist. Available: https://casp-uk.net/casp-tools-checklists/ [January 15th, 2022].

DANG, D., DEARHOLT, S., BISSETT, K., ASCENZI, J., & WHALEN, M, ed, 2022. *Johns Hopkins evidence-based practice for nurses and healthcare professionals: Model and guidelines.* 4th edn. Sigma Theta Tau International.

DENIS, F., BASCH, E., SEPTANS, A.L., BENNOUNA, J., URBAN, T., DUECK, A.C. and LETELLIER, C., 2019. Two-Year Survival Comparing Web-Based Symptom Monitoring vs Routine Surveillance Following Treatment for Lung Cancer. *Jama,* **321**(3), pp. 306-307.

DENIS, F., LETHROSNE, C., POUREL, N., MOLINIER, O., POINTREAU, Y., DOMONT, J., BOURGEOIS, H., SENELLART, H., TRÉMOLIÈRES, P., LIZÉE, T., BENNOUNA, J., URBAN, T., EL KHOURI, C., CHARRON, A., SEPTANS, A.L., BALAVOINE, M., LANDRY, S., SOLAL-CÉLIGNY, P. and LETELLIER, C., 2017. Randomized Trial Comparing a Web-Mediated Follow-up With Routine Surveillance in Lung Cancer Patients. *Journal of the National Cancer Institute,* **109**(9), pp. 10.1093/jnci/djx029.

DENIS, F., YOSSI, S., SEPTANS, A.L., CHARRON, A., VOOG, E., DUPUIS, O., GANEM, G., POINTREAU, Y. and LETELLIER, C., 2017. Improving Survival in Patients Treated for a Lung Cancer Using Self-Evaluated Symptoms Reported Through a Web Application. *American journal of clinical oncology,* **40**(5), pp. 464-469.

DEPARTMENT OF HEALTH (UK), 2000. *The NHS Cancer Plan.* Department of Health Publication, London, UK.

DETMAR, S.B., MULLER, M.J., SCHORNAGEL, J.H., WEVER, L.D. and AARONSON, N.K., 2002. Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. *Jama,* **288**(23), pp. 3027-3034.

DIGITAL THERAPEUTICS ALLIANCE, 2019. *Digital Therapeutics Definition and Core Principles.*

DIGITAL THERAPEUTICS ALLIANCE, 2018-last update, Digital Therapeutics: Combining Technology and Evidence-based
Medicine to Transform Personalized Patient Care. Available: https://www.dtxalliance.org/wp-content/uploads/2018/09/DTA-Report_DTx-Inf [20th October, 2021].

DOYLE, C., LENNOX, L. and BELL, D., 2013. A systematic review of evidence on the links between patient experience and clinical safety and effectiveness. *BMJ open,* **3**(1), pp. e001570. doi: 10.1136/bmjopen-2012-001570.

DUFFY, S., 2021-last update, **Digital therapeutics vs. digital care: defining the landscape**. Available: https://www.statnews.com/2020/02/20/digital-therapeutics-vs-digital-care/ [November 2nd, 2021].

DUFFY, J.R., 2005. Critically appraising quantitative research. *Nursing & health sciences,* **7**(4), pp. 281-283.

DUMAIS, K.M., DIAS, N., KHURANA, L., GARY, S.T., WITHERSPOON, B., EVANS, C.J. and DALLABRIDA, S.M., 2019. Preferences for Use and Design of Electronic Patient-Reported Outcomes in Patients with Chronic Obstructive Pulmonary Disease. *The patient,* **12**(6), pp. 621-629.

ENGAN, H.K., HILMARSEN, C., SITTLINGER, S., SANDMÆL, J.A., SKANKE, F. and OLDERVOLL, L.M., 2016. Are web-based questionnaires accepted in patients attending rehabilitation? *Disability and rehabilitation,* **38**(24), pp. 2406-2412.

EVIDERA, 2020. ***Digital Therapeutics: Past Trends and Future Prospects*** UK: .

GERMAN FEDRAL MINISTRY OF HEALTH, 2020-last update, **Driving the digital transformation of Germany's healthcare system for the good of patients**. Available: https://www.bundesgesundheitsministerium.de/en/digital-healthcare-act.html [Febrary 2nd, 2021].

GILBODY, S., SHELDON, T. and HOUSE, A., 2008. Screening and case-finding instruments for depression: a meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne,* **178**(8), pp. 997-1003.

GIORDANO, F.A., WELZEL, G., SIEFERT, V., JAHNKE, L., GANSLANDT, T., WENZ, F., GROSU, A.L., HEINEMANN, F. and NICOLAY, N.H., 2020. Digital Follow-Up and the Perspective of Patient-Centered Care in Oncology: What's the PROblem? *Oncology,* **98**(6), pp. 379-385.

GWALTNEY, C.J., SHIELDS, A.L. and SHIFFMAN, S., 2008. Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: a meta-analytic review. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research,* **11**(2), pp. 322-333.

HORTON, N.J. and SWITZER, S.S., 2005. Statistical methods in the journal. *The New England journal of medicine,* **353**(18), pp. 1977-1979.

HOWELL, D., MOLLOY, S., WILKINSON, K., GREEN, E., ORCHARD, K., WANG, K. and LIBERTY, J., 2015. Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. *Annals of oncology : official journal of the European Society for Medical Oncology,* **26**(9), pp. 1846-1858.

HRÓBJARTSSON, A., EMANUELSSON, F., SKOU THOMSEN, A.S., HILDEN, J. and BRORSON, S., 2014. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind substudies. *International journal of epidemiology,* **43**(4), pp. 1272-1283.

HRÓBJARTSSON, A., THOMSEN, A.S., EMANUELSSON, F., TENDAL, B., HILDEN, J., BOUTRON, I., RAVAUD, P. and BRORSON, S., 2013. Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne,* **185**(4), pp. E201-11.

HRÓBJARTSSON, A., THOMSEN, A.S., EMANUELSSON, F., TENDAL, B., HILDEN, J., BOUTRON, I., RAVAUD, P. and BRORSON, S., 2012. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. *BMJ (Clinical research ed.),* **344**, pp. e1119.

IIVANAINEN, S., ALANKO, T., PELTOLA, K., KONKOLA, T., EKSTRÖM, J., VIRTANEN, H. and KOIVUNEN, J.P., 2019. ePROs in the follow-up of cancer patients treated with immune checkpoint inhibitors: a retrospective study. *Journal of cancer research and clinical oncology,* **145**(3), pp. 765-774.

IIVANAINEN, S., EKSTROM, J., VIRTANEN, H., KATAJA, V.V. and KOIVUNEN, J.P., 2021. Electronic patient-reported outcomes and machine learning in predicting immune-related adverse events of immune checkpoint inhibitor therapies. *BMC medical informatics and decision making,* **21**(1), pp. 205-021-01564-0.

INTERNATIONAL CONSORTIUM FOR HEALTH OUTCOMES MEASUREMENT (ICHOM), 2022-last update. Available: https://www.ichom.org/ [April, 2022].

JENSEN, R.E., SNYDER, C.F., ABERNETHY, A.P., BASCH, E., POTOSKY, A.L., ROBERTS, A.C., LOEFFLER, D.R. and REEVE, B.B., 2014. Review of electronic patient-reported outcomes systems used in cancer clinical care. *Journal of oncology practice,* **10**(4), pp. e215-22.

JONASSAINT, C.R., SHAH, N., JONASSAINT, J. and DE CASTRO, L., 2015. Usability and Feasibility of an mHealth Intervention for Monitoring and Managing Pain Symptoms in Sickle Cell Disease: The Sickle Cell Disease Mobile Application to Record Symptoms via Technology (SMART). *Hemoglobin,* **39**(3), pp. 162-168.

JOYCE, M., 2018. *Digital therapeutics: Preparing for takeoff* . McKinsey & Company.

KAIKU HEALTH WHITE PAPER, 2019. *Remote assessment enables more timely and accurate self-reporting and may avoid potential recall bias.* Helsinki: .

KAIKU HEALTH WHITE PAPER, 2017-last update, **Patient-Reported Outcome Measures in Cancer Care: A Review of the Scientific Evidence Patient-Reported Outcome Measures in Cancer Care: A Review of the Scientific Evidence** Patient-Reported Outcome Measures in Cancer care: A review of scientific evidence . Available: https://kaikuhealth.com/whitepapers/patient-reported-outcome-measures-cancer-care-review-scientific-evidence/ [October, 2021].

KIM, H.S., 2020. Apprehensions about Excessive Belief in Digital Therapeutics: Points of Concern Excluding Merits. *Journal of Korean medical science,* **35**(45), pp. e373.

KIM, K.S., JO, J.K., CHUNG, J.H., KIM, J.H., CHOI, H.Y. and LEE, S.W., 2017. Quality analysis of randomized controlled trials in the International Journal of Impotence Research: quality assessment and relevant clinical impact. *International Journal of Impotence Research,* **29**(2), pp. 65-69.

KOLACHALAMA, V.B. and GARG, P.S., 2018. Machine learning and medical education. *NPJ digital medicine,* **1**, pp. 54-018-0061-1. eCollection 2018.

KONGSVED, S.M., BASNOV, M., HOLM-CHRISTENSEN, K. and HJOLLUND, N.H., 2007. Response rate and completeness of questionnaires: a randomized study of Internet versus paper-and-pencil versions. *Journal of medical Internet research,* **9**(3), pp. e25.

KOTRONOULAS, G., KEARNEY, N., MAGUIRE, R., HARROW, A., DI DOMENICO, D., CROY, S. and MACGILLIVRAY, S., 2014. What is the value of the

routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* **32**(14), pp. 1480-1501.

KROENKE, K. and CHEVILLE, A.L., 2016. Symptom Improvement Requires More Than Screening and Feedback. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* **34**(27), pp. 3351-3352.

LIANG, W., GUAN, W., CHEN, R., WANG, W., LI, J., XU, K., LI, C., AI, Q., LU, W., LIANG, H., LI, S. and HE, J., 2020. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *The Lancet.Oncology,* **21**(3), pp. 335-337.

LIVNEH, H., 2000. Psychosocial adaptation to cancer: the role of coping strategies. *Journal of Rehabilitation,* **66**, pp. 40-60.

LOCKLEAR, T., 2014. Strategies for Overcoming Barriers to the Implementation of Patient-Reported Outcomes Measures. *Rethinking Clinical Trilas:A living book of pragmatic clinical trials.* NIH HCS Collaboratory, .

MAGUIRE, R., MCCANN, L., KOTRONOULAS, G., KEARNEY, N., REAM, E., ARMES, J., PATIRAKI, E., FURLONG, E., FOX, P., GAIGER, A., MCCRONE, P., BERG, G., MIASKOWSKI, C., CARDONE, A., ORR, D., FLOWERDAY, A., KATSARAGAKIS, S., DARLEY, A., LUBOWITZKI, S., HARRIS, J., SKENE, S., MILLER, M., MOORE, M., LEWIS, L., DESOUZA, N. and DONNAN, P.T., 2021. Real time remote symptom monitoring during chemotherapy for cancer: European multicentre randomised controlled trial (eSMART). *BMJ (Clinical research ed.),* **374**, pp. n1647.

MEIRTE, J., HELLEMANS, N., ANTHONISSEN, M., DENTENEER, L., MAERTENS, K., MOORTGAT, P. and VAN DAELE, U., 2020. Benefits and Disadvantages of Electronic Patient-reported Outcome Measures: Systematic Review. *JMIR perioperative medicine,* **3**(1), pp. e15588.

MELNYK, B. M., & FINEOUT-OVERHOLT, E., ed, 2015. *Making the case for evidence-based practice and cultivating a spirit of inquiry. Evidence-based practice in nursing & healthcare: A guide to best practice*
. 3rd edn. Philadelphia, PA: Wolters Kluwer.

MORELLE MENEZES, A., 2020. **Patient reported outcome measure applicability in clinical oncology**. *Brazilian Jounal of Oncology,* .

MOUSTGAARD, H., CLAYTON, G.L., JONES, H.E., BOUTRON, I., JØRGENSEN, L., LAURSEN, D.R.T., OLSEN, M.F., PALUDAN-MÜLLER, A., RAVAUD, P., SAVOVIĆ, J., STERNE, J.A.C., HIGGINS, J.P.T. and HRÓBJARTSSON, A., 2020. Impact of blinding on estimated treatment effects in randomised clinical trials: meta-epidemiological study. *BMJ (Clinical research ed.),* **368**, pp. l6802.

NATIONAL INSTITUTE FOR HEALTH & CARE EXCELLENCE, 2022-last update, **Medtech innovation briefings**. Available: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-advice/medtech-innovation-briefings [February 5th, 2022].

NOSEWORTHY, J.H., EBERS, G.C., VANDERVOORT, M.K., FARQUHAR, R.E., YETISIR, E. and ROBERTS, R., 1994. The impact of blinding on the results of a randomized, placebo-controlled multiple sclerosis clinical trial. *Neurology,* **44**(1), pp. 16-20.

OREMUS, M., WOLFSON, C., PERRAULT, A., DEMERS, L., MOMOLI, F. and MORIDE, Y., 2001. Interrater reliability of the modified Jadad quality scale for systematic reviews of Alzheimer's disease drug trials. *Dementia and geriatric cognitive disorders,* **12**(3), pp. 232-236.

OTSUKA AMERICA PHARMACEUTICAL, 2021-last update, IMPORTANT SAFETY INFORMATION and INDICATIONS for ABILIFY MYCITE. Available: https://www.abilifymycite.com/ [October 10, 2021].

PAPPOT, H., BAEKSTED, C.W., NISSEN, A., KNOOP, A., MITCHELL, S.A., CHRISTENSEN, J., HJOLLUND, N.H. and JOHANSEN, C., 2021. Clinical effects of assessing electronic patient-reported outcomes monitoring symptomatic toxicities during breast cancer therapy: a nationwide and population-based study. *Breast cancer (Tokyo, Japan),* **28**(5), pp. 1096-1099.

PARIKH, R.B., MANZ, C., CHIVERS, C., REGLI, S.H., BRAUN, J., DRAUGELIS, M.E., SCHUCHTER, L.M., SHULMAN, L.N., NAVATHE, A.S., PATEL, M.S. and O'CONNOR, N.R., 2019. Machine Learning Approaches to Predict 6-Month Mortality Among Patients With Cancer. *JAMA network open,* **2**(10), pp. e1915997.

PATEL, N.A. and BUTTE, A.J., 2020. Characteristics and challenges of the clinical pipeline of digital therapeutics. *NPJ digital medicine,* **3**(1), pp. 159-020-00370-8.

PATRICK, D.L., FERKETICH, S.L., FRAME, P.S., HARRIS, J.J., HENDRICKS, C.B., LEVIN, B., LINK, M.P., LUSTIG, C., MCLAUGHLIN, J., RIED, L.D., TURRISI, A.T.,3rd, UNÜTZER, J., VERNON, S.W. and NATIONAL INSTITUTES OF HEALTH STATE-OF-THE-SCIENCE PANEL, 2003. National Institutes of Health State-of-the-Science Conference Statement: Symptom Management in Cancer: Pain, Depression, and Fatigue, July 15-17, 2002. *Journal of the National Cancer Institute,* **95**(15), pp. 1110-1117.

RASTEGAYEVA, I., 2019. ***The Rise of Digital Therapeutics***.

RICHTER, J.G., BECKER, A., KOCH, T., NIXDORF, M., WILLERS, R., MONSER, R., SCHACHER, B., ALTEN, R., SPECKER, C. and SCHNEIDER, M., 2008. Self-assessments of patients via Tablet PC in routine patient care:

comparison with standardised paper questionnaires. *Annals of the Rheumatic Diseases,* **67**(12), pp. 1739-1741.

RIVA, J.J., MALIK, K.M., BURNIE, S.J., ENDICOTT, A.R. and BUSSE, J.W., 2012. What is your research question? An introduction to the PICOT format for clinicians. *The Journal of the Canadian Chiropractic Association,* **56**(3), pp. 167-171.

RUBENSTEIN, L.V., MCCOY, J.M., COPE, D.W., BARRETT, P.A., HIRSCH, S.H., MESSER, K.S. and YOUNG, R.T., 1995. Improving patient quality of life with feedback to physicians about functional status. *Journal of general internal medicine,* **10**(11), pp. 607-614.

SCHICK-MAKAROFF, K. and MOLZAHN, A., 2014. Brief communication: patient satisfaction with the use of tablet computers: a pilot study in two outpatient home dialysis clinics. *Canadian journal of kidney health and disease,* **1**, pp. 22-014-0022-9. eCollection 2014.

SCHOUGAARD, L.M., LARSEN, L.P., JESSEN, A., SIDENIUS, P., DORFLINGER, L., DE THURAH, A. and HJOLLUND, N.H., 2016. AmbuFlex: tele-patient-reported outcomes (telePRO) as the basis for follow-up in chronic and malignant diseases. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation,* **25**(3), pp. 525-534.

SCHULZ, K.F., CHALMERS, I. and ALTMAN, D.G., 2002. The landscape and lexicon of blinding in randomized trials. *Annals of Internal Medicine,* **136**(3), pp. 254-259.

SCHULZ, K.F., CHALMERS, I., HAYES, R.J. and ALTMAN, D.G., 1995. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Jama,* **273**(5), pp. 408-412.

SCHWARTZBERG, L., 2016. Electronic Patient-Reported Outcomes: The Time Is Ripe for Integration Into Patient Care and Clinical Research. *American Society of Clinical Oncology educational book.American Society of Clinical Oncology.Annual Meeting,* **35**, pp. e89-96.

SEPAH, S.C., JIANG, L. and PETERS, A.L., 2015. Long-term outcomes of a Web-based diabetes prevention program: 2-year results of a single-arm longitudinal study. *Journal of medical Internet research,* **17**(4), pp. e92.

SHARMA, A., HARRINGTON, R.A., MCCLELLAN, M.B., TURAKHIA, M.P., EAPEN, Z.J., STEINHUBL, S., MAULT, J.R., MAJMUDAR, M.D., ROESSIG, L., CHANDROSS, K.J., GREEN, E.M., PATEL, B., HAMER, A., OLGIN, J., RUMSFELD, J.S., ROE, M.T. and PETERSON, E.D., 2018. Using Digital Health Technology to Better Generate Evidence and Deliver Evidence-Based Care. *Journal of the American College of Cardiology,* **71**(23), pp. 2680-2690.

STEPHEN H. HALPERN, M. JOANNE DOUGLAS, 2005.
Jadad scale for reporting randomized controlled trials. *Evidence-based Obstetric Anesthesia .* Blackwell Publishing Ltd, .

STERN, A.D., GORDON, W.J., LANDMAN, A.B. and KRAMER, D.B., 2019. Cybersecurity features of digital medical devices: an analysis of FDA product summaries. *BMJ open,* **9**(6), pp. e025374-2018-025374.

TAENZER, P., BULTZ, B.D., CARLSON, L.E., SPECA, M., DEGAGNE, T., OLSON, K., DOLL, R. and ROSBERGER, Z., 2000. Impact of computerized quality of life screening on physician behaviour and patient satisfaction in lung cancer outpatients. *Psycho-oncology,* **9**(3), pp. 203-213.

TANGARI, G., IKRAM, M., IJAZ, K., KAAFAR, M.A. and BERKOVSKY, S., 2021. Mobile health and privacy: cross sectional study. *BMJ (Clinical research ed.),* **373**, pp. n1248.

THE JOANNA BRIGGS INSTITUTE, 2019-last update, The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews: Checklist for Randomized Controlled Trials. Available: https://jbi.global/sites/default/files/2019-05/JBI_RCTs_Appraisal_tool2017_0.pdf [January 15th, 2022].

TOROUS, J. and FIRTH, J., 2016. The digital placebo effect: mobile mental health meets clinical psychiatry. *The lancet.Psychiatry,* **3**(2), pp. 100-102.

TOUVIER, M., MÉJEAN, C., KESSE-GUYOT, E., POLLET, C., MALON, A., CASTETBON, K. and HERCBERG, S., 2010. Comparison between web-based and paper versions of a self-administered anthropometric questionnaire. *European journal of epidemiology,* **25**(5), pp. 287-296.

VAN TULDER, M., FURLAN, A., BOMBARDIER, C., BOUTER, L. and EDITORIAL BOARD OF THE COCHRANE COLLABORATION BACK REVIEW GROUP, 2003. Updated method guidelines for systematic reviews in the cochrane collaboration back review group. *Spine,* **28**(12), pp. 1290-1299.

VELIKOVA, G., BOOTH, L., SMITH, A.B., BROWN, P.M., LYNCH, P., BROWN, J.M. and SELBY, P.J., 2004. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* **22**(4), pp. 714-724.

VELIKOVA, G., WRIGHT, E.P., SMITH, A.B., CULL, A., GOULD, A., FORMAN, D., PERREN, T., STEAD, M., BROWN, J. and SELBY, P.J., 1999. Automated collection of quality-of-life data: a comparison of paper and computer touch-screen questionnaires. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* **17**(3), pp. 998-1007.

WARRINGTON, L., ABSOLOM, K. and VELIKOVA, G., 2015. Integrated care pathways for cancer survivors - a role for patient-reported outcome measures

and health informatics. *Acta Oncologica (Stockholm, Sweden),* **54**(5), pp. 600-608.

WELDRING, T. and SMITH, S.M., 2013. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). *Health services insights,* **6**, pp. 61-68.

WIEDERHOLD, B.K., 2021. Data-Driven Digital Therapeutics: The Path Forward. *Cyberpsychology, behavior and social networking,* **24**(10), pp. 631-632.

WILLIAMS, K., 2016. *Patient-reported outcome measures.* Australia: Australian Commission on Safety and Quality in Health Care.

WINTNER, L.M., SZTANKAY, M., AARONSON, N., BOTTOMLEY, A., GIESINGER, J.M., GROENVOLD, M., PETERSEN, M.A., VAN DE POLL-FRANSE, L., VELIKOVA, G., VERDONCK-DE LEEUW, I., HOLZNER, B. and EORTC QUALITY OF LIFE GROUP, 2016. The use of EORTC measures in daily clinical practice-A synopsis of a newly developed manual. *European journal of cancer (Oxford, England : 1990),* **68**, pp. 73-81.

WOLF, S., 1950. Effects of suggestion and conditioning on the action of chemical agents in human subjects; the pharmacology of placebos. *The Journal of clinical investigation,* **29**(1), pp. 100-109.

WORLD HEALTH ORGANISATION, 2022-last update, Cancer Key Facts. Available: https://www.who.int/news-room/fact-sheets/detail/cancer [October, 2021].

YU, J., OUYANG, W., CHUA, M.L.K. and XIE, C., 2020. SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China. *JAMA oncology,* **6**(7), pp. 1108-1110.

8 APPENDIX

8.1 Template mCASP Checklist

		Check List Questions							
		Part A (Study Design)							
Q1	Did the study address a clearly focused research question?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0
Q2	Does the researcher identify what is known and not known about the problem?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0
Q3	Does the researcher identify how the study will address any gaps in knowledge?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0
		Part B (Methodology) Internal Validity							
Q4	Was the assignment of participants to interventions randomised?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0
Q4a	Was Randomisation process appropriate?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0
Q5	Was blinding performed?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0
Q5a	Were the investigators 'blind' to the intervention they were giving to participants?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0
Q5b	Were the people assessing/analysing outcome/s 'blinded'?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0
Q6	Were the study groups similar(baseline) at the start of the randomised controlled trial?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0
Q7	Was sample size sufficient based on study design and rationale?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0
Q8	Are data collection methods described clearly ?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0
Q9	Were instruments used to measure the	Yes	1	No	-1	Somewhat	0.5	Can´t say	0

	outcomes valid and reliable?								
Q10	If surveys or questionnaires were used, was the response rate > 25%?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0
	Section C (Results) Internal Validity								
Q11	Were the results presented clearly?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0.25
Q12	Were the effects of intervention reported comprehensively?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0.25
Q13	Was the precision of the estimate of the intervention or treatment effect reported (P values, CI, SD)?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0.25
Q14	Were all participants who entered the study accounted for at its conclusion?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0.25
Q15	Did the RCT analyse in groups to which people were randomised to (intention-to-treat analysis)?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0.25
Q16	Was there any loss of follow up(attrition bias)? If yes was it < 20% ?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0.25
Q17	Were study limitations identified and addressed	Yes	1	No	-1	Somewhat	0.5	Can´t say	0.25
	Part D (Applicability of results) External Validity								
Q18	Do the benefits of the experimental intervention outweigh the harms and costs?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0.25
Q19	Can the results be applied to your local population/in your context?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0.25

Q20	Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	Yes	1	No	-1	Somewhat	0.5	Can´t say	0.25
Scoring	Each questions has 4 options with a certain score points : 1.Yes (score points= 1) 2. No (score points=0) 3. Somewhat (score point = 0.5) 4. cant´s say (score point =0.25). Each question carried a maximum score of 1 (except for questions from section A which carried maximum of 0.5 marks) and minimum score of zero.								
Quality	There were a total of 23 questions with a maximum score of 23 points. Studies with score points ≥17.25 were classified as high quality (H) while those between 11.5-17 as of medium quality (M) and studies with a score of <11.5 as low quality (L) Two questions were avoided from the checklist: “Were the participants blind to the intervention they were given?” Since it was very difficult to blind the patients given the nature of intervention “Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?” Apparently IV groups receive better attention from the healthcare team as compared to usual care groups which results in better outcomes.								

8.2 Template Modified Jadad Scale

Item	Response	Score	Response	Score	Response	Score
1.Was the study described as randomized?	Yes	1	No	0	Not described	0
2. Was the method of randomization appropriate?	Yes	1	No	-1		0
3. Was the study described as blinded (Were both the patient and the assessor appropriately blinded)?	Yes	1	No	0		0
4.Was the method of blinding appropriate[a]?	Yes	1	No	-1	Not described	0

5.Was there a description of withdrawls and dropouts	Yes		No	0		NA
6.Was there a clear description of the inclusion/exclusion criteria?	Yes		No	0		NA
7.Was the method used to assess adverse effects described?*	Yes		No	0		
8.Was the methods of statistical analysis described?	Yes		No	0		NA
	Total Score	8	No	0 to -2		0
Grading	High quality studies 4-7; Low quality studies: 0-3					
[a]double blind score point 1 single blind score point 0.5,*item excluded due to non-applicability						

[a] **where both participants and personnel/assessors are blinded**

8.3 Template van Tulder Scale

Template

A	Was Method of Randomisation Adequate?	Yes/No/Don't know
B	Was treatment allocation concealed?	Yes/No/Don't know
C	Were the groups similar at baseline regarding the most important prognostic indicators?	Yes/No/Don't know
D	Was the patient blinded to the intervention?	Yes/No/Don't know
E	Was the care provider blinded to the intervention?	Yes/No/Don't know
F	Was the outcome assessor blinded to the intervention?	Yes/No/Don't know
G	Were co-interventions avoided or similar	Yes/No/Don't know
H	Was the compliance acceptable in all group?	Yes/No/Don't know
I	Was the drop-out described and acceptable?	Yes/No/Don't know
J	Was the timing of the outcome assessment in all groups similar?	Yes/No/Don't know

K	Did the analysis include an intention-to-treat analysis?	Yes/No/Don´t know

8.4 Template EPOC Quality Assessment Form /Risk of Bias Tool

Cochrane Effective Practice and Organisation of Care (EPOC) Risk of Bias Tool – *EPOC modified tool for assessing risk of bias for randomised trials.* EPOC Quality Assessment Form /Risk of Bias Tool - Part A			
Part A assesses the risk of bias that may be encountered during recruiting participants; allocating to intervention and control groups; inadequate implementation of the intervention; and confounding. Using the guidance provided at the end of this form, select either “high”, “low” or “unclear” for each judgment			
Domain	Risk of Bias		
	High	Low	Uncertain
1. Random sequence generation	Scored as “High risk” when a non-random method is used (e.g. performed by date of admission). Non-randomised trials and controlled before-after studies should be scored “High risk”.	Score “Low risk” if a random component in the sequence generation process is described (e.g. Referring to a random number table).	Score “Unclear risk” if not specified in the paper.
2. Allocation concealment	Controlled before-after studies should be scored “High risk”.	Score “Low risk” if the unit of allocation was by institution, team or professional and allocation was performed on all units at the start of the study; or if the unit of allocation was by patient or episode of care and there was some form of centralised randomisation scheme, an on-site computer system or sealed opaque envelopes were used.	Score “Unclear risk” if not specified in the paper. .
3. Baseline characteristics similar	Score “High risk” if there is no report of characteristics in text or tables or if there are differences between control and intervention providers. Note that in some cases imbalance in patient characteristics	Score “Low risk” if baseline characteristics of the study and control providers are reported and similar.	“Unclear risk” if it is not clear in the paper (e.g. characteristics are mentioned in text but no data were presented).

	may be due to recruitment bias whereby the provider was responsible for recruiting patients into the trial.		
4. Knowledge of the allocated interventions adequately prevented during the study [1,2]	Score “High risk” if the outcomes were not assessed blindly.	Score “Low risk” if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective, e.g. length of hospital stay. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors.	Score “Unclear risk” if not specified in the paper
5. Other risks of bias *Bias due to problems not covered elsewhere in the table.*	Score “High risk” if any important concerns about bias not addressed above. If questions/entries were pre-specified in the study’s protocol, responses should be provided for each question/entry.	Score “Low risk” if there is no evidence of other risk of biases	Score “Unclear risk” if there may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias.
Part B of this form will assess the Risk of bias for the domains for each group of outcomes. Please indicate the specific outcome and complete the assessment for each.			
6. Protection against contamination	Score “High risk” if it is likely that the control group received the intervention (e.g. if patients rather than professionals were randomised or there was evidence of interaction between the two groups)	Score “Low risk” if allocation was by community, institution, or practice, and it is unlikely that the control group received the intervention.	“Unclear risk” if professionals were allocated within a clinic or practice and it is possible that communication between intervention and control professionals could have occurred (e.g. physicians within practices were allocated to intervention or control)
7. Selective outcome reporting	Score “High risk” if some important outcomes are subsequently omitted from the results.	Score “Low risk” if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section).	Score “Unclear risk” if not specified in the paper. For further information see Chapter 13 of the Cochrane handbook: Assessing risk

			of bias due to missing results in a synthesis
8. Baseline outcome measurements similar[1,3]	Score “High risk” if important differences were present and not adjusted for in analysis.	Score “Low risk” if performance or patient outcomes were measured prior to the intervention, and no important differences were present across study groups. In randomised trials, score “Low risk” if imbalanced but appropriate adjusted analysis was performed (e.g. Analysis of covariance).	
9. Incomplete outcome data[1]	Score “High risk” if missing outcome data was likely to bias the results.	Score “Low risk” if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the intervention and control groups or the proportion of missing data was less than the effect	Score “Unclear risk” if not specified in the paper (Do not assume 100% follow up unless stated explicitly).

[1]If some primary outcomes were imbalanced at baseline, assessed blindly or affected by missing data and others were not, each primary outcome can be scored separately.

[2]This refers to blinding of participants and personnel and blinding of outcome assessment.

[3]If “Unclear risk” or “High risk”, but there is sufficient data in the paper to do an adjusted analysis (e.g. Baseline adjustment analysis or Intention to treat analysis) the criteria should be re scored as “Low risk”.