Collaborative Network to Take Responsibility for oral AntiCancer Therapy (CONTACT): Study-protocol investigating the impact of a care pathway

Abstract

Aim

To evaluate the effectiveness, feasibility, meaningfulness and appropriateness of the development and implementation of a transmural care pathway in four hospitals in Flanders to improve self-management support in healthcare professionals and self-management in patients treated with oral anticancer drugs.

Design

A multicenter, prospective, interventional before-after study.

Method

The development and implementation of the care pathway is based on the 7-phase method by Vanhaecht et al, 2011. Before and after, the care process will be evaluated from the perspective of patients, healthcare professionals in the hospital and from primary care, and the available evidence. In both study-parts, a mixed methods approach will be used including observations, semi-structured interviews, focus groups and validated questionnaires for outcome assessments. The primary outcome is self-management in patients and self-efficacy and perception towards self-management in healthcare professionals. This study was funded in October 2015 and has been approved by the Ethics Committee in June 2016.

Discussion

Due to the growing number of patients taking oral anticancer drugs, there is need for a rigorous study that aims to optimize self-management in patients and self-management support provided by an interdisciplinary team of healthcare professionals (including oncology nurses and clinical nurse specialists). The care pathway should therefore consist of effective self-management supporting interventions and should clearly define the role of all stakeholders.

Impact

This study attempts to obtain standardization, uniformity and continuity of self-management support provided by healthcare professionals to patients on oral anticancer drugs with the aim to achieve an adequate level of self-management.

Trial registration: clinicaltrials.gov NCT02861209

Keywords: oral anticancer drugs, care pathway, self-management, adherence, before-after study, self-management support, advanced nursing, oncology nursing

INTRODUCTION

Over the last decades, the development and use of oral anticancer drugs (OACD) have increased exponentially (O'Neill & Twelves, 2002; Weingart et al., 2008). In contrast to intravenous (IV) therapies - that are administered in a controlled environment by specialized healthcare professionals (HCP) - oral anticancer therapies are provided at home by the patient and sometimes by informal caregivers. Hence, patients and their caregivers play a substantial role in their treatment (Kav et al., 2008).

Given the oral administration, OACD offers greater flexibility and convenience, fewer hospital visits, no need for IV access, and a greater sense of independence compared to IV therapies (Bedell, 2003; Weingart et al., 2008). It is therefore not surprising that patients prefer the oral administration to IV therapy (Fallowfield et al., 2006; Liu et al., 1997; Twelves et al., 2006).

Besides these advantages, the use of OACD also poses important challenges for patients. For the majority of OACD, complex dosing regimens need to be followed, that often have to be integrated in an existing therapy plan for the treatment of comorbidities (Weingart et al., 2008). Next, patients should be aware of how to handle OACD safely, how to manage possible side effects and when to contact a specialized HCP in case of serious toxicities and other problems or questions (Findlay, von Minckwitz, & Wardley, 2008; Weingart et al., 2008). Furthermore, issues related to adherence should not be neglected (Moore, 2007). Various studies have been performed in patients following an oral anticancer treatment studying the extent of non-adherence and its contributing factors (Bassan et al., 2014; Verbrugghe et al., 2016). A systematic review (Greer et al., 2016) reports adherence rates between 46% – 100% depending on the studied sample, the calculation-method for adherence, the studied OACD, assessment measures, and the follow-up period. Taking all these challenges into consideration and given the fact that OACD often have to be taken on a long-term basis, achieving an adequate level of patient self-management is essential for a successful oral anticancer treatment.

Given the aforementioned challenges for patients, shifts in traditional roles and responsibilities of HCPs are needed. In IV cancer care, HCPs take the lead and treatment is organised in one single setting around fixed dosing times. This is in contrast with oral anticancer treatment, where the patient takes responsibility for the daily intake, at home, without direct contact with HCPs. Therefore, re-organisation of current care processes for patients treated with OACD might be primordial to ensure optimal and safe cancer care, including patient self-management.

Background

Different approaches and interventions have been described on how to improve quality and safety of oral anticancer treatments and self-management. A recent systematic review by Zerillo et al., 2018 (Zerillo et al., 2018) indicates that interventions to improve care for patients treated with OACD, can range over the total process of drug delivery: prescribing, preparation/dispensing, education, administration, monitoring, and storage. The largest amount of interventions focusses on education and monitoring of care and were usually delivered by nurses and/or pharmacists. Overall, the interventions tested consisted of algorithms to track side effects, tools to assess adherence, intermediate phone calls, and home visits (Zerillo et al., 2018).

Many research papers on self-management support (SMS) stress the importance of patient education (Hartigan, 2003; Kahn et al., 2017; Winkeljohn, 2010). However, in order to realize effective SMS, a multi-faceted approach focussing on 1) disease and symptom management, 2) specific needs regarding the drug (e.g. dose regimen, side effects), and 3) emotional and role management is needed (Institute of Medicine, 2004; Tadic et al., 2015).

In the care for patients treated with OACD, the key players are physicians and oncology nurses (Kav et al., 2008). In Europe, different National Cancer Plans have been implemented with the aim to provide evidence-based strategies for the early detection, diagnosis, treatment, rehabilitation, palliation in cancer care, and for cancer-research (EPAAC, 2015). In some cancer plans, the role of nurses in patient education and in providing ongoing support as a coordinator of the care plan has been stated (EPAAC, 2015). The Belgian Cancer plan also states the implementation of psychosocial support by specifically trained psychologists, social workers, or nurses, but does not specifically focus on the role of the clinical pharmacist (Belgian Cancer Center, 2008). Nonetheless, there is growing evidence that the involvement of clinical pharmacists in oncology is linked to a timely detection of and intervention in medication-related problems. Clinical pharmacists can also play a role in patient education and follow-up (Holle et al., 2017; Zerillo et al., 2018).

Due to the home-based character of an oral anticancer treatment, it is obvious that the HCPs involved in support of patient self-management go far beyond the oncology team from the hospital (Bedell, 2003). Providing intermediate follow-up by HCPs from primary care is essential, not only to achieve an adequate level of self-management in patients taking OACD, but also to decrease the burden in oncology centres in the follow-up of this growing patient population. Therefore, involvement of primary caregivers (general practitioners, community pharmacists, home care nurses) in between hospital-based follow-up consultations, is of high

89 importance. This implies that care for cancer patients should be performed by a transmural, interdisciplinary
90 team in which all stakeholders should be aware of each other's role in the care process. The need for a shared
91 care model has already been stressed (Oakley et al., 2010). However, a seamless collaboration between hospitals
92 and primary caregivers is currently not stably implemented. Various barriers for this collaboration have been
93 listed, such as lack of communication, absence of clear care plans and insufficient coordination of care (Aubin et
94 al., 2012).

95 All the aforementioned challenges and shortcomings illustrate the need for a reorganization of current
96 care processes for patients treated with OACD, including an audit of current workflows to determine barriers
97 and facilitators in the interdisciplinary care process and to find solutions for optimization (Salgado et al., 2017).
98 One possible method to accomplish this reorganization is the development and implementation of a care
99 pathway (Vanhaecht et al., 2010). A care pathway can be defined as a complex intervention for the mutual
100 decision-making and organization of care processes for a well-defined group of patients during a well-defined
101 period (Vanhaecht et al., 2012). Care pathways can be used to optimize care processes when problems arise on
102 communication, coordination, standardization and monitoring of care for a specific group of patients (Vanhaecht
103 et al., 2012). A care pathway for patients treated with OACD, should therefore consist of all relevant sustainable
104 interventions that cover the continuum of the medicines' pathway with the aim to support self-management
105 (Zerillo et al., 2018). The role of each stakeholder in the different interventions should be well-described including
106 communication strategies between HCPs from primary and secondary care (Oakley et al., 2010).

107 This article describes the protocol of a before-after study on the development, implementation and
108 evaluation of a care pathway for patients treated with OACD in four oncology centres in Belgium.

THE STUDY

Aims

The aim of this before-after study is to investigate the Feasibility, Appropriateness, Meaningfulness and Effectiveness (FAME-model) of developing and implementing a care pathway for patients treated with OACD (Pearson et al., 2005). To investigate the impact of the care pathway (Effectiveness), the level of patient self-management will be used as the primary outcome.

The study consists of three major chronologic parts with different aims:

- Part 1: baseline measurements ('before study'), to investigate the Appropriateness and need for a care pathway for patients on OACD. The main aim of this part is to determine outcomes, barriers and facilitators of the current care process as experienced by patients treated with OACD and by HCPs from primary and secondary care. Additionally, we aim to investigate to which extent the current care is in accordance with the available evidence regarding care for patients on OACD care. The results of these baseline assessments can subsequently be used in the conceptualization of the care pathway in each hospital (part 2).
- Part 2: development-phase, including an investigation of the Feasibility of a care pathway. The aim of this part is to develop and co-design a tailored care pathway in each participating hospital (taking into account the results from part 1) and to investigate the feasibility of developing a care pathway with a specific focus on barriers and facilitators that arise during the development process. Furthermore, we aim to investigate the impact of training for HCPs on knowledge regarding OACD and SMS-competencies, as a prerequisite for care delivery.
- Part 3: evaluation phase ('after study') to investigate the Meaningfulness and Effectiveness of the implemented care pathway. More specific, the aim of this part is to study intervention fidelity, perceived benefits of the care pathway (as experienced by HCPs), and impact on patient outcomes and patient experiences.

Study design

A prospective multicentre before-after study will be conducted between November 2015 and November 2022. The intervention is the implementation of a care pathway in four hospitals in Belgium. The impact of the care

pathway will be investigated by comparing the data obtained from patients and HCPs before and after the implementation. The general framework throughout the study will be the 7-phase model by Vanhaecht et al., 2012 (Vanhaecht et al., 2012). This framework offers a systematic approach to support an interdisciplinary team in the development and evaluation of new care pathways. Figure 1 shows a general overview of the different phases of the 7-phase model, adapted to the setting of the study, and aggregated into the three main parts of the study, as mentioned before.

PART 1. Before-study: investigation of current care

The before-study aims to investigate the Appropriateness and need for a care pathway for patients on OACD. The before-study includes the first three phases of the 7-phase model (figure 1). Phase 1 and 2 aim (1) to determine in each hospital whether a care pathway is needed, (2) to appoint a local study-coordinator, (3) to set up an interdisciplinary project team including relevant stakeholders involved in the care for patients on OACD and representatives from primary care for the further development of the care pathway, and (4) to decide for which oncology departments the care pathway will first be developed. Building an interdisciplinary project team is the first crucial step in the development of a care pathway (Raijmakers et al., 2015; Vitaz, McIlvoy et al., 2001). Not only disciplines with a potential role within the care pathway but also members of the hospital management team should be represented (Raijmakers et al., 2015).

Phase 3 "detailed mapping of current practice" aims to gain profound insight in the current care process. In implementation research, it is crucial to have insight into practice patterns and other contextual factors that might influence the conceptualization of complex interventions (i.e. care pathway) (Pfadenhauer et al., 2017). Therefore, an in-depth investigation of systems of care in the hospital and of the collaboration with primary care is needed. Based on these insights, a tailored care pathway respecting the individual context of each setting can be subsequently developed (part 2). The 7-phase model suggests to investigate current practice from four different perspectives (figure 1). For this study, we added a fifth perspective "independent observer" in which the research team will perform observations at the oncology department in order to familiarize with the workflow in each hospital. In phase 3, a mixed-methods approach will be used; the different assessments performed within this phase are outlined in figure 1 and described in detail below.

PERSPECTIVE 1: OWN ORGANIZATION AND TEAM

Sample of participants, data collection and procedures

To gain insight in current care from the perspective of the organization and team, healthcare professionals from each hospital (HCP H) as well as staff members (STAFF) will be recruited (figure 2). For HCP H, a convenience sampling method will be used to recruit HCPs who are currently involved in the care process for patients treated with OACD (mainly physicians, (specialized) oncology nurses and head of nursing staff) as well as HCPs that might be involved in the new care pathway (psychologist, clinical pharmacist). Launch calls and a presentation of the aims and protocol of the study will be used to recruit HCPs.

For this perspective, both quantitative and qualitative data will be obtained.

First, teams of HCP (HCP H) as well as staff members (STAFF) will be asked to complete the Care Process Self Evaluation Tool (CPSET) The CPSET is a validated questionnaire containing 29 items that helps a team (or a potential team) to score the current organization of the care process in five areas: person-centeredness of the organization, coordination within the process, communication with patients and families, cooperation with primary care, and follow-up of the care process (Vanhaecht et al., 2007; Vanhaecht et al., 2012). Each discipline should come to one completed CPSET based on a mutual agreement on each item of the scale. The obtained answers will be entered in an online survey (Limesurvey®).

Second, individual HCPs (HCP H) will be asked to complete the validated Clinician Support for Patient Activation Measure – questionnaire (CS PAM) which explores the beliefs of HCPs on patient self-management and the Self-Efficacy and Performance in Self-management Support instrument (SEPSS-36) which assesses self-efficacy and performance of SMS (table 1) (Duprez et al., 2016; Rademakers et al., 2015). Additionally, socio-demographics will be asked such as age, gender, educational level, employment.

Qualitative data will be collected by means of semi-structured interviews performed in a sub sample of participating HCPs (HCP H) from different disciplines. The interviews aim to gain in-depth insight into practice patterns of current practice including barriers and facilitators. Healthcare professionals will also be asked to express their dreams for a future care pathway. A qualitative approach is an appropriate method to gain insight into feelings, perspectives and experiences of participants (Holloway & Wheeler, 2010). A topic guide, tailored to the HCPs, will be used. Semi-structured interviews will be audio recorded and transcribed verbatim. Interviews will be performed until data-saturation has occurred.

PERSPECTIVE 2: PATIENTS

Sample of participants, data collection and procedures

Two different methods will be used to investigate patients' perspective on current care: 1) semi-structured interviews and 2) outcome assessments. Therefore, two different samples of patients will be recruited (figure 1). For the qualitative part, patients taking OACD > 3 months (PAT CCP) will be recruited purposively by a local study-coordinator (figure 3). For outcome assessments (PAT OUTC 1), all patients who start an oral anticancer therapy for the first time, will be recruited consecutively.

Semi-structured interviews with patients (PAT CCP) will be performed to gain in-depth insight into the experiences of patients with the care provided by different HCPs. Patients will also be asked to describe the flow of an appointment in the hospital, the different HCPs involved, communication with primary care, and the extent of shared-decision making. A topic guide will be used. The interviews will be audio recorded and transcribed verbatim. Interviews will be performed until data-saturation has occurred.

For the outcome assessments, two types of outcomes will be investigated: 1) patient-reported outcomes (at baseline, after 1 month and after 3 months) and 2) clinical outcomes (table 1). Patient-reported outcomes include both patient-related outcomes (i.e. self-management, adherence, quality of life, distress), outcomes on patient-satisfaction (i.e. satisfaction with care, with information about medicines, and with the oral treatment) and healthcare utilization. Outcomes will be assessed using validated questionnaires and a self-developed diary (table 1). The primary outcome is the level of patient self-management, assessed by the validated subscales for oncology patients of the Health Education Impact Questionnaire (HEIQ) (Maunsell et al., 2014) and the Patient Activation Measure (PAM) (Hibbard et al., 2005). The diary has been approved by a panel of experts with expertise in oncology, nursing, home care and primary care. The diary (assessing healthcare utilization) was pilot tested in a group of oncology patients focusing on comprehensibility prior to its use in the study. The assessment at baseline will be performed by telephone by a study collaborator within three days after the start of the treatment. For the next assessments, patients will be offered the option to complete the questionnaires by telephone, online or on paper. Clinical outcomes (table 1) will be collected by the clinicians or by a study nurse (at baseline, after 1 month and after 3 months) using Case Report Forms (CRFs). Standardized forms (including CRFs to be used in case of end of treatment or death) will be developed. CRFs will be offered on paper or electronically. Patients will be recruited over a period of 12 months.

Sample size calculation was based on a cohort-study from (Turner et al., 2015). In this study the effect of a self-management program for patients with chronic conditions was assessed by the use of PAM and HEIQ. For our study, the sample size was calculated based on results from the five different HEIQ subscales only, as they seem to be the most appropriate measures for self-management (Turner et al., 2015). The central comparison within our study will be the comparison of the results on each subscale of the HEIQ at baseline and after 3 months of treatment in the before-group (phase 3) *versus* the after-group (phase 6) (figure 1). Sample size was calculated based on the unpaired t-test for each subscale. To observe an effect size of 0,29 in three out of five HEIQ subscales,

considering a statistical power of 80%, a statistical significance of 5% and a drop out of 25%, 228 patients should be recruited (i.e. 114 before and 114 after).

PERSPECTIVE 3: EXTERNAL PARTNERS

Sample of participants, data collection and procedures

To understand the views of external partners on the current care process, representatives of primary care (PC), including general practitioners, community pharmacists and nurses will be recruited. These HCPs might be involved in intermediate follow-up between hospital visits and hence their perceptions are important to take into account. The representatives will be recruited purposively within the transmural network of each hospital by means of launch calls. Semi-structured interviews will be performed to learn more about the current level of involvement of primary care including its barriers and facilitators and perspectives for a future care pathway focusing on continuity of care. A topic guide will be used. Semi-structured interviews will be audio recorded and transcribed verbatim. Socio-demographics will also be questioned.

PERSPECTIVE 4: AVAILABLE EVIDENCE

Sample of participants, data collection and procedures

Participants from the hospital, primary care and patients, HCP H, STAFF, PC and PAT CCP, will be asked to assess the current care process in relation to the available evidence. The available evidence will be presented in a set of 82 key elements (KE) that have been developed by the research team, based on international literature and interviews with patients and HCPs. The KE have been validated in a two-round Delphi study including HCPs in primary and secondary care and patients. All KE will be included in a survey, with a two-fold question per KE: 1) is the intervention implemented or not and 2) should the intervention be implemented or not.

PERSPECTIVE 5: OBSERVATIONS BY THE RESEARCH TEAM

In order to familiarize with the workflow and with the organizational culture and climate in each hospital, the research team will perform observations. The researchers will perform different walkthroughs of the care process, from the perspective of patients as well as from different HCPs (physicians, nurses and pharmacists).

PART 2. Development of the care pathway

In part 2, tailored care pathways will be developed, with respect to the results obtained from the mapping of current practice (part 1). This will be done per hospital, in co-creation with the research team and with the local project teams, by means of work-meetings that will be spread over a 18-month period. In the first meeting, results from the qualitative and quantitative assessments of the before-study will be discussed and challenges that should be addressed in the care pathway will be prioritized. In the second meeting, a general flowchart of a care pathway, based on the list of KE (part 1, perspective 4) and experiences from the research team on how care can be organized to provide adequate SMS, will be shown. This general flowchart can be used as a starting point for the local teams to redesign the care process in the hospital, and to develop the collaboration with primary care. Throughout the next work-meetings, this flowchart will be tailored to the local setting. Intermediate follow-up on specific to do's in between working meetings (e.g. implementing new facilities in patient records, reorganizing tasks of involved disciplines), will be provided by the local coordinator. At the end of phase 4, each hospital will have obtained a tailored flowchart as well as a time-task matrix in which all interventions and the role of each stakeholder (primary and secondary care) in each step of the care pathway are described.

Besides structuring and standardizing care in a care pathway, it is also crucial that the involved HCPs have the medical knowledge on OACD and have necessary competencies to provide efficacious SMS (Elissen et al., 2013). Different studies and position papers have shown that medical knowledge on OACD in HCPs from primary and secondary must be improved (Charpentier, Orr, & Taveira, 2012; Kav et al., 2008; Mekdad & AlSayed, 2017; O'Bryant & Crandell, 2008; Oakley et al., 2010). Furthermore, competencies on counseling and SMS, including patient education should be further trained since good communication skills are linked to optimal patient outcomes (Schofield & Butow, 2004; Verbrugghe et al., 2016). There is evidence that e-learning, theory-driven training interventions with time to practice, (video) feedback training and follow-up might generate positive training effects (Cook et al., 2008; Duprez et al., 2017). Therefore, training for HCPs will be provided by means of 1) an e-learning program with the aim to improve knowledge on OACD and their toxicities and 2) an interdisciplinary training program to improve counselling and SMS competencies. Both trainings will be evaluated by means of a satisfaction survey based on the Kirckpatrick model. This is a widely used model to evaluate training programs for professionals focussing on four aspects: reaction, learning, behaviour and results (Kirckpartick Partners, 2008).

At the end of the development phase, an evaluation of the development process will be performed in a qualitative study in which the perspective from the local coordinators (semi-structured interviews) and from the research team (focus group interview) are taken into account. Topics regarding collaboration between the local project team and the research team, composition of the local project team, barriers and facilitators in the development process, readiness to change will be discussed.

PART 3. After-study: implementation and evaluation of the care pathway

The actual implementation of the care pathway is foreseen in phase 5. At least six months after the implementation, an evaluation of the care will be performed (phase 6). This will be done according to the same perspectives as in the before-study, as to study the meaningfulness and effectiveness of the implemented care pathway and the impact on patient outcomes and patient experiences. A mixed-methods approach will be used.

Sample of participants, data collection and procedures

For perspective 1"own organization and team", 3 "external partners" and 4 "available evidence", the same samples of HCPs from primary and secondary care and of hospital staff will be used as in the before-study. A sub-sample will be used for the qualitative part of perspectives 1 and 3 (figure 2). For the evaluation of patient outcomes (perspective 2 "patients"), a new patient-cohort (PAT OUTC 2), meeting the inclusion criteria (figure 3), will be recruited. Another sample of patients (PAT CP) will be recruited for the qualitative part. The latter sample of patients will also be used to evaluate the implementation of key elements (perspective 4 "available evidence").

Concerning perspective 1, the outcome assessment using CS PAM and SEPSS-36 will be repeated following the same procedure as in the before-study (figure 1). Additionally, in a sub sample of HCPs from both primary (perspective 3) and secondary care, focus group interviews will be organized per hospital. A topic guide will be used to discuss the following aspects: adoption, acceptance, appropriateness, and feasibility of the care pathway.

As for perspective 2, outcomes will be assessed following the same procedure as described in the before-study. Furthermore, another sample of patients (PAT CP) will be asked to participate in a semi-structured interview to express their perceptions on the new care pathway.

A second round of observations (perspective 5) will also be organized. The fourth perspective of the available evidence (i.e. KE) will be integrated in this part. Each step in the care pathway will be evaluated (i.e. evaluation of care pathway fidelity) by means of structured observations at regular intervals. A walkthrough the care pathway from the perspectives of different stakeholders (including patients) will be performed. Furthermore, patient consultations will be attended to assess both medical and communicative aspects of SMS. These consultations will be audio-taped to avoid missing important elements during the observations. Patient records (n = 10 – 15 / hospital) will also be assessed to investigate the documentation of specific KE of which the performance can only be checked in a record. We estimate the number of observations to be 5 per patient / HCP and per hospital. A stratified sampling method will be used including three strata: the hospital, the HCP and the type of consultation (initiation of a treatment with OACD / follow-up). For the observations, the research team will use the time-task matrix of the care pathway document and an observation checklist including the proposed KE (i.e. perspective 4). The latter will allow to assess to what extent the KE are implemented in the care pathway. The first set of observations will be performed by two researchers to minimize bias. The interrater reliability will be calculated. For evaluation of this interrater reliability, values ≥ 0,75 will be regarded as substantial (Landis & Koch, 1977).

Data analysis

Given that mixed methods are used in the different study parts (figure 1), both quantitative and qualitative data-analysis will be performed. Combining these two types of data will enrich insights in the current care process, in the development and in the implementation outcomes of the care pathway, such as adoption, acceptance, feasibility and meaningfulness (Proctor et al., 2011). Moreover, the qualitative and observation data will help to better understand the results from the outcome assessments in patients and HCPs and in the quantitative evaluation of the care process and will place these results in a context. Figure 4 gives an overview of the different types of data-analysis on the evaluation of the current care process and the development, implementation and evaluation of the care pathway including the outcomes of data-analysis per study part. Figure 5 gives insight in the different before-after comparisons on patient- and HCP-reported outcomes. Overall, data will be analyzed chronologically per study-part and will provide insights that are useful for the subsequent parts (i.e. data of evaluation of current practice are essential for the development of the care pathway; insight in the development process is useful to understand care pathway performance).

Quantitative statistical analysis will be performed using SPSS 25.0. For the validated questionnaires and surveys used in part 1 and part 3 to evaluate the current care process and the care pathway, scores will be calculated based on scoring protocols and the level of implementation of KE will be calculated. Descriptive statistics (i.e. mean and standard deviation or median and interquartile range and confidence interval) will be presented. Qualitative data in different study parts will be analyzed using NVivo software. All interviews and focus groups will be recorded and transcribed verbatim, coded and analysed inductively using thematic framework analysis by means of the QUAGOL method (Dierckx de Casterle et al., 2012). Quality of data collection and data analyses will be ensured by means of researcher triangulation.

For the before-after comparisons of patient-reported outcomes (figure 5), scoring protocols per questionnaire will be used to calculate scores and data will be presented using descriptive statistics. Both changes over time (M0-M1-M3) by means of a repeated measures ANOVA and differences in results per time point within one cohort will be analyzed using paired t-tests, chi-squared tests and non-parametric alternatives based on the distribution and type (continuous/categorical) of data. To analyze the impact of the care pathway on the level of the patient, before and after data will be compared using tests for unpaired data (e.g. unpaired t-test). Due to the heterogeneity of the study-population (i.e. any oral anticancer treatment) and the different settings, multi-

level analyses will be performed. On the level of the HCP, outcomes from the before- and after-study will be compared (figure 5) and associated factors (i.e. participation to training) will be investigated. Since these are paired data, tests for paired data will be used.

Ethical considerations

Approval was obtained from the Ethics Committee UZ/KU Leuven (central ethics committee) in June 2016 and from the local ethics committee of each participating hospital. Each participant (HCP/patient) will receive written and verbal information, of the respective parts of the study. A written informed consent will be obtained from each participant. All data will be anonymized for further analyses and reports.

Validity, reliability and rigor

In this study, a mixed methods design is used both in the before- and after-study to enrich the collected data. This method creates the opportunity to triangulate and integrate quantitative and qualitative data and to place quantitative data in context (Onwuegbuzie & Leech, 2005). For the quantitative part, mostly validated questionnaires will be used. Own-developed questionnaires have been assessed for reliability and content validity. Moreover, these questionnaires have been pilot tested in a sample of either patients or HCPs prior to the study. Furthermore, a multicenter design is used to enhance the generalizability of the findings. To guarantee the rigor of the qualitative data, the QUAGOL method (Dierckx de Casterle et al., 2012) and triangulation (both on the level of the data and on the level of the researcher) will be used. In order to enhance transferability of the findings, maximum variation sampling will be applied.

Discussion

A multicenter study that aims to study the feasibility, appropriateness, meaningfulness and effectiveness of developing and implementing a tailored care pathway for patients treated with OACD is lacking. This study is the first asset to integrate all relevant interventions in SMS during oral anticancer therapies. This study is highly relevant for oncology nurses and clinical nurse specialists since they are -besides the physician – a key player SMS during oral anticancer treatments. Moreover, using the described methodology and development process

characterized by patient-involvement and co-design between local project teams and the research team, four different tailored care pathways will be obtained. A tailored intervention has been proven to be a key point in achieving a sustainable change in health care (Bosch, van der Weijden, Wensing, & Grol, 2007; Grol & Grimshaw, 2003). Furthermore, this is the first care pathway in oncology that only focusses on the type of treatment, i.e. oral. Hereby, the care pathway can be used for different types of indications for which an oral treatment can be started. All these aforementioned choices have some implications described below.

Limitations

Different limitations can be assigned to this study. First, by choosing a tailored approach in co-design with the different hospitals and the research team, sufficient time and the right resources will be needed to guarantee the sustainable change in health care. The care pathway will be implemented in a real-life context and due to hard-to-control situations, further optimization will be needed in the first months / years. Second, patients eligible for the outcome assessments can suffer from different types of cancer resulting in a heterogeneous patient population. In this study we will focus on the type of anticancer treatment (i.e. oral) rather than on a specific indication and mainly report data on a general level. Due to the heterogeneity of the population, statistical analysis of sub groups will be needed to gain insight in differences in level of self-management and other outcomes among different types of indications and OACD. Furthermore, it might be possible that a positive effect on patient-reported outcomes can only be seen on a long-term basis. Therefore, a process-evaluation of the development and implementation of the care pathway through qualitative studies is essential to gain insight in underlying perceptions of HCPs and patients.

References

Aubin, M., Giguere, A., Martin, M., Verreault, R., Fitch, M. I., Kazanjian, A., & Carmichael, P. H. (2012). Interventions to improve continuity of care in the follow-up of patients with cancer. *Cochrane Database Syst Rev*(7), Cd007672. doi:10.1002/14651858.CD007672.pub2

Bassan, F., Peter, F., Houbre, B., Brennstuhl, M. J., Costantini, M., Speyer, E., & Tarquinio, C. (2014). Adherence to oral antineoplastic agents by cancer patients: definition and literature review. *Eur J Cancer Care (Engl), 23*(1), 22-35. doi:10.1111/ecc.12124

Bauwens, S., Baillon, C., Distelmans, W., & Theuns, P. (2009). The 'Distress Barometer': validation of method of combining the Distress Thermometer with a rated complaint scale. *Psychooncology, 18*(5), 534-542. doi:10.1002/pon.1425

Bedell, C. H. (2003). A changing paradigm for cancer treatment: the advent of new oral chemotherapy agents. *Clin J Oncol Nurs, 7*(6 Suppl), 5-9. doi:10.1188/03.cjon.s6.5-9

Belgian Cancer Center (2008). National Cancer Plan. Retrieved from http://www.e-cancer.be/kankerplan/Documents/2008%20Rapport%20Kankerplan_NL.pdf

Bosch, M., van der Weijden, T., Wensing, M., & Grol, R. (2007). Tailoring quality improvement interventions to identified barriers: a multiple case analysis. *J Eval Clin Pract, 13*(2), 161-168. doi:10.1111/j.1365-2753.2006.00660.x

Brucker, P. S., Yost, K., Cashy, J., Webster, K., & Cella, D. (2005). General population and cancer patient norms for the Functional Assessment of Cancer Therapy-General (FACT-G). *Eval Health Prof, 28*(2), 192-211. doi:10.1177/0163278705275341

Charpentier, M. M., Orr, K. K., & Taveira, T. H. (2012). Improving pharmacist knowledge of oral chemotherapy in the community. *Ann Pharmacother, 46*(9), 1205-1211. doi:10.1345/aph.1R056

Cheung, K., de Mol, M., Visser, S., Den Oudsten, B. L., Stricker, B. H., & Aerts, J. G. (2015). Reliability and validity of the Cancer Therapy Satisfaction Questionnaire in lung cancer. *Qual Life Res*. doi:10.1007/s11136-015-1062-z

Cook, D. A., Levinson, A. J., Garside, S., Dupras, D. M., Erwin, P. J., & Montori, V. M. (2008). Internet-based learning in the health professions: a meta-analysis. *Jama, 300*(10), 1181-1196. doi:10.1001/jama.300.10.1181

De Winter, S., Vanbrabant, P., Spriet, I., Desruelles, D., Indevuyst, C., Knockaert, D., . . . Willems, L. (2011). A simple tool to improve medication reconciliation at the emergency department. *Eur J Intern Med, 22*(4), 382-385. doi:10.1016/j.ejim.2011.03.010

Dierckx de Casterle, B., Gastmans, C., Bryon, E., & Denier, Y. (2012). QUAGOL: a guide for qualitative data analysis. *Int J Nurs Stud, 49*(3), 360-371. doi:10.1016/j.ijnurstu.2011.09.012

Duprez, V., Van Hooft, S. M., Dwarswaard, J., van Staa, A., Van Hecke, A., & Strating, M. M. (2016). The development and psychometric validation of the self-efficacy and performance in self-management support (SEPSS) Instrument. *J Adv Nurs, 72*(6), 1381-1395. doi:10.1111/jan.12918

Duprez, V., Vandecasteele, T., Verhaeghe, S., Beeckman, D., & Van Hecke, A. (2017). The effectiveness of interventions to enhance self-management support competencies in the nursing profession: a systematic review. *J Adv Nurs, 73*(8), 1807-1824. doi:10.1111/jan.13249

Elissen, A., Nolte, E., Knai, C., Brunn, M., Chevreul, K., Conklin, A., . . . Vrijhoef, H. (2013). Is Europe putting theory into practice? A qualitative study of the level of self-management support in chronic care management approaches. *BMC Health Serv Res, 13*, 117. doi:10.1186/1472-6963-13-117

EPAAC, (2015). National Cancer Plans. Retrieved from http://www.epaac.eu/national-cancer-plans

Fallowfield, L., Atkins, L., Catt, S., Cox, A., Coxon, C., Langridge, C., . . . Price, M. (2006). Patients' preference for administration of endocrine treatments by injection or tablets: results from a study of women with breast cancer. *Ann Oncol, 17*(2), 205-210. doi:10.1093/annonc/mdj044

Findlay, M., von Minckwitz, G., & Wardley, A. (2008). Effective oral chemotherapy for breast cancer: pillars of strength. *Ann Oncol, 19*(2), 212-222. doi:10.1093/annonc/mdm285

Greer, J. A., Amoyal, N., Nisotel, L., Fishbein, J. N., MacDonald, J., Stagl, J., . . . Pirl, W. F. (2016). A Systematic Review of Adherence to Oral Antineoplastic Therapies. *Oncologist, 21*(3), 354-376. doi:10.1634/theoncologist.2015-0405

Grol, R., & Grimshaw, J. (2003). From best evidence to best practice: effective implementation of change in patients' care. *Lancet, 362*(9391), 1225-1230. doi:10.1016/s0140-6736(03)14546-1

Hartigan, K. (2003). Patient education: the cornerstone of successful oral chemotherapy treatment. *Clin J Oncol Nurs, 7*(6 Suppl), 21-24. doi:10.1188/03.cjon.s6.21-24

476 Hibbard, J. H., Mahoney, E. R., Stockard, J., & Tusler, M. (2005). Development and testing of a short form of the
477 patient activation measure. *Health Serv Res, 40*(6 Pt 1), 1918-1930. doi:10.1111/j.1475-
478 6773.2005.00438.x
479 Holle, L. M., Harris, C. S., Chan, A., Fahrenbruch, R. J., Labdi, B. A., Mohs, J. E., . . . Vela, C. M. (2017). Pharmacists'
480 roles in oncology pharmacy services: Results of a global survey. *J Oncol Pharm Pract, 23*(3), 185-194.
481 doi:10.1177/1078155216629827
482 Holloway, I., & Wheeler, S. (2010). *Qualitative Research in Nursing and Healthcare* (3th ed.).
483 Institute of Medicine (2004). *The 1st Annual Crossing the Quality Chasm Summit: A Focus on Communities*.
484 Washington DC: The National Academies Press.
485 Kahn, J. M., Athale, U. H., Clavell, L. A., Cole, P. D., Leclerc, J. M., Laverdiere, C., . . . Kelly, K. M. (2017). How Variable
486 Is Our Delivery of Information? Approaches to Patient Education About Oral Chemotherapy in the
487 Pediatric Oncology Clinic. *J Pediatr Health Care, 31*(1), e1-e6. doi:10.1016/j.pedhc.2016.06.004
488 Kav, S., Johnson, J., Rittenberg, C., Fernadez-Ortega, P., Suominen, T., Olsen, P. R., . . . Clark-Snow, R. (2008). Role
489 of the nurse in patient education and follow-up of people receiving oral chemotherapy treatment: an
490 international survey. *Support Care Cancer, 16*(9), 1075-1083. doi:10.1007/s00520-007-0377-x
491 Kirckpatrick Partners (2008). The Kirkpatrick Model. Retrieved from https://www.kirkpatrickpartners.com/Our-
492 Philosophy/The-Kirkpatrick-Model
493 Kleppe, M., Lacroix, J., Ham, J., & Midden, C. (2015). The development of the ProMAS: a Probabilistic Medication
494 Adherence Scale. *Patient Prefer Adherence, 9*, 355-367. doi:10.2147/ppa.s76749Landis, J. R., & Koch, G.
495 G. (1977). The measurement of observer agreement for categorical data. *Biometrics, 33*(1), 159-174.
496 Liu, G., Franssen, E., Fitch, M. I., & Warner, E. (1997). Patient preferences for oral versus intravenous palliative
497 chemotherapy. *J Clin Oncol, 15*(1), 110-115.
498 Maunsell, E., Lauzier, S., Brunet, J., Pelletier, S., Osborne, R. H., & Campbell, H. S. (2014). Health-related
499 empowerment in cancer: validity of scales from the Health Education Impact Questionnaire. *Cancer,*
500 *120*(20), 3228-3236. doi:10.1002/cncr.28847
501 Mekdad, S. S., & AlSayed, A. D. (2017). Towards safety of oral anti-cancer agents, the need to educate our
502 pharmacists. *Saudi Pharm J, 25*(1), 136-140. doi:10.1016/j.jsps.2015.06.007
503 Moore, S. (2007). Facilitating oral chemotherapy treatment and compliance through patient/family-focused
504 education. *Cancer Nurs, 30*(2), 112-122; quiz 123-114. doi:10.1097/01.NCC.0000265009.33053.2d
505 Nguyen, T. V., Bosset, J. F., Monnier, A., Fournier, J., Perrin, V., Baumann, C., . . . Mercier, M. (2011). Determinants
506 of patient satisfaction in ambulatory oncology: a cross sectional study based on the OUT-PATSAT35
507 questionnaire. *BMC Cancer, 11*, 526. doi:10.1186/1471-2407-11-526
508 O'Bryant, C. L., & Crandell, B. C. (2008). Community pharmacists' knowledge of and attitudes toward oral
509 chemotherapy. *J Am Pharm Assoc (2003), 48*(5), 632-639. doi:10.1331/JAPhA.2008.07082
510 O'Neill, V. J., & Twelves, C. J. (2002). Oral cancer treatment: developments in chemotherapy and beyond. *Br J*
511 *Cancer, 87*(9), 933-937. doi:10.1038/sj.bjc.6600591
512 Oakley, C., Lennan, E., Roe, H., Craven, O., Harrold, K., & Vidall, C. (2010). Safe practice and nursing care of patients
513 receiving oral anti-cancer medicines: a position statement from UKONS. *Ecancermedicalscience, 4*, 177.
514 doi:10.3332/ecancer.2010.177
515 Onwuegbuzie, A. J., & Leech, N. L. (2005). On Becoming a Pragmatic Researcher: The Importance of Combining
516 Quantitative and Qualitative Research Methodologies. *International Journal of Social Research*
517 *Methodology, 8*(5), 375-387. doi:10.1080/13645570500402447
518 Pearson, A., Wiechula, R., Court, A., & Lockwood, C. (2005). The JBI model of evidence-based healthcare. *Int J Evid*
519 *Based Healthc, 3*(8), 207-215. doi:10.1111/j.1479-6988.2005.00026.x
520 Pfadenhauer, L. M., Gerhardus, A., Mozygemba, K., Lysdahl, K. B., Booth, A., Hofmann, B., . . . Rehfuess, E. (2017).
521 Making sense of complexity in context and implementation: the Context and Implementation of Complex
522 Interventions (CICI) framework. *Implement Sci, 12*(1), 21. doi:10.1186/s13012-017-0552-5
523 Proctor, E., Silmere, H., Raghavan, R., Hovmand, P., Aarons, G., Bunger, A., . . . Hensley, M. (2011). Outcomes for
524 implementation research: conceptual distinctions, measurement challenges, and research agenda. *Adm*
525 *Policy Ment Health, 38*(2), 65-76. doi:10.1007/s10488-010-0319-7
526 Rademakers, J., Jansen, D., van der Hoek, L., & Heijmans, M. (2015). Clinicians' beliefs and attitudes toward patient
527 self-management in the Netherlands; translation and testing of the American Clinician Support for Patient
528 Activation Measure (CS-PAM). *BMC Health Serv Res, 15*, 138. doi:10.1186/s12913-015-0799-y
529 Raijmakers, N., Dekkers, A., Galesloot, C., van Zuylen, L., & van der Heide, A. (2015). Barriers and facilitators to
530 implementation of the Liverpool Care Pathway in the Netherlands: a qualitative study. *BMJ Support Palliat*
531 *Care, 5*(3), 259-265. doi:10.1136/bmjspcare-2014-000684

Salgado, T. M., Mackler, E., Severson, J. A., Lindsay, J., Batra, P., Petersen, L., & Farris, K. B. (2017). The relationship between patient activation, confidence to self-manage side effects, and adherence to oral oncolytics: a pilot study with Michigan oncology practices. *Support Care Cancer, 25*(6), 1797-1807. doi:10.1007/s00520-017-3584-0

Schofield, P. E., & Butow, P. N. (2004). Towards better communication in cancer care: a framework for developing evidence-based interventions. *Patient Educ Couns, 55*(1), 32-39. doi:10.1016/j.pec.2003.07.001

Tadic, D., Spasojevic, I. B., Tomasevic, Z. I., & Dejanovic, S. D. (2015). Oral administration of antineoplastic agents: the challenges for healthcare professionals. *J buon, 20*(3), 690-698.

Turner, A., Anderson, J. K., Wallace, L. M., & Bourne, C. (2015). An evaluation of a self-management program for patients with long-term conditions. *Patient Educ Couns, 98*(2), 213-219. doi:10.1016/j.pec.2014.08.022

Twelves, C., Gollins, S., Grieve, R., & Samuel, L. (2006). A randomised cross-over trial comparing patient preference for oral capecitabine and 5-fluorouracil/leucovorin regimens in patients with advanced colorectal cancer. *Ann Oncol, 17*(2), 239-245. doi:10.1093/annonc/mdj023

Vanhaecht, K., De Witte, K., Depreitere, R., Van Zelm, R., De Bleser, L., Proost, K., & Sermeus, W. (2007). Development and validation of a care process self-evaluation tool. *Health Serv Manage Res, 20*(3), 189-202. doi:10.1258/095148407781395964

Vanhaecht, K., Panella, M., Van Zelm, R., & Sermeus, W. (2010). An overview on the history and concept of care pathways as complex interventions. *International Journal of Care Pathways, 14*(3), 117-123. doi:10.1258/jicp.2010.010019

Vanhaecht, K., Van Gerven, E., Deneckere, S., Lodewijckx, C., Janssen, I., van Zelm, R., . . . Sermeus, W. (2012). The 7-phase method to design, implement and evaluate care pathways. *The International Journal of Person Centered Medicine, 2*(3), 341-351.

Verbrugghe, M., Duprez, V., Beeckman, D., Grypdonck, M., Quaghebeur, M., Verschueren, C., . . . Van Hecke, A. (2016). Factors Influencing Adherence in Cancer Patients Taking Oral Tyrosine Kinase Inhibitors: A Qualitative Study. *Cancer Nurs, 39*(2), 153-162. doi:10.1097/ncc.0000000000000250

Verbrugghe, M., Timmers, L., Boons, C., Van Den Bemt, B. J. F., Hugtenburg, J. G., & Van Hecke, A. (2016). Adherence to oral anticancer agents: Healthcare providers' perceptions, beliefs and shared decision making in Belgium and the Netherlands. *Acta Oncologica, 55*(4), 437-443. doi:10.3109/0284186x.2015.1119307

Vitaz, T. W., McIlvoy, L., Raque, G. H., Spain, D., & Shields, C. B. (2001). Development and implementation of a clinical pathway for severe traumatic brain injury. *J Trauma, 51*(2), 369-375.

Weingart, S. N., Brown, E., Bach, P. B., Eng, K., Johnson, S. A., Kuzel, T. M., . . . Walters, R. S. (2008). NCCN Task Force Report: Oral chemotherapy. *J Natl Compr Canc Netw, 6 Suppl 3*, S1-14.

Winkeljohn, D. (2010). Adherence to oral cancer therapies: nursing interventions. *Clin J Oncol Nurs, 14*(4), 461-466. doi:10.1188/10.cjon.461-466

Zerillo, J. A., Goldenberg, B. A., Kotecha, R. R., Tewari, A. K., Jacobson, J. O., & Krzyzanowska, M. K. (2018). Interventions to Improve Oral Chemotherapy Safety and Quality: A Systematic Review. *JAMA Oncol, 4*(1), 105-117. doi:10.1001/jamaoncol.2017.0625

Figures

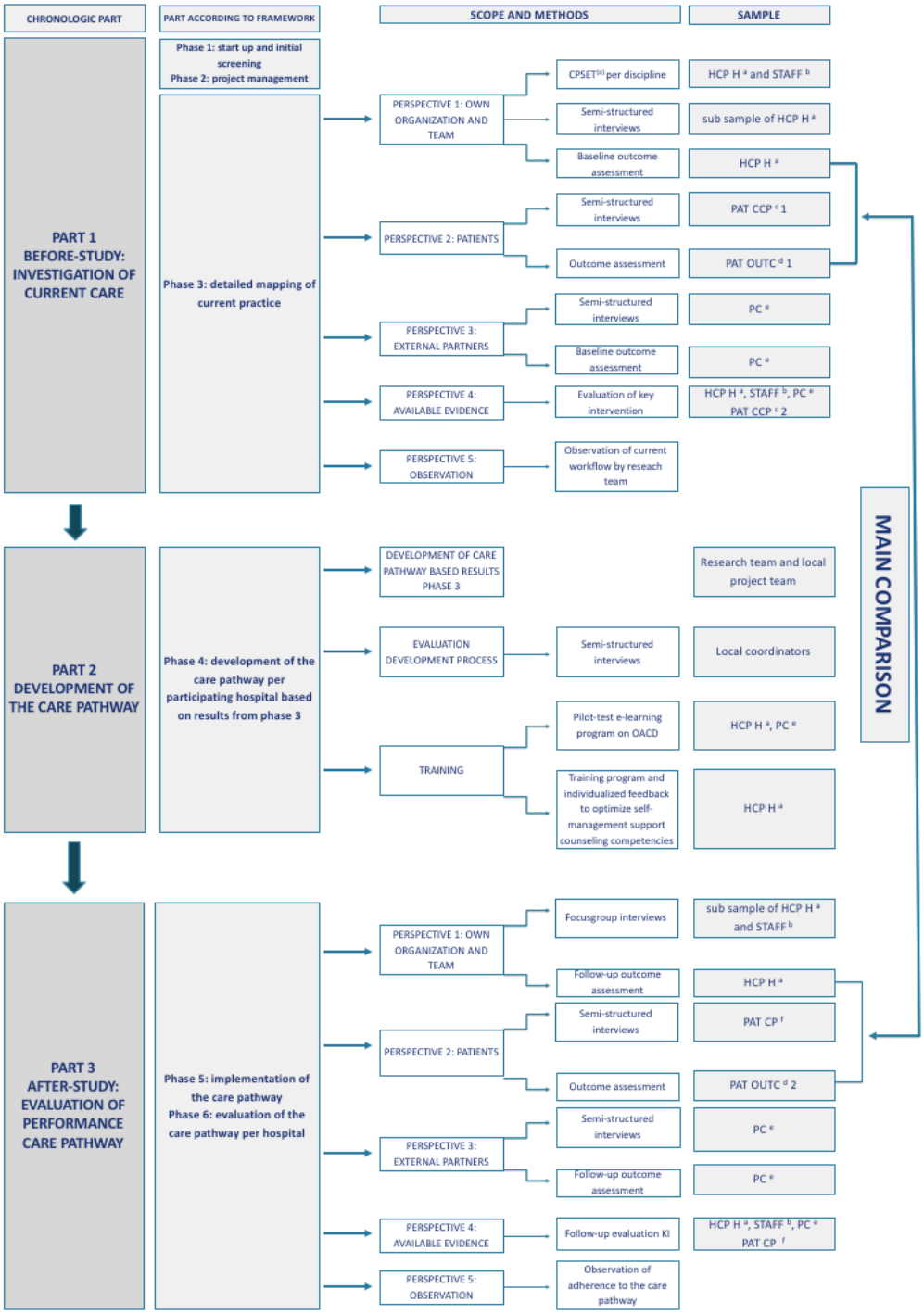

Figure 1. General overview of the before - after study with integration of the first six phases from the 7-phase model by Vanhaecht et al., 2011 (Kris Vanhaecht et al., 2012) and the different assessments per phase. The samples used per assessment are also indicated. [a] HCP hospital; [b] hospital staff; [c] patients involved in evaluation of the current care process; [d] patients recruited for outcome assessments; [d] primary care; [f] patients involved in the evaluation of the care pathway

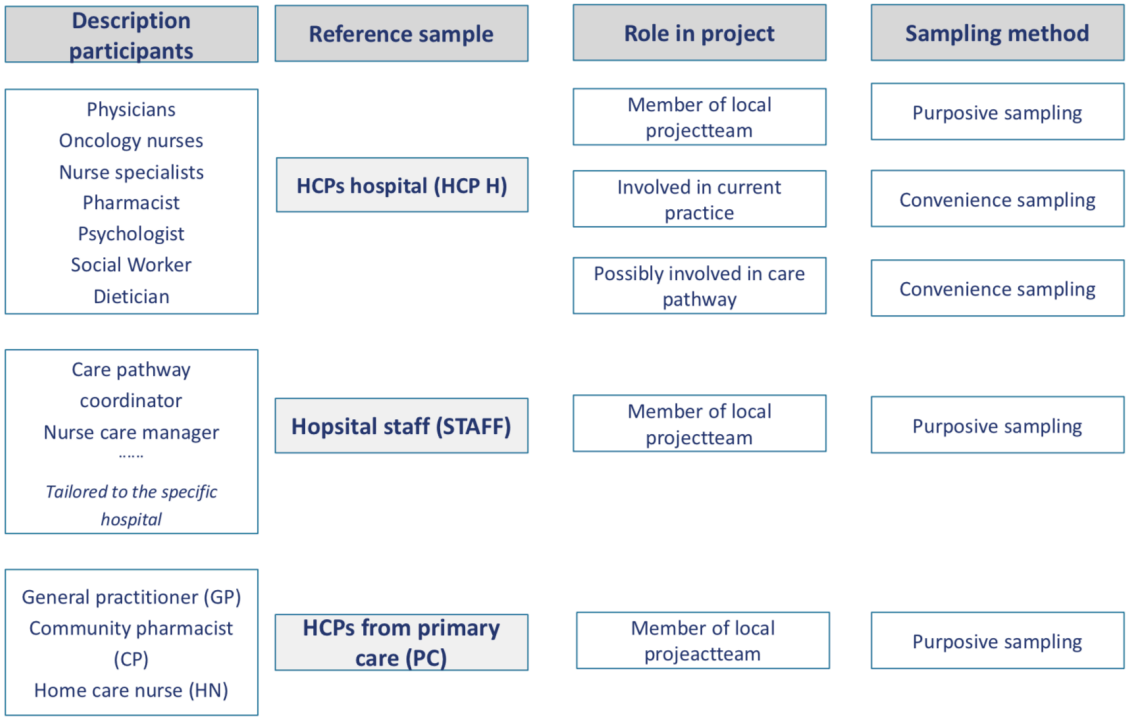

Figure 2. Overview of the HCPs that will be recruited for the different assessments in the before- and after-study. Each group of participants is encoded – HCPs hospital (HCP H); hospital staff (STAFF); primary care (PC) - for further use throughout this study protocol.

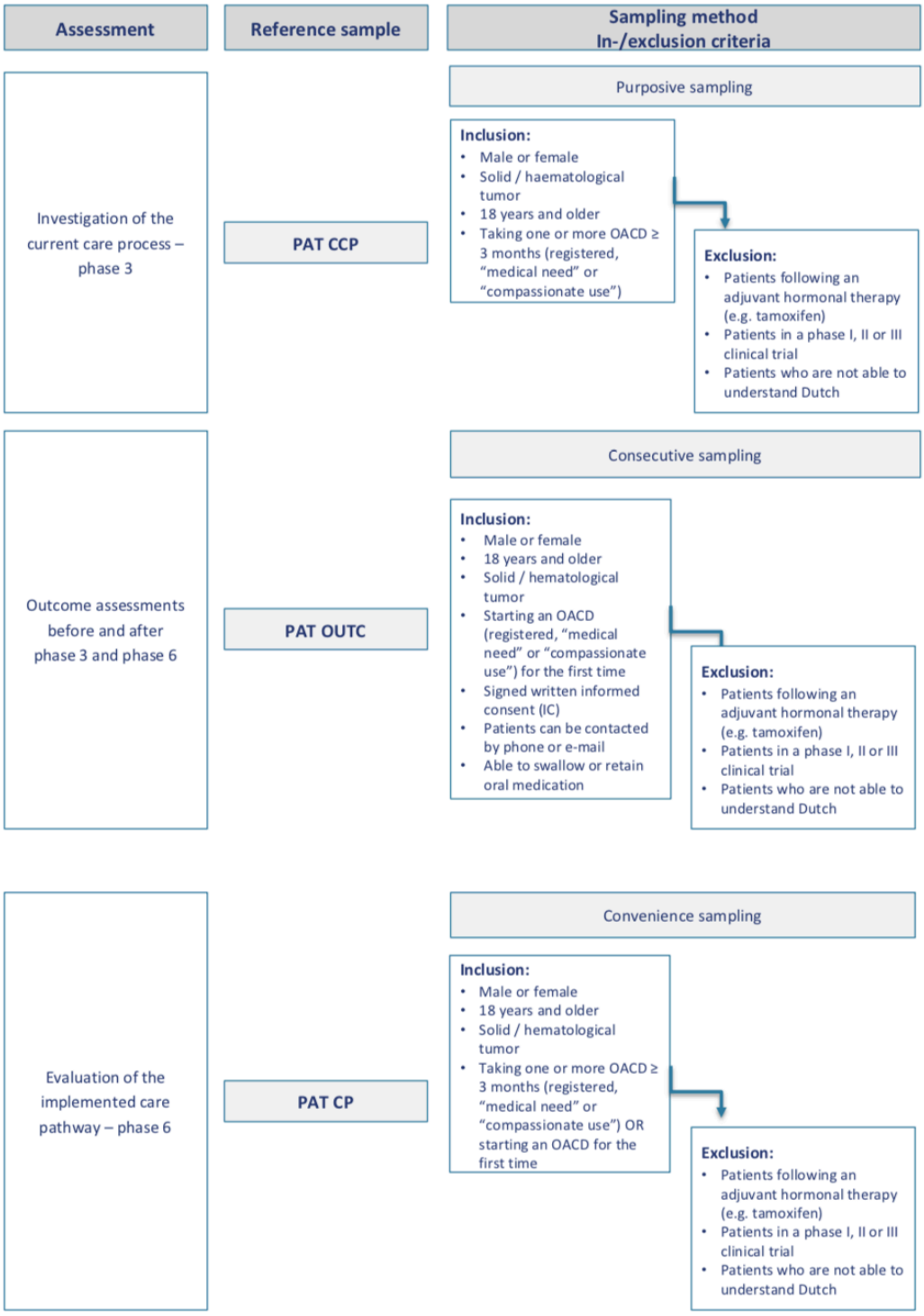

Figure 3. Overview of the patients that will be recruited for the different assessments in the before- and after-study. Each sample of patients is encoded – patients involved in the investigation of the current care process (PAT CCP); patients recruited for outcome assessments (PAT OUTC), patients involved in the evaluation of the performance of the care pathway (PAT CP) - for further use throughout this study protocol.

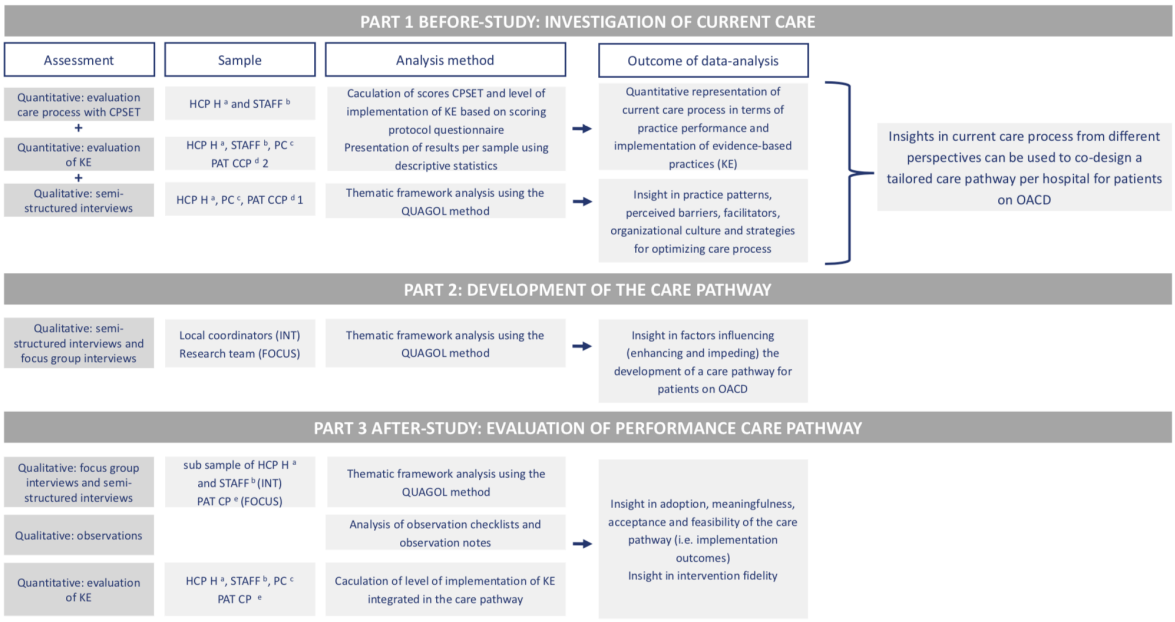

Figure 4. Overview of the different types of data-analysis on the evaluation of the current care process and the development, implementation and evaluation of the care pathway including the outcome of data-analysis per study part. [a] HCP hospital; [b] hospital staff; [c] primary care; [d] patients involved in evaluation of the current care process patients recruited for outcome assessments; [e] patients involved in the evaluation of the care pathway

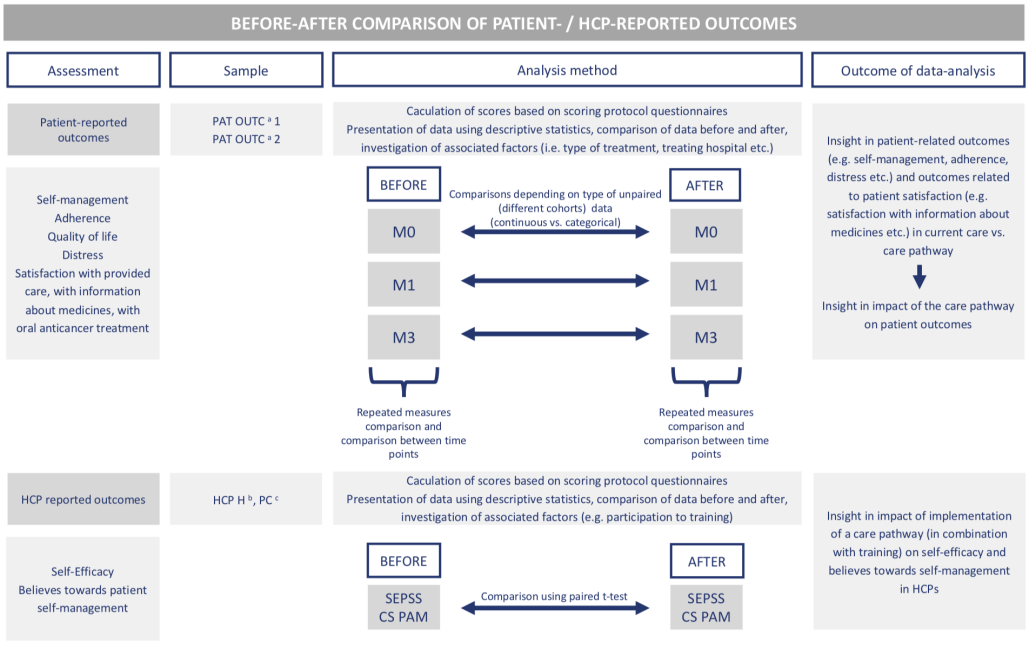

Figure 5. Overview of the before-after comparisons that will be performed on patient-reported and HCP-reported outcome measures to investigate the impact of the care pathway. [a] patients recruited for outcome assessments; [b] HCP hospital; [c] primary care

612

613 # Tables

614

615

Table 1. Overview of outcomes assessed in patients and in HCPs before and after the implementation of the care pathway				
OUTCOME ASSESSMENTS IN PATIENTS (before and after same procedures)				
Outcome/data	Method/scale	Start of treatment (0 months)	Follow-up visits (after 1 month)	Follow-up visits (after 3 months)
Self-management	Health Education Impact Questionnaire (HEIQ) (Maunsell et al., 2014)	X	X	X
	Patient Activation Measure (PAM) (Rademakers, Jansen, van der Hoek, & Heijmans, 2015)	X	X	X
Adherence	Probabilistic Medication Adherence Scale (ProMAS) (Kleppe, Lacroix, Ham, & Midden, 2015)	NO DATA COLLECTION	X	X
Patient satisfaction with treatment	CTSQ (Cheung et al., 2015)	NO DATA COLLECTION	X	X
Patient satisfaction with care	Outpatient Satisfaction Questionnaire (Out-Patsat 35) (Nguyen et al., 2011)	X	X	X
	Satisfaction about Information Medicines Scale (SIMS) (Horne, Hankins, & Jenkins, 2001)	X	X	X
Health related quality of life	Functional Assessment Cancer Therapy – General (FACT G) (Brucker et al., 2005)	NO DATA COLLECTION		X
Distress	Distress Barometer (DB) (Bauwens et al., 2009).	X	X	X
Sociodemographics: age, gender, nationality, marital status, education, occupation/employment	Patient survey during patient-reported outcome assessments	X		
Co-medication	Patient survey during patient-reported outcome assessments	X	X	X
Illness related data: tumor anamnesis, time since diagnosis previous tumor treatment(s), metastases, comorbidities, symptoms	Case report form (CRF)	X	X	X
Therapy-related data: type/name OACD, doses regimen	Case report form (CRF)	X	X	X

Efficacy of therapy	RECIST reported in case report form		X	X
	ECOG performance scale reported in case report form	X	X	X
Interruptions or changes in therapy regimen	Case report form and Patient survey		X	X
Side effects	CTC-NCI 4.0 documented in case report form		X	X
Number and timing of consultations; type of healthcare professionals involved, main reason / topics discussed during consultation, emergency visits, hospitalisation, visits to the GP	Therapy-related diary	X	X	X
Cost of the total oral anticancer therapy	Therapy-related diary	X	X	X
OUTCOME ASSESSMENTS IN HCPs (before and after same procedures)				
Outcome/data	Method/scale	Before-study	After-study	
Beliefs towards self-management	Clinician Support for Patient Activation Measure – questionnaire (CS PAM) (Rademakers et al., 2015)	X	X	
Self-efficacy	Self-Efficacy and Performance in Self-management Support instrument (SEPSS-36) (Duprez et al., 2016)	X	X	

Table 1. Overview of outcomes assessed in patients and in HCPs before and after the implementation of the care pathway