Prospective Dutch colorectal cancer cohort: an infrastructure for long-term observational, prognostic, predictive and (randomized) intervention research


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Prospective Dutch colorectal cancer cohort: an infrastructure for long-term observational, prognostic, predictive and (randomized) intervention research


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ABSTRACT

Background: Systematic evaluation and validation of new prognostic and predictive markers, technologies and interventions for colorectal cancer (CRC) is crucial for optimizing patients' outcomes. With only 5–15% of patients participating in clinical trials, generalizability of results is poor. Moreover, current trials often lack the capacity for post-hoc subgroup analyses. For this purpose, a large observational cohort study, serving as a multiple trial and biobanking facility, was set up by the Dutch Colorectal Cancer Group (DCCG).

Methods/design: The Prospective Dutch ColoRectal Cancer cohort is a prospective multidisciplinary nationwide observational cohort study in the Netherlands (yearly CRC incidence of 15 500). All CRC patients (stage I–IV) are eligible for inclusion, and longitudinal clinical data are registered. Patients give separate consent for the collection of blood and tumor tissue, filling out questionnaires, and broad randomization for studies according to the innovative cohort multiple randomized controlled trial design (cmRCT), serving as an alternative study design for the classic RCT. Objectives of the study include: 1) systematically collected long-term clinical data, patient-reported outcomes and biomaterials from daily CRC practice; and 2) to facilitate future basic, translational and clinical research including interventional and cost-effectiveness studies for both national and international research groups with short inclusion periods, even for studies with stringent inclusion criteria.

Results: Seven months after initiation 650 patients have been enrolled, eight centers participate, 15 centers await IRB approval and nine embedded cohort- or cmRCT-designed studies are currently recruiting patients.

Conclusion: This cohort provides a unique multidisciplinary data, biobank, and patient-reported outcomes collection initiative, serving as an infrastructure for various kinds of research aiming to improve treatment outcomes in CRC patients. This comprehensive design may serve as an example for other tumor types.

Worldwide, colorectal cancer (CRC) is the third most common malignancy in men and second in women [1]. With a continuously rising incidence, an estimated 1.35 million new cases are diagnosed yearly, associated with 694 000 annual deaths. In the past decades, substantial progress has been made in diagnosis and treatment of CRC, resulting in an increasing number of CRC survivors [2–8]. The implementation of national CRC screening programs is expected to increase the incidence of CRC [9]. The increasing incidence of CRC, in combination with improved survival rates, has led to high numbers of people living with (the consequences of) CRC. In addition to treatment parameters and outcomes, also quality of life, workability, and daily functioning during and after CRC treatment are becoming increasingly important parameters in research.

There is no consensus on the use of prognostic parameters in CRC, and predictive factors for treatment are scarce. Also, there is a growing availability of new molecular markers [10–13] and innovative treatment options. This puts increasing pressure on the current research system, as large
numbers of patients are required to assess relevance or superiority before their implementation into clinical practice. This warranted large number greatly exceeds the amount of patients that currently participate in clinical trials (5–15%) [14–16]. Low recruitment rates may also imply selective inclusion of patients in trials rather than representative population samples [17], which may result in limited external validity of outcomes. The danger of the extrapolation of study results to the general population was recently shown. Survival outcomes of patients with metastatic CRC (mCRC) treated within the scope of a randomized study were significantly better than the survival outcomes in patients not fulfilling the study eligibility criteria and treated outside the trial with the same drugs during the same period [17,18]. Moreover, study designs classically used for comparative research often lack the ability to provide sufficient data for subgroup treatment effects or post-hoc evaluation. For example, immunotherapy showed to be effective in mCRC patients with microsatellite instability (MSI). As MSI is only observed in 3–5% of the mCRC patients, the conduction of a large randomized phase 3 trial will be challenging [19]. It is therefore desirable to include all these patients in a large representative cohort of CRC patients who are prospectively followed for relevant outcomes that enables to study the value of novel prognostic and predictive biomarkers in large, but also small subgroups of patients. It would be ideal to use data from routine sources, such as hospital systems or (cancer) registries, but these sources often lack the required detail about (changes in) treatments, doses, toxicity, and response, which is paramount for this purpose. As an alternative, a large observational cohort has the advantage that it can provide a standardized data collection, dedicated data monitoring and intensive follow-up, all of which are especially valuable for long-term research in prognostic or predictive determinants.

Ideally, all new interventions should be evaluated in randomized controlled trials (RCTs) as this is considered the gold standard to prove effectiveness. However, this design in itself is often not only complicated by slow recruitment rates and limited generalizability [15], it is also subject to a considerable delay between conceptualization and start, limited long-term follow-up, inadequate collection of patient-reported outcomes (PROMs), high non-completion rates and high costs [16]. An innovative alternative proposed for the classic RCT is the ‘cohort multiple randomized controlled trial’ (cmRCT) [20]. This design was originally developed as an alternative for classic pragmatic RCTs, and combines useful features from both classic RCTs (randomization) and prospective observational cohort studies. The design is characterized by three features: (1) patient-centered informed consent approach; (2) framework to systematically collect long-term clinical follow-up as well as PROMs; and (3) efficient recruitment for trials by asking patients to give ‘broad consent for randomization’ in future trials. Unique features of the cmRCT design are that it allows multiple randomized trials to be conducted simultaneously and that patients can participate in multiple non-conflicting trials at the same time [20]. The design itself and its implementation in this study are explained in more detail in Box 2.

We believe that a prospective observational cohort study can provide a standardized and validated collection of long-term clinical data, tissue and blood samples and PROMs to establish a continuous source for a variety of research purposes. This research database can, among others, be used to investigate what (intrinsic and environmental) factors are associated with survival and PROMs, to find new predictive markers for treatment outcomes and side effects, and to develop more accurate diagnostic tests and efficient follow-up surveillance strategies.

Methods/design

Design and objectives

This is a project of the Dutch Colorectal Cancer Group (DCCG) and was launched as the prospective Dutch colorectal cancer cohort (Dutch: ‘Prospectief Landelijk ColoRectaal kanker Cohort’ (PLCRC)). The cohort is designed in accordance with the ‘Strengthening the Reporting of Observational Studies in Epidemiology’ (STROBE) statement' guidelines [21]. The project aims to collect high quality clinical data, biomaterials and PROMs of a large cohort of CRC patients that are prospectively followed from primary diagnosis until death. All data are collected under a broad informed consent to facilitate future basic, translational and clinical research (Box 1). Furthermore, the cohort aims to serve as an infrastructure to conduct multiple simultaneous (randomized controlled) trials (according to the cmRCT design (Box 2)).

Study population

Patients with histologically proven CRC are eligible for participation if they are 18 years or older and have given written informed consent. Only mentally incompetent and non-Dutch speaking patients are withheld from participation. The aim of the PLCRC project is to include all eligible patients in the Netherlands, a country with a yearly incidence of 15 500.

Box 1. the main objectives of the Prospective Dutch ColoRectal Cancer cohort (PLCRC) are:

- To execute a prospective observational cohort study aiming to include all Dutch CRC patients and follow them until death.
- To prospectively collect high quality data on medical history, comorbidities, clinical characteristics, imaging, pathology results, tumor characteristics, treatment, survival, recurrence, hospitalization, adverse events, toxicity and (long-term) outcomes of experimental interventions (Table 1).
- To collect, store and make available blood and tumor tissue samples.
- To systematically collect patient-reported outcomes on quality of life, workability and functional outcomes.
- To provide detailed data on daily clinical care in the Netherlands.
- To create an infrastructure to facilitate studies of different nature, including:
  A. Prognostic and predictive research;
  B. Biological research and (epi-)genetic research;
  C. Studies that compare novel therapies or interventions in a target population according to the innovative cohort multiple randomized controlled trial (cmRCT) design serving as a pragmatic alternative for classic RCTs;
  D. Cost-effectiveness studies.
Informed consent

Study information is given by researchers, research assistants, non-physician clinicians and/or physicians during routine hospital visits after initial diagnosis, preferably before start of treatment. ‘General’ informed consent is mandatory for participation in this study and allows the collection of long-term clinical and survival data. Subsequently, patients are given the option to consent to: 1) filling out questionnaires on health-related quality of life, functional outcomes and workability; 2) biobanking of tumor and normal tissue; 3) collection of blood samples; and 4) to be offered studies conducted within the infrastructure of the cohort, either in accordance with the cmRCT design or not. When participants are offered to participate in a trial or intervention, an additional informed consent needs to be signed before patients can be enrolled in that trial (Box 2). The PLCRC informed consent procedure is a dynamic process as patients can withdraw or alter their consent preferences at any time during the study.

After inclusion, participants are assigned a unique study identification (ID), which remains the only patient identifier throughout all further processes in the cohort’s infrastructure. Cohort inclusion does not limit participation in other observational studies. However, patients may become temporarily ineligible to participate in clinical trials outside the cohort in case they already participate in a cohort-embedded trial that has interfering endpoints.

Box 2. The cohort multiple randomized controlled trial design.

The basis of the cohort multiple randomized controlled trial (cmRCT) design is a prospective observational cohort of patients with a certain condition [20], in our case CRC, in which all patients in principle undergo standard care. Within this cohort, clinical characteristics and standardized outcome measures are collected at baseline and regularly during follow-up. Clinical and self-reported data are used to compare effectiveness and safety of trialed interventions. Practically, when an RCT is conducted within the cmRCT cohort, the first step is to identify a subcohort of all patients eligible for the intervention. Some of these patients are randomly selected and offered the experimental intervention (intervention group). If patients accept the offer, they are sure to undergo the experimental intervention. If they refuse they will undergo standard care. Eligible patients in the subcohort not randomly selected (control group), undergo standard treatment and do not receive any information on the trial. Outcomes are compared between randomly selected and non-selected patients. This process can be repeated for multiple (experimental) interventions simultaneously, offering (more) reliable direct comparisons between interventions and standard care.

In the cmRCT design a patient-centered informed consent procedure is obtained [42] by asking all patients to give ‘broad consent for randomization’ after enrollment [42,43]. This allows researchers to randomly select patients from the cohort, and offer them experimental interventions, while patients who are not randomly selected serve as controls and undergo standard care without further notification. When informing patients about broad consent for randomization, we explicitly state that not all patients that consent will be offered an experimental intervention as offers are based on random selection. When they got offered an experimental intervention they can either accept the intervention or they can refuse and undergo standard care. Also, they are told that they may become (temporarily) ineligible for future trials if they already participate in a trial which measures interfering endpoints. We ensure that patients will never be withheld proven effective care.

With this consent procedure we aim to mimic clinical practice, where people are usually not told about treatments they will not/cannot receive. The patient-centered informed consent is expected to prevent cross-over and disappointment bias, especially in situations where, regardless of clinical equipoise, a new intervention is highly preferred by doctors and patients. Asking broad consent for randomization also deals with the controversial ethical aspect of pre-randomization [44] by obtaining upfront consent from all patients for randomization and data use in future comparative research, thereby not randomizing patients without prior notification and their consent.

Ethics

The study was originally initiated as a monocenter study for which it received approval of the medical ethical review committee of the University Medical Center Utrecht (The Netherlands) in June 2013 (METC 12-510). Subsequently, approval was extended by the same IRB for a multi-center setup, which was implemented in September 2015. All new intervention studies trialed within the cohort require separate approval from a medical ethical review committee. Study protocols and final results of PLCRC trials are available on the website: www.plcrc.nl excluding study protocols of cmRCT trials, since this design does not allow patients enrolled in the control arm to be informed on these studies (Box 2). PLCRC is registered at Clinicaltrials.gov under NCT02070146.

Data collection and endpoints

Observational clinical and survival data

Extensive observational clinical data (Table 1) are collected from medical charts by trained data managers of the ‘Netherlands Comprehensive Cancer Organisation’ [Dutch: Integraal Kankercentrum Nederland (IKKNL) [22]] and does not require additional effort from participating hospitals or patients. The collected data is stored in the ‘Netherlands Cancer Registry’ [Dutch: Nederlandse Kankerregistratie (NKR) [23]]. Study-specific data, not standardly collected in the NKR, is gathered separately by IKNL data managers, or by study personal or researchers.

Biobanking of blood and tumor tissue materials

Tumor tissues are collected after routine surgery and stored as five snap frozen tissue samples, two Formalin-fixed paraffin-embedded (FFPE) tissue samples and two tissue sample cores for tissue micro arrays. Blood samples (10 ml serum and 10 ml EDTA) are collected during routine blood withdrawal before treatment. Serum is divided over six 0.5 ml samples and the EDTA sample is divided over six 0.5 ml plasma samples and three 0.9 ml pellet samples before being frozen and stored. Snap freezing of tumor tissue, FFPE processing and blood sample processing are performed locally in participating hospitals and transported to regional biobank facilities for long-term storage. To provide a sustainable infrastructure for biobanking, we established close collaborations with existing national organizations for use of their expertise, and to prevent duplicate data entry and unnecessary costs. These initiatives include the Dutch Biobanking and BioMolecular resources Research Infrastructure (BBMRI-NL; www.bbmri.nl) and the CTMM Translational Research IT (TraIT, www.ctmm-trait.nl).

Longitudinal assessment of PROMs

Nationally and internationally accepted and validated questionnaires are used to measure PROMs, which include EORTC QLQ-C30 [24], -CR29 [25] and -CIPN20 [26], Euroqol-5 dimensional (EQ-5D) [27], Work Ability Index (WAI) [28], Low Anterior Resection Syndrome (LARS) [29], Stoma quality of life
scale (SQOLS) [30], Short Questionnaire to assess Health-enhancing physical activity (SQUASH) [31], Hospital Anxiety and Depression Score (HADS) [32], multidimensional fatigue score (MFI-20) [33] and the Self-administered Comorbidity Questionnaire (SCQ) [34]. Patients have the option to fill out paper questionnaires, or use the digital patient tracking system PROFILES (Patient Reported Outcomes Following Initial Long term treatment and Survivor Ship) [35].

Table 1. Clinical data collection within the prospective Dutch colorectal cancer cohort.

<table>
<thead>
<tr>
<th>PART A: Patient ID and data sources</th>
<th>PART B: Pretreatment record</th>
<th>PART C: Treatment record</th>
<th>PART D: Post-treatment/follow-up record</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient identification &amp; demographics</strong></td>
<td><strong>Medical history</strong></td>
<td><strong>Radiotherapy</strong>*</td>
<td><strong>Oncological follow-up</strong></td>
</tr>
<tr>
<td>– Patient-ID code</td>
<td>Cancer specific</td>
<td>Setting (neo-adjuvant/adjuvant)</td>
<td>Recurrence*</td>
</tr>
<tr>
<td>– Birth information (date and city)</td>
<td>Date, location, type, treatment, treatment outcome</td>
<td>Indication for radiotherapy</td>
<td>– Recurrence [date, number, location(s)]</td>
</tr>
<tr>
<td>– Gender</td>
<td></td>
<td>Treatment</td>
<td>– Treatment of recurrence (new PART C entry)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Start date first fraction</td>
<td>– Setting (curative/palliative)</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Cardiac, pulmonary, vascular, gastro-intestinal</td>
<td></td>
<td></td>
<td>– Metachronic metastases [date, number, location(s)]</td>
</tr>
<tr>
<td>– Neurological, gynecological, urological</td>
<td></td>
<td></td>
<td>– Treatment of metastases (new PART C entry)</td>
</tr>
<tr>
<td>– Muscle/bones, endocrine</td>
<td></td>
<td></td>
<td>– Setting (curative/palliative)</td>
</tr>
<tr>
<td><strong>Data source</strong></td>
<td><strong>Intoxication</strong></td>
<td><strong>Adverse events</strong> (date, cause, management)</td>
<td><strong>Complications</strong>*</td>
</tr>
<tr>
<td>– Hospital</td>
<td>– Smoking at diagnosis</td>
<td></td>
<td>– Grade 3/4 adverse events or complications</td>
</tr>
<tr>
<td>– Patient number within hospital</td>
<td>– Alcohol use at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Data capture</strong></td>
<td></td>
<td></td>
<td>– Date of last hospital visit</td>
</tr>
<tr>
<td>– ID of person who captures data</td>
<td></td>
<td></td>
<td>– Death (including date and cause)</td>
</tr>
</tbody>
</table>

* Multiple entries are allowed within each tumor episode
Questionnaires are provided at enrollment (baseline) and 3, 6, 12, 18 and 24 months thereafter, followed by an annual questionnaire for the remainder of their participation or until death. The comprehensive selection of PROM questionnaires which are administered frequently at predefined time points enable the use of PROMs as consistent endpoints in research. Within PROFILES, the option exists to compare PROMs of the PLCRC patient population to those of large population-based samples of cancer patients and a normative Dutch cohort.

**Data for future studies**

Data collected and stored in the NKR is at all times available to centers where the data were originally captured. Additional data required for future research, including study-specific data not standardly collected in the NKR, PROMs and biomaterials, is available upon request.

**Safety**

The observational nature of this study eliminates the appearance of adverse events (AEs) and serious adverse events (SAEs) as a result of participation in this study. However, grade 3/4 incidents according to the Common Terminology Criteria for Adverse Events (CTCAE) are important outcome parameters in research, and are therefore systematically collected. In cohort-embedded trials, reporting of SAE’s occurs as specified in the separate trial protocols.

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Recruitment of patients initially started in one center in February 2013. At this first site, a highly dedicated patient-routine was introduced in which almost all CRC patients visiting the radiotherapy department were approached for participation. During the observed period, 90% of all approached patients consented to inclusion, of whom 90% additionally consented to receive questionnaires, 83% to the storage of biomaterials and 85% to ‘broad consent for randomization’ in future trials. From September 2015 onwards, recruitment has been extended to multiple centers throughout the Netherlands and more centers expect to start recruitment in the (near) future. Currently, eight hospitals are open for inclusion, 15 hospitals are preparing or awaiting IRB approval and 650 patients have been enrolled of which 160 patients were included over the last three months. In addition nine cohort studies that are currently recruiting patients have been embedded within the PLCRC infrastructure, including two RCTs that are designed according to the cmRCT design (Table 2). For both RCTs inclusion rates have looked promising so

<table>
<thead>
<tr>
<th>Name study</th>
<th>Design</th>
<th>Description of study</th>
<th>Study population</th>
<th>Sample size (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal Boost</td>
<td>RCT*</td>
<td>Effect of a pre-operative dose-escalation BOOST versus standard chemoradiation on pathologic response rates in locally advanced rectal cancer [42]</td>
<td>T3 with threatened mesorectal fascia (&lt;1 mm), T4 or N2M0 rectal cancer</td>
<td>60 vs. 60</td>
</tr>
<tr>
<td>Sponge</td>
<td>RCT*</td>
<td>Effect of a retractor SPONGE during laparoscopic rectal cancer surgery versus Trendelenburg positioning on peri-operative complications and hospital stay [44]</td>
<td>Stage I-IV CRC undergoing laparoscopic surgery</td>
<td>94 vs. 94</td>
</tr>
<tr>
<td>PROTECT</td>
<td>Prospective cohort</td>
<td>PlRC cOhoT: diEtary intake after diagnosis and ColorecTal cancer outcomes</td>
<td>Stage I-IV CRC</td>
<td>1000</td>
</tr>
<tr>
<td>CONNECTION</td>
<td>Validation study with different work packages including a prospective cohort study</td>
<td>A nationwide COloN CaNcer eGistry and stratifieCaTion effort for the development and validation of genomic, proteomic and histopathological assays to stratify patients for adjuvant therapy</td>
<td>Stage II-III colon cancer</td>
<td>NA</td>
</tr>
<tr>
<td>MEDOCC</td>
<td>Prospective cohort</td>
<td>Molecular Early Detection of Colorectal Cancer study to investigate the prognostic value of circulating tumor DNA [45]</td>
<td>Stage II colon cancer</td>
<td>846</td>
</tr>
<tr>
<td>SPECTRE</td>
<td>Pilot study</td>
<td>Ultra-high field 7.0 Tesla MR SPECTroscopy to monitor capEctabine metabolism in liver metastases</td>
<td>metastatic CRC</td>
<td>26</td>
</tr>
<tr>
<td>Recap</td>
<td>Case-control</td>
<td>Case match control study investigating the benefit of last line regorafenib treatment</td>
<td>Metastatic colon cancer and metastatic RAS wildtype rectal cancer</td>
<td>125 vs. 125</td>
</tr>
<tr>
<td>Quality of life study 1</td>
<td>Prospective cohort</td>
<td>Impact of short-course radiation versus long-course chemoradiation for rectal cancer on quality of life</td>
<td>Stage II-IV rectal cancer</td>
<td>&gt;60 vs. &gt;60</td>
</tr>
<tr>
<td>Quality of life study 2</td>
<td>Prospective cohort</td>
<td>Quality of life comparison between patients undergoing radiation followed by low anterior resection versus abdomino-perineal excision</td>
<td>Stage II-IV rectal cancer</td>
<td>&gt;100 vs. &gt;100</td>
</tr>
</tbody>
</table>

*Randomized controlled trial according to the cohort multiple randomized trial design (Box 2).
far, with numbers greatly exceeding those of other RCTs [16,17]. PLCRC patients may be eligible for both trials; therefore patients that participate in both trials are stratified according to their received neo-adjuvant treatment as a first step to investigate the feasibility of overlapping trials within the cmRCT infrastructure.

**Discussion**

This multidisciplinary prospective observational cohort study provides a validated and standardized collection of high quality clinical data, PROMs and biomaterials of a large cohort of CRC patients to facilitate future basic, translational and clinical research. By making this collection available to researchers upon request, the cohort foresees in the growing need for comprehensive data collection and sharing [36]. Through its broad eligibility the cohort is likely to reach high recruitment rates, thereby allowing to conduct highly powered analyses, improve recruitment rates to trials and reduce long inclusion periods for studies that use stringent inclusion criteria, i.e. aim to include specific subgroups of patients.

Over the past decades several other cancer registries and prospective observational cohort studies have been initiated in the Netherlands [37–40]. These initiatives serve different purposes, such as providing insight in incidence and prevalence, in the effects of nutrition, lifestyle or treatments in current daily practice, or to serve as a platform for monitoring quality of care. Often these databases or registries are used for various types of research, even though they were originally not intended for this (specific type of research) purpose. In addition, most of these existing cohorts are closed cohorts, or maintain restricted inclusion criteria that limit the inclusion to patients with certain cancer subtypes or to patients that received certain treatment(s). The PLCRC initiative differs in respect to these limitations by its dynamic design, its unlimited accrual potential, and by allowing the inclusion of CRC patients of all stages, independent of their received treatments. Furthermore, some of the registries contain data that are provided by healthcare professionals themselves. Therefore, these registries may lack adequate validation and monitoring of the included data, which likely increases the risk of misclassification and/or underreporting of (adverse) outcomes. By harboring independent data managers and monitors for the PLCRC cohort, we attempt to limit incorrect data registration, which should improve the robustness of outcomes and trial results from our cohort. Finally, the PLCRC cohort is unique in the sense that it provides a comprehensive dataset, which includes aggregated high quality multidisciplinary clinical information, biomaterials and PROMs, and with the possibility of performing studies according to the cmRCT design.

We acknowledge potential challenges and limitations arise from our cohort’s infrastructure. First, by asking informed consent we introduce the risk of selection at a patient level (if specific subgroups do not provide consent as much as other subgroups), or, in case hospitals decide not to participate, at a hospital level. However, as we parallel our data to data from the Netherlands cancer registry (recording baseline and clinical data from all histologically confirmed CRC patients in the Netherlands), we are able to obtain insight in the selection that exists in our cohort both within and between participating and non-participating centers. Second, the cmRCT infrastructure is not appropriate for all types of research. As experimental interventions are compared against standard care, the design does not allow placebo-controlled settings or the use of non-standardly measured outcomes. Nevertheless, such trials can still be embedded in the cohort as classic RCTs for which the cohort can be used as a recruitment pool. The high participation rates, high levels of consent to the additional consent options and the willingness of hospitals to participate in PLCRC indicate that this innovative design is feasible in the oncology practice, acceptable for patients and healthcare professionals, facilitate research projects and is likely to provide generalizable results. Future results are needed to confirm whether the cmRCT design indeed provides an acceptable alternative for classic pragmatic RCTs.

In summary, this cohort provides a unique high quality multidisciplinary data collection initiative, including biobanking and PROMs, which serves as an infrastructure to perform various kinds of research in the field of CRC. The set-up allows evaluation of long-term clinical and PROMs of patients treated in current routine care, and that of patients treated by experimental interventions in a randomized controlled setting. This comprehensive design may serve as an example for research in other tumor types.

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**Disclosure statement**

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**Authors’ contributions**

JB, SK, VD, JM, HK, Ji, CJ, GV, CP, AM, PS, MO, HV, MK contributed to the design of the study. All authors participated in writing and reviewing of the manuscript. Final approval was obtained from all authors.

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