Nationwide comprehensive gastro-intestinal cancer cohorts: the 3P initiative


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Abstract

Background: The increasing sub-classification of cancer patients due to more detailed molecular classification of tumors, and limitations of current trial designs, require innovative research designs. We present the design, governance and current standing of three comprehensive nationwide cohorts including pancreatic, esophageal/gastric, and colorectal cancer patients (NCT02070146).

Multidisciplinary collection of clinical data, tumor tissue, blood samples, and patient-reported outcome (PRO) measures with a nationwide coverage, provides the infrastructure for future and novel trial designs and facilitates research to improve outcomes of gastrointestinal cancer patients.

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Material and methods: All patients aged ≥18 years with pancreatic, esophageal/gastric or colorectal cancer are eligible. Patients provide informed consent for: (1) reuse of clinical data; (2) biobanking of primary tumor tissue; (3) collection of blood samples; (4) to be informed about relevant newly identified genomic aberrations; (5) collection of longitudinal PROs; and (6) to receive information on new interventional studies and possible participation in cohort multiple randomized controlled trials (cmRCT) in the future.

Results: In 2015, clinical data of 21,758 newly diagnosed patients were collected in the Netherlands Cancer Registry. Additional clinical data on the surgical procedures were registered in surgical audits for 13,845 patients. Within the first two years, tumor tissue and blood samples were obtained from 1507 patients; during this period, 1180 patients were included in the PRO registry. Response rate for PROs was 90%. The consent rate to receive information on new interventional studies and possible participation in cmRCTs in the future was >85%. The number of hospitals participating in the cohorts is steadily increasing.

Conclusion: A comprehensive nationwide multidisciplinary gastrointestinal cancer cohort is feasible and surpasses the limitations of classical study designs. With this initiative, novel and innovative studies can be performed in an efficient, safe, and comprehensive setting.

Background

Patients with gastrointestinal cancer are traditionally treated according to several clinical and histopathological characteristics (e.g., tumor location, TNM stage, tumor grade). However, patients with similar clinical features, undergoing similar treatment, may show important differences in clinical outcome [1–3]. The underlying biological differences result in an increasing number of disease sub-classifications, based on efforts towards more individualized (or tailored) patient treatment.

However, due to the increasing sub-classifications of patients, there is a need for novel clinical trial designs and methods for data acquisition and patient recruitment. Current clinical trials have important limitations. First, recruitment is extremely restricted: only 5–10% of all patients are enrolled in a clinical trial [4]. Second, clinical trials include only highly selected patient populations, which leads to low inclusion rates and further limits their external validity. Third, data collection may be inadequate, due to insufficient follow-up or the absence of patient-reported outcomes (PROs); this, in turn, results in high costs or premature termination of the study. Finally, clinical trials are often underpowered for post-hoc subgroup analyses [4, 5]. Consequently, the current clinical trial system has been described as ‘broken’, ‘in crisis’, and ‘not fit for purpose’ [6]. However, there is a paucity of data on a population level. Current nationwide data initiatives such as the Surveillance, Epidemiology, and End Results (SEER) and the Medicare database, contain selected populations and do not include biobanking or data on quality of life [7].

In an effort to address these issues, three comprehensive nationwide cohorts of pancreatic, esophageal/gastric, and colorectal cancer patients were started in the Netherlands (the Dutch Pancreatic Cancer Project ‘PACP’; the Prospective Observational Cohort study of Oesophageal-gastric cancer Patients ‘POCOP’; and the Prospective Dutch ColoRectal Cancer cohort ‘PLCRC’).

Collaborating as the 3P initiative, these three cohorts collect clinical data, tumor tissue, blood samples, and PROs of gastrointestinal cancer patients. The goal is to facilitate research by (inter)national research groups to improve the survival and quality of life of patients with one of these three cancers. The protocol of PLCRC (describing the practical procedures and considerations of the cohort) was previously published [8].

We present the design, proceedings, governance, opportunities, and pitfalls of the three collaborating comprehensive prospective nationwide gastrointestinal cancer cohorts.

Material and methods

Inclusion and informed consent

All patients aged ≥18 years with pancreatic, esophageal/gastric, or colorectal cancer are eligible. Excluded from participation are patients with mental incompetence or insufficient understanding of the Dutch language to provide informed consent. Patients are asked to sign a multi-source informed consent including the following components: (1) reuse of clinical data from all medical files; (2) tissue sampling; (3) blood sampling; (4) to be informed about relevant newly identified genomic aberrations; (5) PROs; and (6) receiving information on new interventional studies and possible participation in cohort multiple randomized controlled trials (cmRCT) in the future. Patients can provide written informed consent for each component separately, and may alter or retract consent for each component at any point in time. As clinical data are crucial to the cohorts for obvious reasons, patients that do not give informed consent for this part of the study are considered ineligible.

Patients who want to consent to receiving information on new interventional studies in the future are informed in detail about the cmRCT design. They are informed: (i) that their data may be (re)used for the evaluation of new interventions offered to patients within the cohort; (ii) that they may in future be randomly selected for an experimental intervention, which they may accept or refuse at a later stage; and (iii) that when enrolled in the cmRCT, they cannot participate in other studies investigating the same intervention or outcome. This procedure is identical to current practice for classical RCTs. However, patients participating in one of the 3P cohorts, but who are not enrolled in a cmRCT, may participate in other studies (e.g., classical RCTs) outside of the cohorts.
Clinical data

Clinical data are obtained from the Netherlands Cancer Registry (NCR), hosted by the Netherlands Comprehensive Cancer Organization. The NCR contains clinical data from all relevant medical charts registered by trained data managers for every patient diagnosed with cancer in the Netherlands [9]. In 2015, the item set of the NCR was renewed and expanded to meet the requirements of the gastrointestinal cancer cohorts and to facilitate research. Items focus on patient, tumor and treatment characteristics, adverse events, and survival. Importantly, medical files are revisited multiple times to ensure the registration of clinical items from diagnosis until death. For every new cancer patient, 200–400 clinical data items are stored in an online secured database using Snowmed ontologies. A collaboration between the national tumor working groups, research groups, and the NCR has resulted in data sharing initiatives allowing data from the NCR to be merged with other databases, e.g., for surgical audits. In these audits, oncologic surgeons collect data for a nationwide auditing initiative, supervised by the Dutch Institute for Clinical Auditing (DICA) [10]. Participation in these audits is mandatory for each hospital. For each surgical patient, an additional set of 100–150 surgical clinical data items is collected.

Importantly, according to Dutch law, collection of clinical data in the NCR and surgical audits does not require informed consent; patients sign informed consent for reuse of these data (as described above).

Tissue and blood samples

For POCOP and PACAP, tissue and blood sampling is organized in close collaboration with the Parelsnoer Institute, an existing national initiative facilitating biobanking for 17 different diseases, including esophageal/gastric and pancreatic cancer [11,12]. Fresh frozen tumor and normal tissue samples are taken from the surgical resection specimen of the primary tumor. Blood samples are withdrawn before and after surgery.

For colorectal cancer, the Parelsnoer Institute facilitates biobanking for hereditary cases. Therefore, patients enrolling in PLCRC cohort can consent to tumor and tissue collection and biobanking separately, in order to collect biomaterial of all cases of colorectal cancer [8]. Both fresh frozen and formalin-fixed paraffin embedded tumor and normal tissue samples are obtained from the surgical resection specimen of the primary tumor. Furthermore, blood samples may be collected as needed for specific study protocols. In PLCRC, the informed consent allows for the withdrawal of blood samples for future research questions without precisely specifying the time point of withdrawal, the patient population studied, and/or the specific tests that will be performed. There is a limit of 10 tubes per patient per year, collected only at the time of regular blood withdrawals. Details of the biobanking standard operating protocols are available in the Supplementary Materials.

Patient-reported outcomes

PROs, including health-related quality of life (HRQoL), are increasingly important outcomes for patients and physicians, and are also of growing interest to other healthcare partners. The PROs that are administered longitudinally were selected in close collaboration with national experts, international advisors, patients, and patient advocates. A core set of validated questionnaires is used to measure generic and diseasespecific HRQoL (e.g., the EuroQol and European Organization for Research and Treatment of Cancer (EORTC) questionnaires) [13,14]. In addition, a cohort-specific set of questionnaires is used to measure, e.g., self-reported adverse events and work productivity. The composition of questionnaires is flexible and may be altered depending on the inclusion of new studies.

To increase patient participation and response rates, patients may complete questionnaires on paper, or online (computer, tablet or smartphone). Questionnaires are provided by the digital tracking system Patient-Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES), a noncommercial initiative with an online patient management system used to send online or paper PROs and automatic reminders [15].

Data access and integration

As mentioned, the main goal of the 3P initiative is to facilitate (inter)national research by collecting and sharing high-quality data. Every researcher (national and international) can use the data and biomaterial gathered to improve the outcome for patients with pancreatic, esophageal/gastric, and colorectal cancer. To ensure a sustainable and secure use of the data, a procedure to evaluate requests to access the data is in place (see: ‘Governance’ below). Furthermore, participating centers may at any time request data of patients enrolled at their own center. Besides the evaluation of the request, a generic and easy-to-use information technology (IT) infrastructure to facilitate the actual use of data is essential. The IT backbone of the three cohorts is based on the FAIR (Findable, Accessible, Interoperable, and Reusable) principles [16] and has been created in close collaboration with national and international research initiatives, such as the Dutch national node of the Biobanking and BioMolecular resources Research Infrastructure (BBMRI), Dutch Translational Research IT (TraIT), and the AACR (American Association for Cancer Research) project ‘Genomics, Evidence, Neoplasia, Information, Exchange’ (GENIE). As mentioned, the different data types are gathered through existing best practices (e.g., NCR, PROFILES) and are combined using an IT solution in which the data types are matched through a unique study registration (USR) number which is assigned to each patient at enrollment. A separate enrollment log, only containing USR numbers with corresponding patient identifiers (name, date of birth, gender and date of inclusion), is stored on a different secured server to secure patients’ identity. Data from the different sources are regularly added using data dumps. In the future, the databases can and will be enriched with data from other studies. Eventually all clinical,
biological, and PROs data are integrated and made accessible in a secure way. This allows (among other tasks) to scrutinize the data for selection bias of the informed consent components, and attrition or responder bias in patients that did respond compared with those who did not respond to the PROs.

**Statistical analysis**

Data were analyzed using IBM SPSS statistics version 21 (IBM, Armonk, NY, USA). Frequency tables were provided, and categorical data were presented as frequencies with percentages. No comparative analyses were performed.

**Prospective studies**

The 3P initiative provides the infrastructure for efficient, safe and comprehensive clinical evaluation of new interventions for patients with pancreatic, esophageal/gastric, and colorectal cancer based on classical observational and interventional clinical study designs, or on the cmRCT design (Figure 1) [17]. Studies based on the latter design can be performed because clinical data are collected for all patients enrolled in the cohorts, including patients who will be randomized to the standard of care arm and do not need to be approached for informed consent at the time of a new cmRCT study.

Both cmRCT and multiple simultaneous prospective observational studies can be performed within the cohorts, as many variables and endpoints are collected in a standardized way. If required, the composition of clinical data and PROs can be altered to accommodate prospective studies. Additionally, data from the cohorts may be used for studies performed outside the 3P initiative.

Because clinical data are collected for all patients enrolled in the cohorts, the cohorts are well suited to serve as the basis for cmRCTs [17]. To enable cmRCT studies within the cohorts, patients are not only asked for informed consent for

Figure 1. Flowchart of the cohort multiple randomized clinical trial (cmRCT) design. At enrollment in one of the three cohorts, patients can consent to be selected and randomized according to the cmRCT design. When a patient is eligible to enter a cmRCT trial, the patient is randomized. When a patient is randomized to the standard of care arm, no additional steps are undertaken. When a patient is randomized to the intervention arm, the patient is approached and offered the intervention, and signs an additional informed consent when participating in the trial.
data collection and to be approached for future clinical trials, but are also specifically asked for future randomization according to the cmRCT design. To use the database for cmRCT to evaluate a new intervention, eligible patients within the cohort can be identified. A randomly selected subgroup will be offered the experimental intervention. The outcomes of these patients are compared to the routinely collected outcomes of eligible patients who were not randomly selected to receive the intervention (i.e., the control group). Patients not receiving the intervention will not be informed that they are serving as controls, as is explained at initial enrollment in the cohort. The intervention is described in a separate protocol that requires approval of the institutional review board. To avoid overlap with other studies, each center can decide if it wants to participate in a specific cmRCT. Patients who accept the intervention have to sign a separate informed consent.

**Governance**

In order to obtain data, (inter)national researchers can file a study proposal using a pre-specified format which will be assessed by the appropriate tumor-specific scientific committee (www.dpcg.nl, www.ducg.nl, and www.plcrc.nl). Submitted research proposals are then reviewed to determine feasibility and quality, and to ascertain possible duplicate studies. For POCOP and PACAP, study proposals that are approved by the scientific committee are subsequently presented to the Dutch Upper GI Cancer Group and the Dutch Pancreatic Cancer Group, respectively. Participating centers requesting data of patients enrolled at their own center can obtain data without following this procedure.

The scientific committees meet 3–4 times a year and are composed of a multidisciplinary team (including basic scientists, social scientists, clinicians, and patient advocates), representatives from all participating centers, and representatives of the boards of the respective research groups. The scientific committees control the release of clinical data, PROs, and blood or tissue samples, to various healthcare partners such as government and industry (Supplementary Figure S1).

**Funding**

Financial support of the 3P initiative is based on ad hoc funding and structural funding. Ad hoc funding consists of public funds (e.g., the Dutch Cancer Society; The Netherlands Organization for Health Research, and Development) and public–private partnerships with pharmaceutical companies. These partnerships are increasingly popular to create the critical mass of partners in specific areas and allow to combine resources, expertise and complementary skills to advance the understanding of the factors underlying differences in the clinical outcome. Furthermore, these collaborations allow to develop drugs at a (possibly) lower cost and faster rate, and to evaluate the cost-effectiveness of new and costly medications [18]. Besides the financial support, the 3P initiative is also supported through data and knowledge-sharing, and access to information technology (IT) tools.

**Ethical considerations and privacy**

Studies on the three cohorts are conducted in accordance with the principles of the Declaration of Helsinki [64th WMA (World Medical Association) General Assembly, Fortaleza, Brazil, October 2013] and in accordance with the Dutch Medical Research Involving Human Subjects Act.

**Results**

In 2015, clinical data of all newly diagnosed patients with gastrointestinal cancer were collected within the NCR including 2284 pancreatic, 3925 esophageal/gastric, and 15,549 colorectal cancer patients. Additional clinical data regarding the surgical procedure (registered in the surgical audit) were available for patients who underwent surgery: 881 (39%) pancreatic, 1244 (32%) esophageal/gastric, and 11,720 (76%) colorectal cancer patients. Extensive data on clinical characteristics and data completeness are reported elsewhere [8, 19].

In an increasing number of participating hospitals, the informed consent procedure for PACAP, POCOP, and/or PLCRC has been implemented (n = 22, n = 16, and n = 12 centers, respectively, as at 1 December 2016). At time of manuscript acceptance, informed consent to collect tumor tissue and blood samples was obtained from 538 pancreatic, 199 esophageal/gastric, and 1313 colorectal cancer patients. During this period, 309 pancreatic, 416 esophageal/gastric, and 1145 colorectal cancer patients were included in the PRO registry. Analysis showed that >90% of the patients who were informed, provided informed consent for one or more

**Table 1.** Number of patients in the Netherlands Cancer Registry, surgical audits, patient-reported outcomes registries, and biobanking.

<table>
<thead>
<tr>
<th></th>
<th>PACAP Pancreas</th>
<th>POCOP Esophageal/gastric</th>
<th>PLCRC Colorectal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands Cancer Registry</td>
<td>2284</td>
<td>3925</td>
<td>15,549</td>
<td>21,758</td>
</tr>
<tr>
<td>Surgical Audit</td>
<td>881</td>
<td>1244</td>
<td>11,720</td>
<td>13,845</td>
</tr>
<tr>
<td>Biobank</td>
<td>538</td>
<td>199</td>
<td>1313</td>
<td>2050</td>
</tr>
<tr>
<td>PROs (eligible)</td>
<td>309 (506)</td>
<td>416 (675)</td>
<td>1145 (1575)</td>
<td>2580 (2756)</td>
</tr>
<tr>
<td>PROs response rate, t = 0 month</td>
<td>98%</td>
<td>95%</td>
<td>79%</td>
<td>91%</td>
</tr>
<tr>
<td>PROs response rate, t = 3 months</td>
<td>63%</td>
<td>73%</td>
<td>63%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Informed consent was obtained from all patients in the patient-reported outcomes registry and biobanking, as collection of clinical data does not require informed consent.

a2015 only.
bNumber of registered resections.
cDate of inclusion until 31 August 2016.

**Table Note**: PACAP: Dutch Pancreatic Cancer Project; POCOP: Prospective Observational Cohort study of esophageal-gastric cancer Patients; PLCRC: Prospective Dutch Colorectal Cancer cohort; N/A: not applicable.
components. Of all patients that consented to receiving questionnaires, at baseline the response rate was 91%, whereas this decreased to 64% after 3 months and to 31% after 6 months.

Table 1 and Figure 2 provide overviews of patients in the clinical data collection, the PROs, and the biobanking initiatives per tumor type. The decrease in response rate over time is partly because some patients died or dropped out between the two time points, or had not yet reached the 3-month or 6-month time point. Of all patients who completed at least one questionnaire, 54% completed the questionnaires online. In the first 67 PACAP patients, the median completion time was 40 (IQR 30, range 15–350) min, which was acceptable to most (70%) of the patients. Over 80% of patients were satisfied with the questionnaire and would participate in the cohort on a regular basis. In addition, most patients (80%) felt that physicians should pay more attention to HRQoL.

Consent to receive information about intervention studies and to participate in cmRCT studies in the future were provided by 94% of PACAP, 84% of POCOP, and by 85% of PLCRC patients.

Discussion
The 3P initiative provides a comprehensive, nationwide, multidisciplinary research infrastructure that accommodates studies on a national level, providing population-based data. Extensive and accurate clinical data, tissue samples, blood samples, and PROs are collected from diagnosis until the death of patients with pancreatic, esophageal/gastric, and colorectal cancer after a broad-based informed consent has been given. The participation rate for each informed consent item was >80%, including consent to be informed about interventional studies and to participate in cmRCT studies in the future. The cohorts overcome many limitations of classical study designs and allow the performance of multiple concurrent studies. The collaborative nature of the 3P initiative combined with involvement of all relevant disciplines and mandated representatives of professional associations ensures a broad nationwide support.

Although many other clinical registries and biobank initiatives are available, only a few initiatives manage to combine both. The 3P initiative not only contains detailed longitudinal clinical data and biomaterial of patients, the PROs are collected and patients can easily be approached for future clinical trials. Based on collaboration with the NCR, which contains clinical data of all Dutch patients diagnosed with (pancreatic, esophageal/gastric, and colorectal) cancer, a nationwide coverage is ensured. Completeness of the NCR is reported to be at least 95% [20]. For comparison: although the SEER program in the USA has greater absolute numbers, coverage is only 28% of the total US population [7]. Regarding the Nordic cancer registries (Denmark, Finland, Iceland, Norway, Sweden, and Faroe Islands), their national coverage is comparable to the NCR and is reported to be close to 100% [21]. Recognizing the importance of PROs, Sweden has also started to collect PROs prospectively over time and organized by tumor type [22].

In the Netherlands, considerable experience has been obtained with surgical auditing, leading to case ascertainment of 95%, data completeness of almost 100%, and data accuracy of 95–99% [10]. The main equivalent for these audits is the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) [23]; although the reported completeness and accuracy is lower compared to the Dutch audits [24], the absence of universal definitions or scoring systems hampers proper comparison. Therefore, a generic and easy-to-use IT infrastructure based on the FAIR (Findable, Accessible, Interoperable, and Reusable) principles is essential, but not easy to achieve [16]. Until now, many
integration/sharing initiatives in (translational) research have failed to achieve full potential. This may be due to either focusing on technology push without sufficient user buy-in and content, or on supplying only technical solutions for one individual dataset thereby creating information silos instead of accessible data. The Handbook for Adequate Natural Data Stewardship (HANDS) published by the Netherlands Federation of University Medical Centers, illustrates the active attitude to break down these information silos and converge the current (inter)national ongoing efforts [25].

Continuously evolving ethical and legal changes lead to more stringent criteria, lengthier protocols/patient information leaflets, and more informed consents for the use and even (retrospective) reuse of patient data and biomaterials. Between 1987 and 2007, the length of the informed consent documents has doubled, mostly due to formal components that aim to inform patients as fully as possible [26]. However, patients who receive brief/simple documents remember the information provided better than those who receive detailed/lengthy information [27]. To maximize information retention of the informed consent procedure of the 3P initiative, information is provided through multiple sources including: the treating physician, a research nurse or physician assistant, study websites, an online patient movie, brochures, and small executive summary folders. Cervo et al. studied a similar multisource informed consent procedure and showed that these patients retain much more information (≥95% of the questions about the informed consent answered correctly) [28] compared to 56-88% without the provision of multisource information [27].

In the Netherlands, the cmRCT design complies with the laws on human medical research and is becoming increasingly accepted in clinical practice. Nevertheless, the design and the possible future impact on patients have provoked resistance in other countries. Patients consenting to randomization following the cmRCT design, may be included in an intervention study in the future [17]. Patients who consent to be approached for future investigations and are later selected for an cmRCT intervention arm, will receive additional detailed information and will be asked to sign a separate informed consent for the intervention. Patients in the control group previously consented at baseline and are fully aware that, when selected for the control group, they will not be informed about that particular cmRCT. Although it remains debatable whether it is ethical not to offer the intervention to these (control) patients, this is no different from a classical RCT. A progressive, practice-changing agreement in the PLCRC cohort is that a maximum of 10 tubes per year may be withdrawn at regular blood withdrawals without the need to amend the study protocol to specify the timing, type of tube, and processing steps. This avoids multiple informed consents, while the assessment of study proposals from researchers or research groups by the tumor-specific scientific committees ensures scientific and ethical integrity.

Although the 3P initiative has a nationwide coverage, intrinsic features of the study population (e.g., the distribution of age/gender/race, and what is considered the standard of care in the Netherlands) may limit external international validity. However, the large number of included patients allows the selection of sufficiently large subgroups. Also, the standardized collection of data and biomaterials using international guidelines allows researchers to integrate data from multiple population-based registries, and to analyze differences in the standard of practice and subsequent clinical outcome.

A second limitation is that the clinical data in the NCR are only as accurate as the information provided in the relevant medical files. Therefore, synoptic and standardized reporting initiatives are ongoing [29]. A third limitation (or challenge) is the current dependency on ad hoc funding. This may result in additional costs for researchers if funding is insufficient to maintain the initiative, which might raise the threshold for researchers to make use of the cohorts. However, since the data and biomaterials are shared with multiple researchers, the financial contribution per research protocol will (if introduced) be lower than the costs for conducting each protocol separately. Importantly, retrospective observational studies using the available data can be performed without making a financial contribution. Nevertheless, structural financial support is preferable to ad hoc funding, which has been (in part) realized through public-private partnerships. Ideally, public funds may redirect part of their funding towards structural funding of longitudinal research initiatives, or the maintenance of longitudinal research initiatives may be considered part of daily clinical practice and be reimbursed as such.

Conclusions

The 3P initiative provides a comprehensive nationwide multidisciplinary research infrastructure to accommodate studies on a national level and complement the paucity of population-based data. Three nationwide comprehensive cohorts for gastrointestinal cancer combine long-term clinical data, biobank material (including tissue and blood), and PROs. These are implemented using available best practices, internationally accepted standards for data collection, and a broad multi-step informed consent. Funding remains a challenge. Data from this initiative are accessible for further (inter)national research that aims to improve health outcomes for pancreatic, esophageal/gastric, and colorectal cancer patients.

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