The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: Scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts

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ABSTRACT

‘Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES)’ is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and are linked directly to clinical data from the population-based Eindhoven cancer registry. This paper describes the rationale and design of PROFILES.

The primary aims of studies that use the PROFILES registry are: (1) psychosocial risk and outcome assessment to identify patients at high risk for poor physical and mental health outcomes, (2) to analyse mediating mechanisms to better understand the biological and behavioural factors associated with cancer treatment outcomes, and (3) to evaluate physical and psychosocial care needs of cancer survivors.

PROFILES is a tool that enables data collection management; from inviting patients to participate in studies, to collecting patient-reported outcomes data via web-based or mailed questionnaires and linking these data with clinical data. The availability of a control cohort of approximately 2000 persons from the general population who complete the same basic questionnaire annually will provide the opportunity to estimate the unique impact of cancer, beyond that of normal ageing and comorbidities. Raw data from the PROFILES registry will be available for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration (www.profilesregistry.nl).

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1. Introduction

Cancer is viewed as a chronic disease for an increasing portion of cancer patients. Due to increasing incidence rates, earlier diagnosis and improved treatments, the number of cancer survivors is rising rapidly in the Western world. In the year 2000, there were approximately 400,000 cancer survivors in the Netherlands; this is expected to increase to 700,000 in 2015. The majority of these survivors will be relatively long-term (>5 years after diagnosis).

The evaluation of new treatments and care protocols for cancer patients is traditionally focused on biological outcomes, specifically disease-free and overall or relative survival. However, today health-related quality of life (HRQoL) is also recognised to be important, especially since many new therapies have only a marginal impact on survival rates, and many survivors face continuing physical and psychosocial problems after completion of primary treatment. Achieving and maintaining optimal well-being is an important objective of current cancer treatment and of cancer rehabilitation and aftercare.

There is a growing body of literature on cancer survivorship, but the majority of studies to date have focused on a few major diagnostic groups (e.g. breast and prostate cancer) or have used cross-sectional designs; longitudinal data are less readily available. Also, most studies have focussed on the HRQoL impact of the primary diagnosis and treatment; less attention has been paid to the HRQoL across the whole cancer continuum.

A recent policy report from the Health Council of the Netherlands about desirability of and evidence for follow-up in oncology concluded that there is a strong need for specific research into the late (side) effects of cancer treatments, including their psychosocial impact. Such studies have often focused on selected populations or convenience samples. To broaden this research area, the Health Council has recommended that an infrastructure be created that will facilitate the on-going evaluation of the short- and long-term effects of new cancer therapies. This will provide information useful in improving current treatment and follow-up strategies, and stimulating future survivorship research. The availability of health outcomes or patient-reported outcomes (PROs) registries that can be linked with cancer registries is very important in achieving these goals.

The Eindhoven Cancer Registry (ECR) compiles clinical data of all individuals newly diagnosed with cancer in the southern part of the Netherlands, an area with 10 hospitals serving 2.3 million inhabitants. On a daily basis, cancer registration clerks register newly diagnosed cancer patients in the ECR since 55 years. Over the past 35 years, this registry has provided clinicians and researchers with a wealth of clinical data (e.g. stage and primary treatment) on cancer patients of all ages. However, data on PROs have not been available in the ECR as in any other cancer registry. In the past 10 years, several studies have, therefore, been set up among currently >10,000 cancer survivors to add PROs to this clinical database. PROs were collected using paper-and-pencil questionnaires, with response rates of 75–80%. Although this form of data collection proved to be feasible, it was also time-consuming and expensive, especially in longitudinal projects with repeated assessments of large cohorts of cancer survivors.

The high penetration rate of internet access in the Netherlands (88.6% in 2010), and more specifically, among cancer survivors in the ECR makes it feasible to develop a web-based registry. Online administration of questionnaires has a number of advantages compared to paper-and-pencil questionnaires, including convenience for the participant, potentially large cost savings, efficiency in data collection, and high quality of the data. Therefore, we have developed a registry, including a large web-based component, for the collection of longitudinal data on the physical and psychosocial impact of cancer and its treatment. This PROFILES (‘Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship’) registry is linked to the ECR, thus allowing merging of PRO and clinical data and discussion of the results with the various clinical groups at the CCC South. This paper describes the rationale and design of the PROFILES registry.

2. Objectives for PROFILES

PROFILES is a web-based registry which can be used to facilitate data collection on PROs from cancer survivors. It can be used simultaneously for multiple studies with different purposes. The main objectives of PROFILES are to generate data relevant to:

- Psychosocial risk and outcome assessment to identify patients at high risk for poor health outcomes. Relevant questions include: Which factors are associated with ongoing health concerns of cancer survivors? Which patients are in need of (psychosocial) support? Do new systemic treatments, especially the new targeted ones, have a beneficial or adverse impact on PROs (e.g. HRQL, disease-specific complaints, anxiety, depression and fatigue)?

- To analyse mediating mechanisms to better understand the biological and behavioural factors associated with cancer treatment outcomes. For example, what is the impact of co-morbidity on PROs in cancer survivors?

- To evaluate physical and psychosocial care (needs) of cancer survivors. For example, does information disclosure relate to satisfaction with care, and health-care utilisation?

3. Relevance and limitations of PROFILES

PROFILES has a number of advantages when collecting data on PROs. The linkage of PROs to details of patients’ diagnosis and initial cancer treatment already available through the ECR provides a unique monitoring system for outcome assessment. This linkage makes it possible to interpret psychosocial outcomes in relation to medical and demographic characteristics. Additional characteristics of PROFILES that
makes it a particularly useful data source for both national and international studies are: (1) the availability of more than 10,000 newly diagnosed cancer patients each year who potentially can be invited to provide PRO data; (2) the high participation rate of the physicians in the ECR area; and (3) the high response rates from cancer survivors, in combination with the high penetration rate (89%) of internet access in the Netherlands.22 This facilitates efficient data collection, particularly in longitudinal panel studies. Internet-based surveys can also improve the quality and completeness of data collection.

We recognise several possible limitations to the approach taken in developing PROFILES. First, use of internet is inversely related to age. Thus, although internet penetration is high in the Netherlands,22 it is likely that participants who complete online questionnaires tend to be younger and have a higher socio-economic status. To minimise this potential bias, PROFILES continues to make use of traditional, paper-and-pencil data collection methods in situations where internet access poses difficulties. Sociodemographic and clinical differences between internet users and non-users can be evaluated with data available from the ECR. Importantly, the available evidence suggests that there are few if any differences in the reliability and validity of PRO data collected online versus via paper-and-pencil questionnaires.23–25 We would note that, given current trends in the use of internet, the percentage of patients from all age groups and socioeconomic strata with access to internet will continue to increase in the coming years.

Currently, PROFILES is a regional project and it is linked to a regional cancer registry (the ECR) covering 2.4 million inhabitants that is part of the uniform national cancer registry in the Netherlands. PROFILES can be expanded to other cancer registries in the Netherlands or abroad. This will be important for the study of survivors of relatively rare tumours for which wider coverage is necessary in order to achieve sufficient statistical power.

PROFILES can be used in many ways: (1) data from PROFILES can be used by clinicians and patients in deciding upon optimal treatment that balances clinical and HRQoL effects and outcomes. (2) Data from PROFILES can be used by health care policy makers to identify the needs of, and to guide health care planning for, the growing group of cancer survivors; (3) it can provide information potentially helpful to patient organisations in developing services and facilities to meet the unmet needs of cancer survivors; and (4) PROFILES data can facilitate appropriate surveillance of those survivors who are at high risk for late consequences of cancer treatment. For example, if results show that certain subgroups (based on tumour, gender, age, comorbidity or personality characteristics) are at higher risk of developing psychosocial problems in certain domains, aftercare programs can be directed in a more tailored fashion.

4. Design of PROFILES

4.1. Panel management system

PROFILES consists of two components, one component for patients’ use, and one component for use by researchers. Patients can visit the website (www.profielstudie.nl) to learn more about its background, the different studies, the researchers, recent publications, etc. This website also contains a link to a secure the environment in which patients can complete questionnaires and make changes in their personal details (e.g. an address change, preference for paper-and-pencil questionnaires, and decision to leave the study).

The PROFILES-team uses PROFILES primarily to ‘manage’ studies with the panel management system. For example, new samples or cohorts of patients (with additional clinical data from the ECR) can be selected from the ECR to be included in any given study. The system automatically produces invitation letters for these patients. Also, it can be used to handle follow-up assessments for those already participating in the study. Since patients are also offered the possibility of completing paper-and-pencil versions of questionnaires, PROFILES can be used to import those data (once scanned) and merge them with web-based questionnaire data. The panel management system offers different user levels, each with its own function and privileges, such as researcher (to view and export anonymous databases), data-entry employees (to register new patients), and panel managers (access to all processes and modules, but not the databases).

5. Inclusion of patients and normative sample

5.1. Process of patient selection and invitation

The population-based ECR offers the unique opportunity to be used as a recruitment tool to select eligible patients for PRO data collection. The ECR registers all newly diagnosed cancer patients within 6 months after diagnosis. This facilitates approaching cancer survivors for study participation soon after their initial diagnosis and primary treatment. Also, previous survivorship studies have shown that patient selection via the ECR works well for long-term survivors (5–15 years after diagnosis) who often are no longer in clinical follow-up.9–20

The ECR is merged on a regular annual basis with civil municipal registries to confirm cancer survivors’ vital status and can be linked at any moment to check current vital status at any point in time. This is very important, particularly in the case of longer term survivors for whom such data may not be readily available via hospital databases. After excluding recently deceased patients, the (former) treating physicians are asked to verify the patients’ study eligibility (e.g. excluding patients’ with serious cognitive impairment or who are in transition to terminal care).

The final selection of cancer patients is then uploaded into PROFILES, and patients are invited to participate via mail by their (former) treating physician. The invitation package consists of a letter, a patient information leaflet and a postcard. The letter explains the goals of the specific study for which patients are being invited. It includes a link to a secure website, a login name, and a password, so that interested patients can provide informed consent and complete questionnaires online. The patient information leaflet contains information about PROFILES in general. Patients are assured that non-participation has no consequences for their treatment or follow-up care. If the patient does not have access to internet, or prefers written rather than digital communication, (s)he can
complete the postcard and return it by mail to the PROFILES-team. Informed consent forms and questionnaires are then sent by mail within 1 week of receipt of the postcard.

The PROFILES-team actively assists the (former) treating physicians in mailing the invitation packages. Patients receive questionnaires between 1 and 4 times a year, depending on the specific research questions. Patients must be able to read and write Dutch, and complete a self-report questionnaire without extensive assistance.

5.2. Normative cohort

PROFILES also contains a reference cohort of approximately 2000 adult individuals from the general Dutch population generated by Centerdata (www.centerdata.nl), a research institute at Tilburg University. This Centerpanel is an online household panel representative of the Dutch-speaking population in the Netherlands. Households without internet access are provided with a so-called ‘Net.box’, enabling connection via a telephone line and a television set. If the household does not have a television, Centerdata provides that as well. A professional helpdesk and panel management support the data collection. Individuals participating in the Centerpanel are asked to complete a subset of the questionnaires used in PROFILES on an annual basis. This includes measures of sociodemographics, comorbidity, HRQoL, psychological distress, fatigue, etc. This normative cohort provides a useful benchmark against which the results based on cancer survivorship samples can be compared. Importantly, the normative cohort is large enough to allow extraction of tailored samples, matched on age, gender and socioeconomic status, to specific survivorship samples (e.g. the 2009 response rate was 78%; N = 1731).26

6. Clinical data, sociodemographic data and patient-reported outcomes

6.1. Clinical data available from the cancer registry

For each patient included in a PROFILES-study, high quality clinical data are available through the ECR. Since 1955, the ECR routinely collects data on cancer patient characteristics and clinical variables such as date of diagnosis, primary tumour site, TNM tumour classification, clinical stage, primary treatment and other primary tumours (second malignancies). Since 1995, the ECR also collects data on comorbid conditions at time of cancer diagnosis, which is unusual for such cancer registries. In addition, the cancer registry is increasingly collecting follow-up data such as disease progression (metastasis and recurrence) from medical record audits. Finally, linkage of the ECR and the PHARMO Record Linkage System creates the possibility to study patient centric drug utilisation, health resources utilisation and their costs, in addition to the effectiveness and safety of pharmaceuticals in routine daily practise in cancer patients.29

6.2. Sociodemographic data

Each PROFILES-study uses the same basic set of questionnaires. In addition to questionnaires on patient-reported outcomes, it contains questions on sociodemographics not routinely collected as part of the ECR. This includes marital status, educational level and current occupation. Socioeconomic status is determined by an indicator developed by Statistics Netherlands based on individual fiscal data from the year 2000 on the economic value of the home and household income, and provided as aggregate level data for each postal code (average 17 households),30 which is categorised into tertiles.

6.3. Patient-reported outcomes data

National and international comparison of outcome data is of great importance. Therefore, PROs are assessed using internationally accepted and validated questionnaires. In all PROFILES-studies, the same basic set of questionnaires is completed annually to evaluate changes over time. This core PROFILES dataset can be used to compare different subgroups of cancer patients (from different PROFILES-studies), and to compare cancer patients with the normative cohort (with respect to EORTC-QLQ-C30, FAS, HADS, comorbidities and sexuality items). In accordance with our objectives to study to assess patient-reported outcomes of cancer and its treatment, to identifying mediating mechanisms, and to assess the physical and psychosocial care (needs) of cancer survivors the basic set of PRO questionnaires includes the following:

- HRQoL of cancer patients will be assessed by the EORTC-QLQ-C30.31
- Fatigue will be assessed by the Fatigue Assessment Scale (FAS), which consists of five items reflecting physical fatigue and five items reflecting mental fatigue.32
- Anxiety and depression will be assessed by the Hospital Anxiety and Depression Scale (HADS).33 We will use a score of 8 as a cut-off value for both depression and anxiety.33,34
- Health care utilisation will be assessed with separate items (e.g. how often did you visit your general practitioner in the past 12 months?).12,17
- Health behaviours, including tobacco use, alcohol use and physical activity will be assessed with separate questionnaires.
- Comorbidity at the time of the study will be assessed according to the adapted Self-administered Comorbidity Questionnaire which also assesses the perceived severity and burden of the comorbid condition.
- The level of information received by cancer patients at different stages of their disease and treatment will be assessed by the EORTC QLQ-INF026 questionnaire.36
- For each specific group of cancer survivors, where available, we include an EORTC condition-specific questionnaire module (e.g. for breast, lung, colon, and prostate cancer). The sexuality items from these EORTC modules are also completed by the control cohort.
In addition to this basic set of questionnaires, PROFILES offers the flexibility to add new measures that are relevant to a specific PROFILES-study, and to add questions that may become relevant as changes take place in treatment (e.g. side-effects). Cancer treatments are continually being refined, and toxicity profiles are a moving target.37

7. From data collection to a complete registry: what does it take?

7.1. High participation rates from physicians

In our previous and ongoing studies, almost all (95%) physicians in our area participate(d). This high participation rate can be explained by the strong involvement of all physicians in the survivorship studies, which is established in the active ‘tumour’ working groups. For each specific type of cancer, multidisciplinary ‘tumour’ working groups meet several times a year to discuss treatment guidelines and new studies. The fact that the PROFILES logistics are completely managed by the PROFILES-team and registration clerks of the ECR undoubtedly has a positive effect on the willingness of busy clinicians to participate.

7.2. Ethical issues

When patients agree to take part in a PROFILES-study, they are asked to sign an informed consent form. By signing and returning that form (online or by mail), patients consent to participating in the study and agree to the linkage of the questionnaire data with the clinical data stored in the ECR. Non-participation has no consequences on follow-up care or treatment.

Returned questionnaires do not contain any overt identifiers (i.e. names) but rather are coded by number, for purposes of data collection tracking and linkage with the ECR database. Only a few PROFILES-team members have access to a record that links patient numbers to identifiable information.

A local certified Medical Ethics Committee is required to approve each study that is conducted using the PROFILES registry. PROFILES is also registered with the Dutch Data Protection Authority (registration code 1433221), who supervises the fair and lawful use and security of personal data collected in the Netherlands.

7.3. Data entry and retrieval

Online data collection carries with it a number of clear advantages. Patients will complete questionnaires online, and data are immediately entered into a database. This avoids errors that can occur when transferring data either manually or electronically (e.g. scanning) into a database. Missing values are minimised, as the online system only allows questions to be skipped if they are of a particular sensitive nature (e.g. on sexuality). For all other questions, patients are prompted to respond if left missing.

Patients who prefer a paper-and-pencil based questionnaire will receive a questionnaire by mail. Patients can return these questionnaires with a prepaid return envelope. The responses to these questionnaires are scanned, after which a control check takes place on that database. Finally, the scanned database is merged with the web-based database by the PROFILES panel management system.

7.4. PROFILES helpdesk

The PROFILES registry has a helpdesk that handles patients’ phone calls and emails. The helpdesk answers questions about the studies that take place using PROFILES, and offers help with the online questionnaire (e.g. login problems). Patients can also contact the helpdesk to request a paper-and-pencil version of the questionnaire. Patients who contact the helpdesk with questions of a clinical nature, or who seek psychosocial support, are referred to either their medical specialist, their family physician, or to other health care professionals in their community. To date, only a very small percentage (≤2%) of the patients has contacted the helpdesk.

The helpdesk has access to the panel management system in order to confirm any changes in information received from patients or their family members (e.g. change of (email) address and wish to discontinue participation). Patients can also discontinue participation directly via the online panel management module. Although they are not required to do so, patients are asked to provide the reason(s) for discontinuing participation.

7.5. Panel management: cohort retention, non-response and follow-up

In previous cancer survivorship studies conducted by our research group, high (i.e. ≥75%) response rates were achieved when using paper-and-pencil questionnaires.8–20 Several efforts have been made to enhance participation in studies that are set up using PROFILES. Once a year, a digital newsletter will be sent to all the participants. This newsletter contains information on the current status of the different PROFILES-studies within the registry, study results (new publications or presentations given) and interviews with researchers, among others. We keep our website up-to-date by regularly adding press releases and information on PROFILES presentations given at (inter-)national conferences. Finally, cooperation of each patient’s (ex)-attending physician and the PROFILES helpdesk help cohort retention.

Based on other Dutch cohort studies we estimate that a maximum of 25% of patients will dropout during follow-up. Non-respondents are sent a reminder letter and a paper-and-pencil version of the questionnaire within 2 months after the initial invitation. Mortality rates depend on tumour type and stage. An important advantage of using the ECR as a sampling frame is that we are able to examine whether selective response or loss to follow-up occurs, as we have patient, tumour and treatment characteristics of those who do not wish to participate or who choose to discontinue participation.

7.6. Data storage

The web-based facility is hosted on multi-processor servers for which infrastructure, configuration, licence, security and patching are established in accordance with current norms (NEN-ISO/IEC 27002). Participants log in with their own user
name and password into a PHP web application that communicates with a MySQL database located on a different server. This database server is shielded through a firewall from the internet and stores the personal data of the participant. Both PHP and MySQL database servers run Linux as Operating System. Participants fill in their questionnaire on a separate server cluster, consisting of Windows 2008 R2 Servers running BlaiseIS questionnaire software (Statistics Netherlands). The answers to the questions are stored on a dedicated data storage server, shielded through firewalls from the internet. All servers are located in a secured room with access only for authorised personnel. The PROFILES infrastructure and software is updated regularly to optimise system operations and security. Digital PDF-files of questionnaires are stored at the ECR, which complies with privacy regulations regarding data collection among cancer patients.

8. Data dissemination

The wealth of medical information from the ECR has always been available for scientific research, and has resulted in several hundred scientific publications written by researchers from the Netherlands and abroad. The PROFILES registry aims to provide a national resource for research into the psychosocial well-being of cancer survivors in conjunction with the ECR and its clinical embedding that builds on high quality cancer registry data. Therefore, data from PROFILES will be freely available for non-commercial scientific research, subject only to privacy and confidentiality restrictions. Data will be made available through Questacy (DDI 3.x XML) and can be accessed by our website (www.profilesregistry.nl). In order to arrange optimal long-term data warehousing and dissemination, we follow the quality guidelines that are formulated in the ‘Data Seal of Approval’ (www.datasealofapproval.org) document, developed by Data Archiving and Networked Services. In short, this means that (1) the data can be found on the internet; (2) research data are accessible (while taking into account ruling legislation with regard to personal information and intellectual property of the data); (3) research data are available in a usable data format; (4) research data are reliable; and (5) research data can be referred to. Also, PROFILES data will be provided with contextual information (metadata). This means that after data collection, the data will be cleaned, coded and provided with sufficient information to enable fellow scientists to access the research data. Also, we will perform first analyses on the data to check the quality and validity. After this process, the data will be freely available for research questions from other non-commercial groups in the Netherlands and abroad after registration.

9. Summary and future perspective

PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of cancer survivors. The linkage of PROs to details of patients’ diagnosis and initial cancer treatment already available through the ECR provides a unique monitoring system for outcome assessment. This linkage makes it possible to interpret psychosocial outcomes in relation to medical and demographic characteristics. In addition, the availability of a control cohort of approximately 2000 persons from the general population who complete the same basic questionnaire annually provides the opportunity to estimate the unique impact of cancer, beyond that of normal ageing and comorbidities.

Currently, PROFILES is a regional project linked to the ECR covering 2.4 million inhabitants in the Netherlands. In the nearby future, we foresee to expand the data collection by use of the PROFILES system to other cancer registries in the Netherlands or abroad. This will be important for the study of survivors of relatively rare tumours for which wider coverage is necessary in order to achieve sufficient statistical power.

From May 2011 and onwards, raw data from both old and new PROFILES studies will be made available regularly for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration (www.profilesregistry.nl).

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Conflict of interest statement

None declared.

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