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Implementation of patient-reported outcome assessment in routine cancer care – a systematic review of multicentric programs in Europe

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Abbreviations

CHAFEA	Consumers, Health, Agriculture and Food Executive Agency
EDIUM	Ergebnisqualität bei Darmkrebs: Identifikation von Unterschieden und Maßnahmen zur flächendeckenden Qualitätsentwicklung
EMBASE	Excerpta Medica dataBASE
EORTC	European Organization for Research and Treatment of Cancer
EU	European Union
ICHOM	International Consortium for Health Outcomes Measurement
iPAAC	Innovative Partnership for Action Against Cancer
ISOQOL	International Society for Quality of Life Research
MeSH	Medical Subject Headings
NHS	National Health Service
OECD	Organisation for Economic Co-operation and Development
PDCA	Plan-Do-Check-Act
PedsQoL	Pediatric Quality of Life Inventory
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient reported outcome measure
TAPQOL	TNO-AZL Preschool Children Quality of Life
TNGR	TruNTH Global Registry
UK	United Kingdom

Executive summary

Objectives: To give an overview of patient-reported outcome measures (PROMs) programs in routine cancer care that allow for both major purposes of PROM assessment: 1) monitoring of an individual patient's outcome to assist treatment decision making and 2) use in quality improvement initiatives including the benchmarking of providers. We synthesize information on program elements like mode of assessment and questionnaire used as well as information relevant for adaptation following a PDCA-scheme.

Method: We carried out a systematic literature research in the PubMed and EMBASE databases using MeSH terms and keywords related to PROM assessment in routine cancer care to identify eligible studies published between January 2003 and November 2018. We included studies in which PROM assessment programs had been reported as being implemented in clinical practice as well as collected multicentrically with at least one site in Europe and in which PROMs had been collected before and at least once after intervention. Study authors were queried to verify or correct the program elements synthesized during the review. Study quality assessment was not done, since it is not expedient for the objective of this review.

Results: 5,545 unique references were identified of which 5,484 were excluded after screening of titles and abstracts. Of the 61 references assessed, five programs were identified and included in the synthesis. The programs included programs from Germany, Austria, Denmark, the Netherlands and UK and patients with different cancer types and tumor stages, that used both paper-based or purely electronic PROM assessment.

Conclusions: The studies revealed relevant information on existing PROM programs and gave valuable insight into issues that need to be considered when setting up such an infrastructure. Some critical issues, however, were hardly addressed, among them costs, staff resources and methods of reporting and responding.

1 Introduction

Benefits of patient-reported outcome measure (PROM) assessment are well described in the literature. To distinguish PROMs from patient-reported experience measures (PREMs) the OECD provided a brief definition focusing health status and excluding satisfaction with care, quality of interaction with providers and other indicators: "PROMs: Measure patients' perceptions of their health status, clinical outcomes, mobility and quality of life." [1: p. 25] Not only do PROMs help healthcare providers in assessing patients' symptoms and functions more precisely [2,3] and assist clinical decision making [4,5] – recent studies also showed improved survival when cancer patients are monitored with PROMs [6,7]. Though evidence for PROM benefits from studies is substantial, the issue of how to best implement PROM assessment into routine care is widely unsolved. Not only because funding for such programs outside of time-bound research studies is generally difficult to collect, but also because it is not clear what works best in different clinical situations when implementing routine PROM programs. Decisions that need to be made when planning PROM programs include the choice of instruments, the mode of administration (e.g., on-site vs at home, online v paper-based), feedback provision and many more [8].

Recent initiatives defined standards for measuring process and outcome quality including PROMs and guidance on when or how to collect and with which specific questionnaire, such as the ICHOM Standard Set for Colorectal Cancer [9]. Its implementation is still limited to a few sites, typically with variation in data collection that does not allow for the comparison of site outcomes. Large existing programs that collect PROM data include those issued by the NHS from 2009 on [10], that of the Swedish Hip Arthroplasty Register that collects PROMs since 2002 [11], or initiatives led by charities such as the TrueNTH Global Registry that is funded by the Movember Foundation and that collects outcomes data including PROMs in prostate cancer patients in 15 countries [12]. Such programs have the explicit aim to compare/benchmark outcomes of providers, to encourage mutual learning, and in the case of the NHS, to even make parts of reimbursement dependent on PROM results.

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group, one of the leading PROM developers for cancer, issued a manual for the utilization of PROMs in daily practice [13]. Similarly, the International Society for Quality of Life Research (ISOQOL) and others discussed logistics and provided recommendations several years earlier [8,14,15] and in 2017 Franklin and colleagues [16] did likewise, including best practice examples. Similarly, Nordan et al. recently described challenges and success factors for the implementation of electronic PROMs within one large medical center [17]. Recommendations cover major aspects such as measure selection, choice of patients addressed, assessment timing as well as scoring and reporting techniques. Whether these recommendations are met in practice and whether they are feasible in routine care however is less clear. A number of reviews described routine care approaches to PROM assessment in the past [8] and gave insight into facilitating factors and obstacles under different circumstances. Such knowledge is imperative to derive an implementation strategy that suites the situation, e.g. the clinical setting, the country, the stakeholders involved and much more.

In this report we attempt to add to the existing body of knowledge regarding the implementation of PROMs into routine cancer care by conducting a systematic review to identify PROM programs that allow for both major purposes of PROM assessment: 1) identification of an *individual* patient's symptoms and function to assist in communicating and clinical decision making as well as monitoring his or her outcome and 2) use of *group data* in quality improvement initiatives including the benchmarking of providers or sites with respect to outcomes. This research was conducted as part of Work Package 10 of the iPAAC Joint Action – Innovative Partnership for Action Against Cancer – that is co-funded by the Health Programme of the European Union that brings together 24 European countries to develop and implement innovative approaches to cancer control. The aim of Work Package 10 is to "develop practical instruments to support Member States in successful governance of cancer care, ensuring standardized, integrated and comprehensive oncological care" [18: p. 14] including the collection of PROMs. Results of this report will guide the development of a framework for the implementation of PROMs in routine cancer care. Further information on the joint action's aims are provided at https://www.ipaac.eu/. To better be able to suggest recommendations for the integration of PROMs in "comprehensive oncological care" we systematically synthesize attributes of the PROM programs identified in the systematic review like mode of assessment and instrument used as well as attributes that are associated with acceptance and usability of the programs and that thus contribute to the success of PROM routines.

2 Methods

2.1 Literature research

We conducted a systematic literature research to identify existing PROM programs in routine cancer care that allow for decision-making of individual cancer patients as well as provider comparisons. Programs were thus limited to those that were multicentric as well as collected PROMs before and at least once after an intervention to allow for both major purposes *provider comparison* and *patient monitoring* and because pre-intervention assessment is necessary for risk-adjustment of outcomes. The criterion "multicentricity" includes the utilization of an identical infrastructure, uniform recruitment standards as well as that data are or at least may be analyzed across sites to allow for comparability. We furthermore restricted our literature research to programs that already published results to avoid the inclusion of conceptual reports or unsuccessful programs. We intended to identify "programs", not articles, i.e. if two or more original articles on one program were found we integrated the information into one program-specific synthesis. Defining PICOS for the study characteristics proved only partly practical. Since we were not looking for intervention effects but only for programs themselves only the P(opulation) and I(ntervention) dimensions could be defined satisfactory, with "P" being "patients with any kind of cancer diagnosis treated in Europe" and "I" being "multicentric implementation of Patient Reported Outcome Measures (PROMs) in routine cancer care with at least one pre- and one post-intervention assessment". Only primary research "S"(tudies) were considered, but if reviews were identified the reviewed research would have been assessed for inclusion. This

incomplete PICOS definition was included in the study protocol that additionally contained specific questions relevant for deriving good practices following a plan-do-check-act-scheme (s. results section, table 3). We excluded time-bound research projects that were funded for only a limited amount of time without clear hints that the underlying PROM infrastructure is already or may be implemented into routine care afterwards. Since this report will be used to derive recommendations for PROMs to be implemented in cancer centers in Europe and data protection regulations substantially differ from other parts of the world, programs were restricted to those conducted in Europe, using a geographical understanding of Europe including countries with only parts of their land mass being part of Europe including Turkey, Russia, Georgia, and Azerbaijan. Title/abstracts had to be in English and no further language restrictions were defined for full text language. The search was restricted to articles published 2003 - 1 November 2018. The resulting search string is documented in appendix 1. To supplement our literature database search we used the backward snowballing technique and checked reference lists of those studies found and included using our search string. Above that, we carried out a cited reference search to identify relevant studies/papers that have cited the already included studies. Experts from the IPAAC consortium were asked for additional programs. Resulting hits were screened by two authors (CK and MS, who was substituted by AH while on leave) independently after exclusion of duplicates. In a first step, titles and abstracts were screened. In case of any disagreements consensus was reached by discussion. Full texts were retrieved and assessed when both reviewers agreed. If only abstracts were provided, we hand searched for follow-up full-text publications. In case identified articles have been published in languages the review authors could not assess, the articles' corresponding authors were consulted to decide whether inclusion criteria were met or not. Again, at this stage, in case of disagreements consensus was reached by discussion.

2.2 Data extraction

Standardized data abstraction forms were used to depict information on study type, setting, goals (cf. results section, table 1), patient characteristics (number, gender, ethnicity, cancer type, stage) (table 2), as well as qualitative and quantitative information on 20 specific research questions to identify facilitators and obstacles to implementation and acceptance by those involved (Table 3). Items to identify such potential facilitators and obstacles were derived from existing reviews and the above-mentioned manuals/recommendations following a PDCA-scheme. Two authors extracted independently in duplicate the identified studies for program attributes. In case of disagreements, results were discussed until consensus was reached. To verify the identified program attributes, corresponding authors and/or program directors were queried to check for correctness of the abstracted information and to provide further information in case none was identified in the program report. Study quality was not assessed since it is not expedient for the objective of this review, that is we were not interested in the quality of the published articles but attributes of the programs.

3 Results

The flowchart according to PRISMA [19] (figure 1) depicts the study selection process. 5,545 records were screened, of which 61 were assessed for eligibility after title/abstract screening. Five programs were included in the qualitative synthesis [20-24]. Table 1 presents study characteristics, table 2 presents sample characteristics of the identified articles, and table 3 presents the findings of the qualitative synthesis and the author query.

3.1 Study Characteristics

The studies were published between 2010 and 2016. Programs were from Denmark, Germany, Austria, the UK, and the Netherlands. None was cross-national. Studies described interim results for patient samples, typically patients recruited very early since program initiation, and all programs were ongoing at the time of review. Specification of the primary research purpose varied and centered either around quality improvement / evaluation of outcomes, health care monitoring, and prediction of disease progression / research. The study settings ranged from population-based registries in which all patients were included and into which PROMs were additionally documented to hospital-based recruitment of consecutive patients. Number of follow-ups varied, e.g. at 1 and 3 years, up to 5 years after diagnosis, or annually (without specified end date). Types of studies were observational prospective (or "cohort") studies, and one included an interventional, sequential cohort approach (first control, then intervention). Questionnaires used were either not specified, included EORTC-QLQ instruments or instruments specific to pediatric cancers (PedsQoL, TAPQOL).

3.2 Sample characteristics

The five programs included patients with various kinds of cancers. One included only prostate cancer patients and one only bladder cancer patients. One included children up to 18 with all cancers and two included adult patients with different cancer types (breast, colon, rectum cancer and gastrointestinal, gynecological, neuroendocrine tumors, glioma, lung, testicular cancer). Samples consisted of stage 0-III patients in one study, was not restricted in another and was not reported in three studies. The samples consisted of patients of all genders, except for the program on prostate cancer that was restricted to males. No restriction on ethnicity was indicated, but variation in ethnicity was also not reported. Sample sizes ranged from 158 to 22,332 patients.

3.3 Qualitative synthesis of program characteristics

Three of the five queried corresponding authors or their designated deputies responded. Two approved the syntheses [23,24], with [23] adding information on items for which no information was provided in the study. [20] provided comprehensive additional information which is documented in the supplementary material and synthesized in table 3. Only [20] filled out question 20 "Is there anything else that should be mentioned regarding the PROM program?"

Few patterns were identified regarding the "P(lan)" items and often information could not be derived from the publications. The primary purposes of program implementation (in comparison to the *research* purposes of the articles described in table 1), included the monitoring of events following treatment, identifying patients' needs, benchmarking outcomes, improving communication between patients and providers or simply collecting quality of life information without further specification. Patient selection included full surveys of the whole (hospital) population affected as well as several strategies to approach patients during appointments. Regarding proxy support on the completion of surveys, three articles provided no information, one allowed parents to fill out the questionnaires on behalf of their 0-7 year old or their mentally disabled children, and one explicitly mentioned that nurses could be asked for help. For two programs information was given on why the specific questionnaires were selected (during the query), highlighting its psychometric properties and the available translations. Information on costs (items 6 and 7) were given sparsely with two programs providing no details, one hinting at the necessity to provide a study nurse, one indicating that each participating unit had a specially-trained study nurse funded for the program and one recommending one PROM coordinator for each center. No cost estimates were given. Regarding recommendations for necessary conditions before implementation the articles hinted at staff training to use PROM instruments and the IT infrastructure as well as the provision of hardware for the on-site completion of questionnaires.

"D(o)" information regarding the implementation of the programs could be synthesized relatively well from the studies. PROMs implemented included cancer-generic instruments for studies with mixed populations and generic and cancer-type specific instruments for programs that included only one cancer type. The pediatric program tailored the selection of questionnaires according to patient age. PROM assessment was done at very heterogeneous time points, for example "annually" or "prior to each consultation". In two instances, no "baseline" PROMs were collected in that treatment-naïve patients were surveyed but in one program patients were surveyed "within three months of diagnosis" [20] or the point of initial survey was not explicitly mentioned [21]. Since these programs were nevertheless useful for monitoring patients and to investigate events following interventions these studies were considered eligible for the review. In two programs, questionnaires were filled out electronically, in one instance via postal mailings and in one case via face-to face interviews. Assessment was done at home in some and exclusively at time of consultation in other programs. Regarding data processing and result dissemination, three programs provide the results in a processed way to providers, either electronically or on paper. No information was found for the other two programs. PROMs were used for benchmarking in one program. The Austrian program stores data in hospitals separately with no benchmarking effort yet. One program intends to use data for quality improvement purposes prospectively. For two programs no information on benchmarking/provider comparison efforts was found. Two programs provided information on consequences of issues potentially identified with help of PROMs, with one discussing issues in workshops and one providing a decision-tree pocket card.

In the "S(tudy)" dimension we distinguished between the "barriers and enabler" and the "impact and lessons learned" aspect with very little information being collected, primarily from the Austrian and Dutch programs. Critical issues identified for acceptance include internet and data privacy issues and

sociodemographic barriers to electronic PROM collection as well as the inclusion of end-users in the development process. No information on how to promote multicentric implementation was identified. The Dutch program provided information on the impact of PROM implementation identifying better awareness of the providers regarding their patients' health and a better provider-patient communication. Two aspects to be considered during implementation could be identified: the involvement of stakeholders including the training of patients may facilitate implementation and program initiators need to be aware that many difficulties may occur, for example that PROM collection may be more time-consuming than initially expected.

The "A(ct)" dimension inquired whether any modifications were done since program implementation with the only identified change in the Dutch program where – among other things – the infrastructure was changed to a fully web-based tool. The open question 20: "Is there anything else that should be mentioned regarding the PROM program?" was only answered by the Dutch respondent.

Table 1: Study characteristics

	Nguyen-Nielsen et al., 2016	**Meisner et al., 2011**	**Wintner et al., 2015**	**Zeegers et al., 2010**	**Engelen et al., 2012**
Study name	The Danish prostate cancer database	Benchmarking: how to measure outcome quality at the comprehensive oncology centre in Stuttgart	Evaluation of electronic patient-reported outcome assessment with cancer patients in the hospital and at home	The West Midlands Bladder Cancer Prognosis Programme: rationale and design	Reporting health-related quality of life scores to physicians during routine follow-up visits of pediatric oncology patients: Is it effective?
Country	Denmark	Germany	Austria	UK	Netherlands
Time period of PROM collection	May 2011 – April 2015 (ongoing)	September 2003 - December 2008 (ongoing)	February - September 2012 (ongoing)	December 2005 – unclear (ongoing)	March 2006 - November 2009 (ongoing)
Primary research purpose	"systematically collecting key clinical variables for the purposes of health care monitoring, quality improvement, and research"	evaluation and improvement of outcomes	collect information on patients' internet use and their attitudes towards electronic QoL assessment	Objective is to relate health-related quality of life to the recurrence and progression of bladder cancer	investigate the effectiveness of an intervention that provides HRQOL scores of the patient to the pediatric oncologist
Study setting (+ number of follow-ups)	population based registry; clinical data collected by treating physicians in 22 urological and oncological departments. PROM data collection at diagnosis and at 1 and 3 yrs	PROM assessment in 13 comprehensive oncology centers in the region of Stuttgart, Germany, between 30-09-2003 – 31-12-2008; PROM collection annually after diagnosis; first PROM collection N/A	Assessment of patients' QOL before a follow-up / treatment appointment in a hospital setting (clinic-ePRO), and second, as regular monitoring of the symptom burden of chemotherapy outpatients in the home setting (home-ePRO); two Austrian hospitals; follow-up N/A	Hematuria clinics within the West Midlands, assessment of QLQ-C30 questionnaire at baseline in the entire cohort, first follow-up at 3 months after diagnosis, from then up to 5 years after diagnosis	4 University Medical Centers, pediatric oncology patients and their parents surveyed within three months after diagnosis and then all three months; set of surveys tailored to patient group

Type of study	population based registry	"prospective, non-randomized, multi-centred, registry-based cohort study"	observational prospective study	epidemiological prospective cohort study	sequential cohort design (first control, then intervention)
Measuring instrument	N/A	EORTC Quality of Life QLQ-C30, Version3.0	EORTC QLC C30	general cancer questionnaire QLQ-C30 with the addition of disease-specific assessments using the QLQ-C30, the QLQ-BLS24, with 24 questions specific to NMIBC, the EORTC QLQ-BLM30, with 30 questions specific to muscle-invasive bladder cancer	PedsQL self-report, PedsQL proxy report, TAPQOL

Table 2: Sample characteristics

	Nguyen-Nielsen et al., 2016	**Meisner et al., 2011**	**Wintner et al., 2015**	**Zeegers et al., 2010**	**Engelen et al., 2012**
Patient characteristics	The Danish prostate cancer database	Benchmarking: how to measure outcome quality at the comprehensive oncology centre in Stuttgart	Evaluation of electronic patient-reported outcome assessment with cancer patients in the hospital and at home	The West Midlands Bladder Cancer Prognosis Programme: rationale and design	Reporting health-related quality of life scores to physicians during routine follow-up visits of pediatric oncology patients: Is it effective?
Number of patients	22,332	3,213 breast, 1,216 colon, 847 rectum carcinoma patients	113 on-site, 45 at home	771 patients	193
Gender	male	male and female	male and female	any	any
Ethnicity	N/A	N/A	N/A	N/A	any
Cancer type	incident prostate cancer	breast, colon, rectum cancer	gastrointestinal tumors, glioma, gynecological tumors, lung cancer, neuroendocrine tumors, testicular cancer	pathologically confirmed urothelial carcinoma of the bladder	all cancers, children 0-18 yrs
Stage	any	UICC TNM stages 0-III	N/A	any	N/A

Table 3: qualitative synthesis of program characteristics

	Nguyen-Nielsen et al., 2016	**Meisner et al., 2011**	**Wintner et al., 2015**	**Zeegers et al., 2010**	**Engelen et al., 2012**
Research Questions	The Danish prostate cancer database	Benchmarking: how to measure outcome quality at the comprehensive oncology centre in Stuttgart	Evaluation of electronic patient-reported outcome assessment with cancer patients in the hospital and at home	The West Midlands Bladder Cancer Prognosis Programme: rationale and design	Reporting health-related quality of life scores to physicians during routine follow-up visits of pediatric oncology patients: Is it effective?*
PLAN - Preparation:					
1 Who were the primary drivers of program implementation? (for example, doctors, nurses, patients, quality initiatives, other)	N/A	N/A	"Home ePRO resulted from a longstanding initiative of a chief physician at the Kufstein County Hospital and clinic-ePRO at the Medical University of Innsbruck was part of a larger research project initiated by doctors and scientists"*	Cancer Research UK Bladder Cancer Group, University of Birmingham	„[D]uring the initial effectiveness and implementation study, researchers were the primary drivers of the program."
2 What were the primary purposes of program implementation? (for example, patient monitoring, treatment planning, benchmarking, quality assurance, other)	recording of adverse events following treatment	evaluation and improvement of outcome quality; benchmarking outcomes between centers	assessment of patients' QOL	to study the determinants of recurrence and progresssion of NMIBC and to design a prognostic tool that could predict adverse outcomes; "The research objectives in this second project are to study the effects of recurrence and progression on quality of life; to study the effects of repeat cystoscopy, urostomy and self-catheterization on quality of life; and to study the patients' assessments of a hypothetical prognostic	„Monitoring quality of life and screening for psychosocial issues in order to assure patient-centered communication during the consultation, identify patients' needs and refer to necessary intervention if needed."

				model and how this affects their preference for the mode of surveillance"	
3 How are the patients selected? (i.e., choice of population, sampling strategy, who recruits patients)	no selection; All Danish patients with histologically verified prostate cancer are included	patients treated in participating centers	patients were approached before appointments or treatment application in the case of chemotherapy treatment	patients: Potentially eligible patients are being identified at hematuria clinics on the basis of abnormal cystoscopic findings suggestive of bladder cancer; population selection: N/A	"[A]ll patients with cancer (aged 0-18 years) are approached within one month post-diagnosis and their PROMs are being monitored and discussed every 3 months across the illness trajectory. The implementation process is part of standard care of the hospital and there is a PROM coordinator and support team available that approaches all patients."
4 Are proxy respondents allowed?	N/A	N/A	Study nurses could be asked for help	N/A	„Yes; parents (for children aged 0-7 or for mentally disabled children 0-18 years) [..]"
5 How where the questionnaire(s) used selected? (possible criteria: validity, feasibility, languages available, other)	N/A	N/A	"The EORTC PRO measures are valid, reliable and feasible questionnaires covering a broad variety of aspects relevant for cancer patients and available in many different languages"*	N/A	„Mainly standardized questionnaires are selected that are available in Dutch, least burdensome for patients/parents to complete, and applicable to a broad age range. We always start with a standard battery of questionnaires [..]. In addition to this, at the beginning of starting to implement PROMs in a new disease group or population, the PROM coordinator and support

					team sit together with the team to decide on which questionnaires to use in their clinical practice.“
6 How extensive are the resources necessary for PROM implementation and maintenance of the program (e.g. staff, costs)? And can recommendations for minimum resources made?	N/A	N/A	staff available: study nurse; costs: N/A	N/A	„Currently, 1 PROM coordinator and 3 PROM administrative support persons are employed on the implementation and maintenance of the PROM portal. At a minimum, one PROM coordinator per center is recommended. Furthermore, a flexible technology system needs to be available in order to ensure adaptability of PROMs to contextual needs. Ideally, the PROM system can be linked to/integrated in the electronic health record.“
7 Is there an estimate on the overall cost per patient for program participation?	N/A	N/A	staff required: not specified, but study nurse provided an initial training if necessary and further assistance if patients reported any problem with the device or the questionnaire; a study nurse gathered sociodemographic and clinical data from the hospital records and entered them in the database to link with associated QOL data stored in the PROM database; costs: N/A	need for additional human resources in each participating urology unit; A fully funded study-dedicated research nurse has therefore been provided to each participating unit. The BCPP Research Nurses are highly trained in all aspects of the program and undertake all the extra duties required, without adversely affecting clinicians' workload and the normal pathways of clinical care	N/A

8 Which conditions had to be fulfilled in advance of the implementation (e.g. necessary IT infrastructure, data security issues, acceptance among healthcare providers and patients, selection and training of staff) - can recommendations be derived?	N/A	N/A	IT infrastructure: if necessary, an Apple iPad 2 was provided for duration of study participation; specialized software for electronic PRO data collection ("CHES"), result calculation, and presentation for use in clinical practice; data security: Physicians can use CHES via their work desktop, patients are equipped with login data for access to questionnaires via a web-site or an iOS app	training of staff: program-specific training of research nurse necessary, but not further specified	"All healthcare providers are trained before they start with the use of PROMs in their clinical practice. Please see [25] for the most up to date description of the training. [..] IT infrastructure: Since July 1st 2019, the PROM system is linked with a viewer-function (F2F) in the electronic health record, such that healthcare providers can immediately look up PROM data without using a password and external website." Data security issues and solutions have been described by [26].**
DO - Implementation:					
9 What kind of PROMs have been implemented? (instrument, generic vs. disease-specific, single vs. multi-item-scale, response format)	generic QOL-measurements: pain level, physical activity, sexual function, depression, urine and fecal incontinence, no information available on single or multi-item-scales	QOL; instrument: EORTC Quality of Life QLQ-C30, Version 3.0; tool for assessing the generic aspects of QOL; response format: paper based; multi-item-scales	QOL; instrument: EORTC Quality of Life QLQ-C30, tool for assessing the generic aspects of QOL; response format: digital via tablet PC; multi-item-scale	general cancer questionnaire QLQ-C30, with the addition of disease-specific assessments using the QLQ-C30, the QLQ-BLS24, with 24 questions specific to NMIBC, the EORTC QLQ-BLM30, with 30 questions specific to muscle-invasive bladder cancer	"During treatment: About the patient: Questions about school, open question to be asked to healthcare provider, PedsQL generic self-report (8-18 years), PedsQL proxy report (0-7 years), PedsQL Cancer Module self-report (8-18 years), PedsQL Cancer module proxy report (0-7 years) About the parent/the family: Psychosocial assessment tool (PAT),

					Distress Thermometer for Parents (DT-P) After end of treatment: About the patient: Questions about school, open question to be asked to healthcare provider, PedsQL generic (same as described above), PedsQL self-report fatigue (8-18 years), PedsQL proxy report fatigue (0-7 years) About the parent: Distress Thermometer for Parents (DT-P)"
10 In what phases of the course of diagnoses and treatment have the PROMs been implemented?	at diagnosis and at 1 and 3 years follow-up	annually after diagnosis	before each treatment application or appointment	at time of diagnosis, 3 months after diagnosis, then annually up to 5 years	"Starting at one month post-diagnosis and continuing every 3 months at outpatient visit until survivorship."
11 How were the PROS collected? (e.g. survey mode (face-to-face, online), frequency and timing of assessments and intervals, interview location)	N/A	survey mode: postal mailings, staff: N/A, frequency: N/A; intervals: annually; interview location: N/A	self-assessment, survey mode: online, interview location: in hospital, at home, frequency: before each consultation / treatment, intervals: depending on consultations/treatment frequency	at time of diagnosis: PROMs collected by trained research nurses via face-to-face interviews, before transurethral resection of bladder tumor; interview location N/A	"Went from digital (QLIC-ON study) to online Portal ([..] www.hetklikt.nu). Tied to a medical appointment at the outpatient clinic, results discussed once in every 3 months. Parents screened for psychosocial issues: once in every 6 months."

12 How where the collected data processed (including aids to facilitate score interpretation) and how did they fit into clinical workflow (fed into the hospital management system, shared and subsequently used and by whom, assistance in interpretation)?	N/A	PROM usage for benchmarking purposes; shared and used for discussion in internal workshops for quality improvement/ optimization of clinical care	workflow: Computer-based Health Evaluation System (CHES) as specialized software for electronic PRO data collection, result calculation, and presentation for use in clinical practice; usage by clinicians, who had access to patients' self-reports via their work desktop, but no advice was given on how to use PRO data for patient appointments; data is stored at each hospital separately	N/A	"PROfile presents 4 HRQOL domains (physical, emotional, social, and cognitive functioning) to paediatrician by summarizing the answers of child or parent, pediatricians are provided with PRO-reports with answers and graphical representations prior to consultations. Since 2011, healthcare providers could log on to the website and open the electronic PROfile, Since July 2019: healthcare providers can open the electronic PROfile through a viewer-function in the electronic health record."
13 Are PROMs used for Benchmarking purposes between care providers and if so, how?	N/A	yes, annual cancer-site specific benchmarking feedback to participating sites with n≥100; discussed among colleagues in workshops	probably not, because data are stored at each hospital separately	N/A	„N/A Yet, we currently work with the quality improvement team of the hospital to see if we can include patient-reported experience measures (PREMs), such as the PedsQL healthcare satisfaction hematology-oncology module. This will then be used for internal care experiences and quality improvement."

14 What were strategies for responding to issues identified by the questionnaires?	N/A	discussion in workshops	"No advice was given on how to use PRO data for patient appointments"*	N/A	A decision tree pocket-card has been developed [25,27].
STUDY					
Barriers and enablers:					
15 Can recommendations to influence clinical uptake of PROMs in routine care be derived? (e.g. necessary IT infrastructure, data security issues, acceptance among health care providers and patients, sociodemographic of users, costs, time needed, suitable survey instruments)	N/A	N/A	Barriers for patients: internet access, security concerns (older patients) regarding the transmission of health-related data and QOL via the internet; sociodemographic barriers: age; acceptance among health care providers not reported	N/A	"Please see our published paper about the implementation process [28] and the discussion of the thesis of Schepers (p. 179) [29]."
16 What can be recommended for a multicentric implementation of PROMs in comparison to unicentric implementation? What were the lessons learned?	N/A	N/A	not really multicentric in that no central database was used	N/A	„Starting bottom-up (involving the team) works better than top-down; Start small, learn from the implementation process, and slowly start to spread the intervention further; A local PROM coordinator and champion are essential; Always involve the end-users in the process of implementation; Adaption is key (e.g. selection of questionnaires/making it

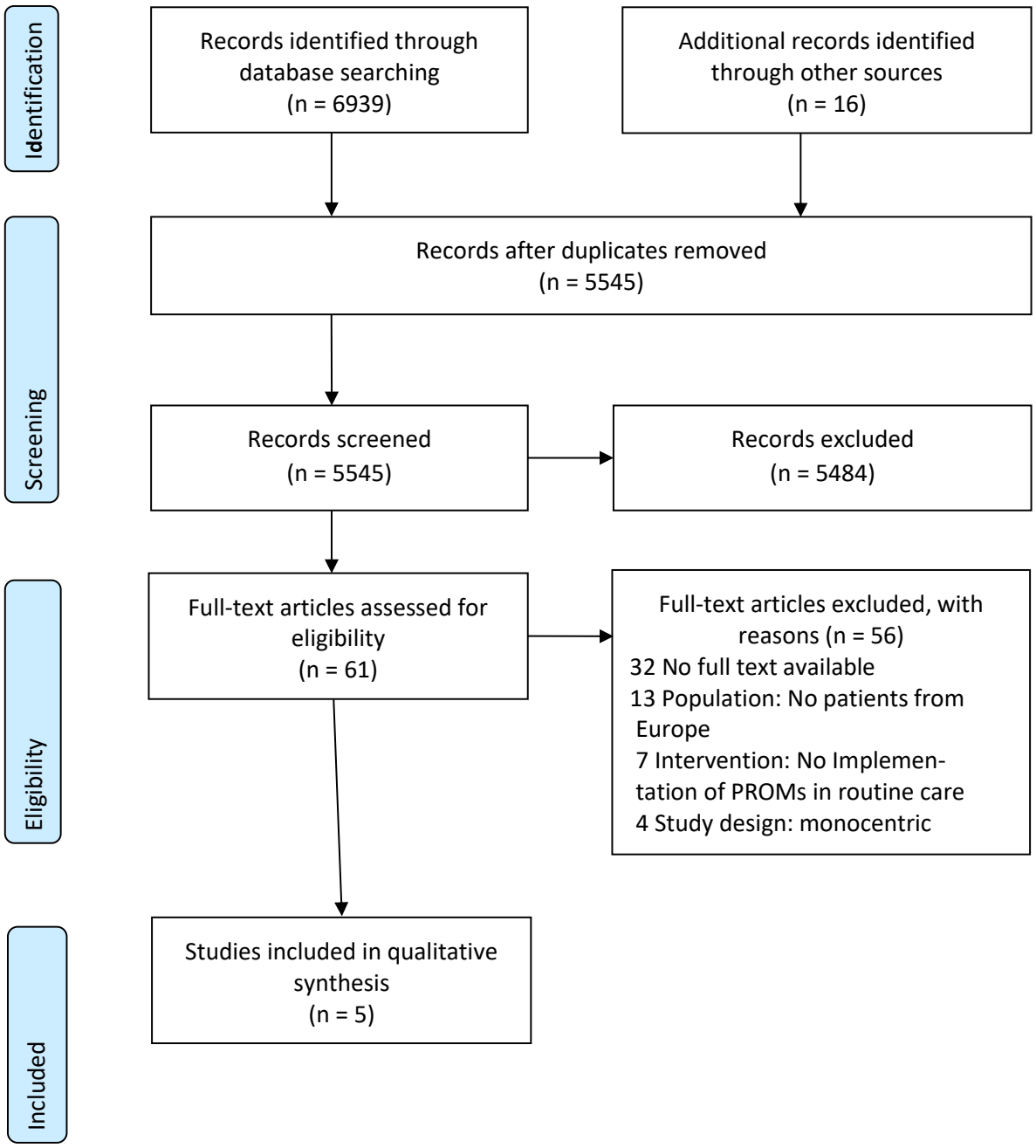
					available in electronic health record) [..]"
Impact and lessons learned:					
17 What was the impact of routine use of PROMS on outcomes at the patient, provider, and system level? How has it been assessed/evaluated? What were the results? Was the aim achieved and did any unintended effects occur?	N/A	N/A	N/A, but a patient evaluation was done to identify attitudes towards ePROMs	N/A	PRO tools facilitate discussion of HRQOL issues and increase physician's awareness of their patients HRQOL; there was also an impact on physician–patient communication with better HRQOL and emotional functioning for some patients; "[W]e showed initial effectiveness as described in [..][30]. Yet, we also showed that when implementing PROMs in a real-world pediatric oncology setting, challenges arise [28], which might impact the originally intended effect of the intervention (i.e. implementation fidelity). Therefore, continuously monitoring the implementation process, and applying implementation strategies, even in the maintenance phase, is very important."

18 What were the lessons learned from PROM implementation?	N/A	N/A	"Involvement of stakeholders and education of patients regarding ePRO and its purpose may ease implementation; common barriers persist (experiencing ePRO as too impersonal or not adequate for the patient's actual situation)"*	N/A	method was more time-consuming than expected and caused logistical problems [31]. "Furthermore, in order for it to be aligned with the clinical workflow, it needs to be integrated in the electronic health record and a PROM coordinator is of utmost importance [28]."
ACT					
19 Was PROM assessment modified following the results of the initial implementation?	N/A	N/A	"No"*	N/A	[..] The IT system (www.hetklikt.nu) furthermore received an update in 2013, such that we can now flexibly use the portal for the purpose of clinical practice (feedback of PROM results to authorized users), research (no feedback of PROM results), and clinical trials (data extraction for authorized trial data managers). Patients do not need to complete questionnaires twice for different purposes if the timeframes of clinic/research/trials overlap. Finally, the pediatric oncology hospital (Princess Máxima Center for pediatric oncology) has established a viewer-

					function in the electronic health record since July 2019."
20 Is there anything else that should be mentioned regarding the PROM program?					"The implementation process of the PROM portal is constantly monitored and is dynamic. For pediatric oncology, we moved from an externally research-funded program towards a program that is fully funded by the hospital (since 2018) and is part of standard care."

* Quotes taken from the author query response. Full documentation of query response for Engelen et al. in appendix 2.

Figure 1: Flowchart of the study selection process



4 Discussion

Demanding the collection of PROMs to monitor patients or benchmark providers in routine cancer care has a long history [14]. Implementing such approaches however has proved to be difficult. Our systematic literature research and the consecutive survey of researchers involved in such approaches gave insight into characteristics of existing programs as well as facilitators and barriers to implementation. Five programs from Europe were identified that met the inclusion criteria and allowed the collection of PROMs in routine cancer care to monitor (or detect changes) of symptoms and function and that used identical data collection infrastructures across centers, to make the comparison of outcomes across providers possible, at least theoretically. In practice, it was often not clear whether and how the latter was done or planned at all, except for the example from Germany [21] that had benchmarking as its focus. Ongoing approaches to provider comparison like the TNGR [12] or EDIUM [32] are yet too early in the process to be included in the review and no results have been published yet. We suspect that there are more programs with data collection having started only recently and with no publications released so far such as the ongoing PROM initiative in the 15 Tuscanian Breast centers[1]. We emphasize that our aim was not to compare successful with unsuccessful approaches. Only "surviving" programs were included, i.e. programs for which at least one publication with routinely collected data was released.

One of the purposes of this review was to give guidance to researchers and/or practitioners (preferably: both together) who want to implement PROM programs into practice. Although some of the studies identified gave valuable insight, many crucial aspects were less clear, particularly those regarding costs, necessary preconditions, how to handle the data collected, and how to allow for comparisons. Research and practice is still at a too early stage to give definite advice for implementation of PROM programs. We highlight some blind spots identified in this review that require further research:

1. Resources/costs: In order to convince those in charge of budget allocation (e.g., funding institutions, hospital board members, policy makers, health insurances) it is imperative to identify costs of PROM collection in routine care, preferably on a per-patient basis. Ideally, these costs are compared to the resulting benefits. Yet, PROM collection is typically not covered by the payers (i. e. health insurances) which thwarts implementation into routine care. We therefore want to encourage a discussion on whether routine PROM collection in cancer care should be financed by funders just like other interventions – and under which conditions.

[1] https://www.santannapisa.it/it/ricerca/progetti/indagini-proms-nella-chirurgia-ricostruttiva-post-mastectomia

2. Prerequisites: Depending on the mode of data collection and the specific aims of PROM use, prerequisites may need to be fulfilled that need thorough advance planning. This may include IT infrastructure, training of providers and acceptance building among those involved. Although the recent controlled PROM trials provide valuable arguments in favor of PROM use in routine care [6,7], oftentimes this means additional workload for those involved that is not sufficiently reimbursed [33,34]. Especially for benchmarking/quality improvement purposes, a high response rate is imperative. This can only be achieved when the health care professionals see added value in routine PROM collection and fully support such programs.

3. Presentation: In order to achieve provider commitment, data collected need to be processed in a way that is useful for clinical practice and fits into the workflow. This may involve the issue of how individual results are presented so that providers can use it in consultations and also when and how (paper, electronically) reports are provided [35]. Ideally, patient-individual reports will be part of the overall electronic infrastructure of the providing institution and as such implemented into the clinical pathway. As obvious as this idea is, apparently such an approach is easier said than done. The literature on this issue typically stems from randomized trials or qualitative research and not from programs that allow for a comparison in routine care [36].

4. Response: Connected to the issue of how results are presented is the question of how to react to the results. This includes the question of whom to include in the discussion of results, how to identify areas of intervention, and what to do once areas of interventions are identified, typically when impaired functioning is detected. This aspect is heavily connected to how reports are presented, e.g. if impaired functioning is flagged, and bears several methodological and ethical challenges. For example, how can thresholds for impairment that require an intervention be defined? Or, if many dimensions of functioning are impaired, should all be “treated” or only the most severe? Klinkhammer-Schalke and colleagues suggested a multidisciplinary approach to discuss results and plan interventions [5]. We want to stress the importance of the inclusion of not only physicians but all relevant disciplines, among them nurses, social workers, and psycho-oncologist. PROM collection and analysis does also not necessarily center around physicians but can be led by other professions as well [37]. If multidisciplinary, comprehensive approaches like [5] can be implemented into routine care certainly depends on the resources a health care system has.

5. Multicentricity: The issue of both presentation and response is a blind spot also for the comparison of results across providers. There is little resistance to the idea that fair comparisons require case mix (or: risk) adjustment including baseline (pre-intervention) PROM data. However, what models and what co-variates should be used for adjustment is less clear but may make a big difference. Also, how data from different providers are transferred to one database may prove difficult when not planned in

advance. Only one program had benchmarking as an explicit aim and we argue that (patient-reported) outcome comparison is critical for quality improvement.

Our systematic review was based on a sensitive search string to identify programs for PROM collection that may be "hidden" in the literature, for example when they are not presented as "programs", but merely provide the basis for controlled trials in which PROMs are collected, for example as secondary outcomes. A supplementary hand search and a query among colleagues were conducted to identify programs not identified with the systematic search. However, we cannot rule out to have missed relevant programs, also because of terminology issues: "Programs" that are part of routine care may be difficult to distinguish from "studies" or "projects". Both may be planned for a limited time, like the three years typically allotted for research, but also with a longer time perspective without being labelled as such. Also, it is often not clear at program initiation how long such an initiative will last.

Insight into "what works" in cancer routine care about PROM implementation may benefit from other areas of healthcare that are beyond the scope of this review. This includes work on surgical procedures like the UK or Swedish examples mentioned above show. Methodological papers based on these programs include the role of patient characteristics on differential recruitment rates or the significance of PROMs for outcome comparisons as compared to mortality [38,39]. Looking beyond Europe allows for the identification of further important methodological aspects like different procedures for risk-adjustment [40]. However, since cancer care with its necessarily multidisciplinary approach differs substantially from many other fields of medicine, we must be careful when adopting conclusions from other fields.

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6 Funding of the included programs

Study included in our review	Sources of funding
Nguyen-Nielsen et al., 2016	DAPROCAdata is funded by the Danish Regions10 and is administered by the Danish Clinical Registries (RKKP).
Meisner et al., 2011	This project was funded by the Robert Bosch Foundation (2009/2010) as part of the funding initiative of the Federal Ministry for Health, Benchmarking in Health Care (BIG) and, since 2007, by the hospitals in the OSP.
Wintner et al., 2015	The study was partly funded by the Society for Tumor Research (Verein für Tumorforschung) and by Janssen-Cilag. The work of LMW was funded by the Austrian National Bank (Österreichische Nationalbank, ÖNB project nr. 14324), the Tyrolean Health Fund (Tiroler Gesundheitsfonds, TGF) and the Austrian Science Fund (FWF P26930). The work of JMG was funded by the Austrian Science Fund (FWF J3353). The work of MS was funded by the Austrian National Bank (ÖNB project nr. 14492).
Zeegers et al., 2010	The BCPP programme is funded by Cancer Research UK and supported by the Department of Public Health and Epidemiology and Institute for Cancer Studies, University of Birmingham. The West Midlands Bladder Cancer Prognosis Programme is funded by Cancer Research UK.
Engelen et al., 2012	Research was funded by the Dutch Cancer Society (KWF) and the Stichting Kindergeneeskundig Kankeronderzoek (SKK).

7 Supplementary material

Response by Schepers for Engelen et al.

Search string